Dual Diagnosis and Psychiatric Treatment

Substance Abuse and Comorbid Disorders

Second Edition

edited by
Henry R. Kranzler
Joyce A. Tinsley

Dual Diagnosis and Psychiatric Treatment

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Preface

As with the first edition of this book, the second edition provides a scientific basis for the clinical care of dually diagnosed patients—specifically, those individuals who suffer from a substance use disorder in combination with either a psychiatric or medical disorder. The attention that was focused on the issue of dual diagnosis, which led to the publication of the first volume, has continued to grow unabated. This growth has been stimulated by a continued high rate of comorbidity and the difficulty inherent in providing appropriate care for dually diagnosed patients. Understanding the basis for such comorbidity is essential in the search for the etiology and pathogenesis of both substance use and comorbid disorders. Increased clarity of diagnostic criteria and improvements in diagnostic methods have enhanced the assessment process. Finally, new models for treatment of dually diagnosed patients continue to be developed and implemented, further underscoring the need for integrated care to ensure adequate attention to the complex treatment needs of this patient group.

The book contains information that is relevant to both the clinician and the investigator interested in the empirical and theoretical dimensions of comorbidity. New chapters have been added and consolidation has occurred to allow greater comprehensiveness. The first part (Chapters 1–4) is devoted to basic issues of epidemiology, genetics, diagnosis, and treatment. It provides the scientific and methodological underpinnings for ongoing developments in the clinical care of patients with dual diagnosis. The second part (Chapters 5–16) focuses on specific comorbid disorders in the large, heterogeneous population of patients with comorbid substance use and psychiatric or medical disorders. Because differential diagnosis is particularly challenging in dually diagnosed patients, each of the chapters in this section of the book provides a detailed discussion of the diagnostic process relevant to the specific comorbid disorder(s) addressed in that chapter. The individual chapters also review in detail the options that exist for the treatment of dually diagnosed patients.

New chapters have been added on the comorbidity of alcohol and drug use disorders. In addition, the growing recognition of the high degree of comorbidity of substance use disorders with compulsive gambling led to the inclusion of a chapter on that topic. These topics were added to chapters covering comorbidity with mood disorders, anxiety disorders, nicotine dependence, personality disorders, eating disorders, attention-deficit disorder, schizophrenia, and cognitive impairment. Finally, chapters are devoted to the diagnosis and treatment of HIV infection and of other major medical disorders that are directly related to substance abuse.

We thank all the contributors for their diligence in providing up-to-date and definitive coverage of their topics in a form that can be useful to researcher and clinician alike.

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1
Comorbidity of Alcohol, Drug, and Psychiatric Disorders: Epidemiology

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COMORBIDITY OF PSYCHIATRIC DISORDERS WITH ALCOHOL AND DRUG USE DISORDERS

The common co-occurrence of psychiatric disorders with alcohol and drug use disorders is well recognized. The reasons for co-occurrence, the best methods to differentiate substance abuse from psychiatric syndromes, and the best treatments for comorbidity remain open research questions. Nevertheless, a consensus is emerging that comorbid psychiatric and substance use disorders present problems and complications that do not occur when the clinical picture is limited to a single disorder. The present chapter describes the prevalence and natural history of the co-occurrence of substance use disorders and psychiatric disorders, and directions for future research in this area.

What is Epidemiology?

Epidemiology is the study of the distribution and determinants of diseases and injuries in human populations. In most branches of medicine, the individual is the primary focus of concern. However, in epidemiology, the primary focus is the community (1). The "community" can consist of the entire population of a country, for example, national surveys of the U.S. population. A community might also be defined as household residents of a particular geographic area, such as a health services catchment area of a city or metropolitan area. Alternatively, the "community" might be more restricted, consisting of the group of patients with alcohol or drug use disorders who are currently seen in treatment facilities. Epidemiological studies of treated samples are known as clinical epidemiology.

Scope of this Chapter

This chapter covers information from four types of sources. These include: 1) historical background on the epidemiology of psychiatric, alcohol and drug use disorders prior to comorbidity research; 2) general population data on comorbidity, from large surveys; 3) clinical epidemiological data; and 4) data on the longitudinal course of disorders when they co-occur. General population data provide information on the co-occurrence of two (or more) conditions without selection bias that may produce overestimates of co-occurrence from treated samples. This selection bias occurs because individuals are more likely to enter treatment if they have two or more conditions (2). However, clinical epidemiological data from treatment facilities indicate the range in the prevalence of comorbidity in settings of interest to clinicians and clinical researchers. Data from longitudinal studies are presented because epidemiology includes study of the natural history of disease, and because one of the most important questions about comorbidity from a treatment perspective is whether the presence of one disorder affects the course of another.

HISTORICAL BACKGROUND

General population epidemiological research on the comorbidity of psychiatric and substance use disorders is a recent phenomenon, dating back only about fifteen years. Prior to that, epidemiological work focused on psychiatric or alcohol-drug abuse domains.

Psychiatric Epidemiological Studies: "First-Generation"

U.S. epidemiological research on mental disorders began in the nineteenth century, when a physician/epidemiologist named Edward Jarvis (3) studied the prevalence of mental disorders in Massachusetts (3). Realizing that a survey of hospital records would miss untreated cases, Jarvis surveyed general practitioners and other "key informants" such as clergy. He also used hospital and other institutional information. His classification system was crude, as his two diagnostic categories were "insanity" and "idiocy." However, he took important initial steps to avoid underestimating prevalence. Although drinking was increasingly a public issue, it was not usually considered in a psychiatric context at that time, and Jarvis did not address alcohol-related conditions in his survey. Additional studies relying on informants were carried out before World War I, in what has been termed the "first generation" of psychiatric epidemiology studies (4). Again, these studies did not address comorbidity.

Psychiatric Epidemiology Studies: "Second-Generation"

After World War II, a second generation of psychiatric epidemiology studies was conducted (4). These utilized interviews with individuals in communities rather than informant reports. However, these studies were conducted when a psychoanalytic

approach to psychiatry was widespread and when the Diagnostic and Statistical Manual of Mental Disorders (DSM I) (5) did not provide specific diagnostic criteria. Since measures were needed that could be used on a large-scale basis, second-generation studies used standardized psychometric scales based on Selective Service screening scales developed during World War II (6). These economical screening scales were used in community surveys such as the Stirling County study (7) and the midtown Manhattan study (8). Each of these scales measured "demoralization" (9), consisting mainly of symptoms of mild depression, anxiety, and non-specific physical symptoms. However, demoralization overlapped only modestly with diagnoses of specific mental disorders (10,11), and comorbidity was not addressed in the second-generation psychiatric epidemiology studies.

Change in the prevalence of psychiatric disorders over time has been a topic of some interest. The psychiatric epidemiological studies just noted did not provide a direct way to study changes in the prevalence of psychiatric disorders over time, because their methods of sampling and measurement were too different. However, time trends have been studied indirectly in cross-sectional surveys by comparing lifetime rates of disorders in the different birth cohorts included in the surveys (e.g., subjects born in the 1940s, 1950s, etc.). This type of study has potential sources of inaccuracy; for example, older respondents may forget disorders that remitted years earlier, increased mortality associated with psychiatric disorder removes potential subjects from older birth cohorts, or there may be differences in reporting styles (12). However, a general consensus exists that depression and possibly other disorders have increased in U.S. cohorts born since World War II (13,14). These findings are consistent with a parallel increase in suicide deaths in the United States (15).

Alcohol Epidemiology (Distinct from Comorbidity Research)

Long-term historical information on U.S. alcohol epidemiology is available through per-capita alcohol consumption statistics derived from alcohol sales figures. These statistics do not reflect the prevalence of alcohol use disorders, but do provide information from the 1700s to the present on alcohol consumption, a necessary condition for the development of alcohol dependence or abuse. These figures show that drinking levels in the U.S. have varied greatly over time, ranging from extraordinarily high per-capita consumption levels during colonial days (16) to a low point before and during Prohibition, which began in 1919. From the end of Prohibition in 1933 until 1982, per capita alcohol consumption increased steadily to a peak of nearly 2.8 gallons of ethanol per year in 1982 (17). Since then, consumption has declined, leveling off to about 2.2 gallons of ethanol per year in the late 1990s. These data are generally consistent with liver cirrhosis mortality statistics, which show similar variations over time (18).

Concerning time trends from surveys, several national alcohol studies prior to the 1990s focused on direct questions about consumption and scales of alcohol-related problems, although these did not correspond closely to present definitions of dependence and abuse (19–22). Conjoint analysis of several of these surveys showed that the lifetime and current prevalence of multiple alcohol-related problems increased in the U.S. general population from 1967 to 1984 (23,24). This information is consistent with the alcohol

per-capita consumption statistics.

Drug Use Epidemiology in Adults (Distinct from Comorbidity Research)

An important source of time trend information on drug use is the Monitoring the Future surveys (25). These are yearly national surveys of drug use among approximately 16,000 high-school students and follow-up surveys of random samples of these students that track the prevalence of drug use into early and mid-adulthood. Data are available for college students from 1980 and for adults from 1986. Since 1980, the percentage of college students reporting *lifetime* use of any illicit drug ranged from 45.5% to 69.4%. The prevalence was highest in 1980, declining to a low point in 1994–1995. At that point, the prevalence began to increase again, reaching 53.6% in 2000. Use of any illicit drug *in the previous 12 months* among college students ranged from a high of 56.2% in 1980 to a low of 29.2% in 1991, after which the percentage began to climb again, reaching 37.9% in 2001.

Data from Monitoring the Future on the prevalence of illicit drug use in the previous 12 months among adults to age 40 was available from 1986, when it was 41.9%. The prevalence declined until 1991, reaching a low of 27.0, and then began to increase, reaching 32.1% in 2001. The prevalence of marijuana use in the previous 12 months closely mirrored the prevalence of any illicit drug use among adults during this time. In contrast, use of cocaine in the previous 12 months showed a dramatic decline in prevalence, from a peak in 1986 of 19.7% to a low of 4.1% in 1996. An increase in the prevalence of cocaine use since then, to 5.8% in 2001, is of concern, but represents a slight change compared to the previous decline.

EPIDEMIOLOGICAL STUDIES ON COMORBIDITY OF SUBSTANCE USE AND PSYCHIATRIC DISORDERS—THE THIRD-GENERATION SURVEYS

In the mid- and late 1970s, a major change took place in diagnostic methods in psychiatry. With the publication of the Research Diagnostic Criteria (RDC) (26) and DSM-III (27), psychiatric diagnosis became much more like diagnosis in other areas of medicine, based on directly observable signs and symptoms. Discrete psychiatric disorders were evaluated using specific diagnostic criteria. Alcohol and drug use disorders were included in the nomenclatures in addition to psychotic, affective, anxiety, and personality disorders. These diagnostic developments laid the groundwork for present-day comorbidity studies at the epidemiological level. This work has been carried out in what are called “third-generation” psychiatric epidemiological studies. Three major studies of this type have been published: the Epidemiologic Catchment Area Survey (ECA) (28), the National Comorbidity Survey (NCS) (29), and the National Longitudinal Alcohol Epidemiological Survey (NLAES) (30). Table 1 shows institutional sponsorship and a number of features of the three third-generation studies. As shown, the surveys vary considerably in size, from about 8000 to about 43,000 respondents. One of the studies was conducted in the early 1980s (28), and the other two (29,30) were conducted in the

Table 1 Design Features of the Three U.S. Third-Generation Psychiatric Epidemiological Studies

Feature	ECA	NCS	NLAES
Sponsoring institution	NIMH	NIMH	NIAAA
Years of data collection	1980–1984	1990–1992	1991–1992
Sample size	20,219	8098	42,862
Response rate (approximate)	77.6%	82.6%	89.2%
Sample	5 U.S. communities	U.S. general population	U.S. general population
Sampling method	Probability	Probability	Probability, oversampling for minorities and young adults
Individuals surveyed	Household+institutional residents	Household and college residents	Household residents
Age range	18 and older	15–54	18 and older
Field work conducted by:	Independent academic researchers at the five sites	Survey Research Institute, U.Michigan	U.S. Bureau of the Census

early 1990s. All three included probability samples of U.S. household respondents, although only the two more recent surveys consisted of national samples.

Diagnostic Assessment in Epidemiological Surveys

To carry out third-generation epidemiological studies, assessment procedures were required that could be administered and supervised in the large numbers required by general population surveys. The sheer size of the studies, in addition to the non-centralized nature of national surveys, precluded the use of clinicians as interviewers. Therefore, interviews were developed to collect data on symptoms and criteria of psychiatric disorders that could be administered by non-clinicians. To ensure standardization, the interviews included only close-ended questions on symptoms. In such interviews, known as fully structured interviews, the interviewer reads all questions verbatim to the subject and scores the items exactly according to subjects' responses. Semi-structured probing methods, explanations of concepts, or judgements by the interviewers are discouraged. The data from these interviews are entered into computer files, from which diagnoses are generated by the application of computer programs.

Table 2 shows the diagnostic assessment procedures used in the three studies. All interviews covered substance use disorders and affective disorders. Two of the three studies (ECA and NCS) also covered anxiety disorders and psychotic disorders. Each diagnostic interview had distinctive structural features. Considerable variability existed in the amount and type of psychometric testing conducted with the instrument, and the time frame for "current" diagnoses also varied.

The Epidemiologic Catchment Area Survey

The Epidemiologic Catchment Area Survey (ECA) was the first of the third-generation studies. This study was designed specifically to generate rates of treated and untreated disorders in five U.S. communities. One of the explicit purposes of this earliest of the three major third-generation studies was the assessment of psychiatric disorders according to the then-new DSM-III nomenclature (28). The five communities surveyed in the ECA were located in New Haven, Connecticut, Los Angeles, Baltimore, St Louis, and Durham, North Carolina. Despite the geographic characteristics of the sample, weights were eventually derived so that national rates of psychiatric disorders and substance use disorders could be estimated from the ECA data. The interview for the study, the Diagnostic Interview Schedule (DIS) (31), was developed specifically for this study, based on earlier instrument development that had been conducted at Washington University in St Louis.

Table 2 Assessment Features of the Three U.S. Third-Generation Psychiatric Epidemiologic Studies

Feature	ECA	NCS	NLAES
Diagnostic criteria used	DSM-III	DSM-III-R	DSM-IV
Diagnostic interview	Diagnostic Interview Schedule (DIS)	Composite International Diagnostic Interview, U.Michigan version (UM-CIDI)	Alcohol Use Disorders and Associated Disabilities Interview Schedule (AUDADIS)
Psychometric testing of interview	Comparison with other diagnostic procedures in varied settings	None for this version of the CIDI	Test-retest reliability, probability sample of 473 general population subjects
Timeframe for "current" comorbidity	Prior 6 months	Prior 6 months	Prior 12 months
Diagnostic coverage	Substance use, affective, anxiety, psychotic disorders	Substance use, affective, anxiety, psychotic disorders	Substance and unipolar affective disorders

Notable interview features	Probe flowchart eliminates psychiatric symptoms if subject attributes them to alcohol/drugs	Screening questions all at start of interview, subject's commitment to disclosure requested then	Past alcohol/drug disorders not diagnosed unless symptoms clustered together syndromically

Table 3 Prevalences of Current and Lifetime Disorders in Three General Population Surveys

	Survey		
Disorder	ECA	NCS	NLAES
Current[a]			
Any alcohol use disorder	4.8	9.7	7.4
Alcohol abuse	1.9	2.5	3.0
Alcohol dependence	2.8	7.2	4.4
Any drug use disorder	2.0	3.6	1.5
Drug abuse	0.9	0.8	1.1
Drug dependence	1.2	2.8	0.5
Major depression	3.0	10.3	3.3
Lifetime			
Any alcohol use disorder	13.5	23.5	18.2
Alcohol abuse	5.6	9.4	4.9
Alcohol dependence	7.9	14.1	13.3
Any drug use disorder	6.1	11.9	6.1
Drug abuse	2.6	4.4	3.1
Drug dependence	3.5	7.5	2.9
Major depression	5.9	17.1	9.9

[a]Current: ECA, 6 months; NCS, 12 months; NLAES, 12 months.

ECA estimates of the prevalence of lifetime disorders were 22.5% for all mental disorders other than alcohol or drug use disorders, and 16.7% for substance use disorders (28). The most common categories of mental disorders included anxiety disorders (14.6%), and affective disorders (8.3%). Table 3 shows the lifetime prevalences of DSM-III alcohol use disorders, drug use disorders, and major depression from the ECA (32). Respondents with any lifetime mental disorder had significantly increased chances of experiencing an alcohol or drug use disorder also. The odds ratio indicating the level of

association for any mental disorder and a drug disorder was 4.5, while the odds ratio for any mental disorder and an alcohol use disorder was 2.3. An even stronger association was shown between alcohol and drug use disorders on a lifetime basis, with an odds ratio of 7.1 for the full sample.

Information was also available on lifetime and current (last 6 months) comorbidity for specific mental disorders. The odds ratio indicating the association of schizophrenia with any substance use disorder was 4.0, broken down further into an odds ratio of 3.8 for alcohol and 6.2 for drugs. The odds ratios for anxiety disorders and substance use disorders were generally lower, with the exception of panic disorder. The association of any lifetime affective disorder with any lifetime substance use disorder was 2.6. When more specific affective disorders were considered, bipolar I disorder had the highest level of association; odds ratio=7.9 for any substance use disorder, 5.6 for alcohol use disorders, and 11.1 for drug use disorders.

Table 4 presents the associations between major depression and alcohol use disorders, as well as those between major depression and drug use disorders. The odds ratios indicate the magnitude of the association. The information in these tables was computed only on respondents in the ECA up to the age of 54, to improve the accuracy of comparisons with a more recent study (33). As shown, the odds ratios were all larger than 1.00, ranging from 1.9 to 3.5. Table 5 shows the odds ratios that indicate the degree of association between alcohol and drug use disorders in the ECA. As shown, the presence of a drug use disorder greatly increased the odds of

Table 4 Comorbidity of Major Depression with Substance Use Disorders in Three General Population Surveys: Odds Ratios

	Survey		
Disorder	ECA	NCS	NLAES
Current[a]			
Alcohol abuse/dependence	2.7	2.6	3.7
Drug abuse/dependence	3.4	3.0	7.2
Lifetime			
Alcohol abuse/dependence	1.9	1.9	3.6
Drug abuse/dependence	3.5	2.4	5.2

[a]ECA and NCS, 6 months; NLAES, 12 months.

Table 5 Comorbidity of Alcohol and Drug Disorders in Three General Population Surveys: Odds Ratios

	Survey		
Timeframe	ECA	NCS	NLAES
Current[a]	7.8	20.6	25.1
Lifetime	5.8	13.7	13.0

[a]ECA and NCS, 6 months; NLAES, 12 months.

having an alcohol use disorder. This relationship was stronger for current disorders (OR=7.8) than for lifetime disorders (OR=5.8).

National Comorbidity Survey

The National Comorbidity Study (NCS) (29) was designed to provide data on the comorbidity of substance use and non-substance use psychiatric disorders, based on a full national sample. With the publication of DSM-III-R in 1987 (34), general population data with the more recent DSM-III-R diagnostic criteria were needed. Tables 1 and 2 show basic design and diagnostic features of the NCS. The interview, the University of Michigan version of the Composite International Diagnostic Interview (UM-CIDI) (29), was developed especially for this survey, and included some features that clearly differentiated it from all other structured diagnostic interviews. In particular, in the UM-CIDI, screening/gateway questions for many disorders are asked early in the interview, and only followed up later with the remaining diagnostic sections. (In most diagnostic interviews, screening/gateway questions occur throughout the interview at the beginning of their respective sections.) Also, respondents are asked to make a verbal commitment to honest, complete answers before the interview is started. The effects of these changes on the reliability and validity of the UM-CIDI have not been formally tested. An additional difference between the NCS and the ECA interviews consisted of the collection of risk factor data in the NCS to offer explanations for the etiology of disorders.

Results from the NCS showed much higher prevalences of many disorders than the prevalences found in the ECA. For example, the NCS lifetime prevalence of any mental disorder including substance use disorders was very high, 48%. Lifetime prevalences for general diagnostic groupings (as distinct from specific disorders) were 19.3% for any affective disorder, 24.9% for any anxiety disorder, and 26.6% for any substance use disorder. These differences in overall rates between the ECA and the NCS could potentially be explained by several methodological factors, including different diagnostic criteria, substantial differences in the interview procedures, and considerably different sampling designs. In addition, since the NCS was conducted about 10 years later than the ECA, temporal effects could also have created true increases in national rates of disorders. At present, no firm conclusions can be drawn about the differences in the

overall rates. However, even though rates of disorders in the two studies were different, the strength of associations between disorders might be the same.

Information on the lifetime association of substance use disorders with other psychiatric disorders was available from the NCS. The odds ratios indicating the association between non-affective psychosis and alcohol disorders was 2.2; between non-affective psychosis and drug disorders, 2.7. Odds ratios for anxiety disorders and substance use disorders ranged from 2.2 (phobia) to 3.2 (PTSD). Odds ratios between bipolar I disorder and substance use disorders were 4.9 for alcohol use disorders and also for drug use disorders. These odds ratios are all somewhat smaller than the corresponding odds ratios from the ECA. When current (last six months) disorders were examined, comorbidity was higher. The association of current alcohol and drug use disorders was very high (OR=20.6). The odds ratios ranged considerably in size for other current disorders. The odds ratios between psychiatric disorders and alcohol use disorders ranged from 1.8 (dysthymia) to 5.6 (mania). Odds ratios between psychiatric disorders and drug use disorders ranged from 2.9 (PTSD) to 5.7 (mania).

Table 4 shows odds ratios of the association between alcohol and drug use disorders and major depression for the ECA and the NCS. All odds ratios shown were significantly higher than 1.00. Odds ratios for comorbidity associations tended to be smaller in the NCS than in the earlier ECA. A speculative (although testable) explanation for the smaller odds ratios in the NCS might be that the much higher prevalences in that study included milder cases that were less likely to have experienced comorbidity.

The associations of alcohol and drug disorders in the NCS are shown in Table 5. In contrast to the tendency of the odds ratios from the NCS to be lower than those from the ECA, as shown in Table 4, the odds ratios in Table 5 show markedly higher levels of association between alcohol and drug use disorders in the NCS than in the ECA. This was true for both current and lifetime diagnoses, and may represent a true closer association between the two types of disorder in the more recent time period.

National Longitudinal Alcohol Epidemiologic Survey

The largest national survey on comorbidity published to date was conducted in 1992 (30,35). This study focused on alcohol, drug, and depressive disorders, particularly major depression. The survey was conducted to provide stable estimates of specific alcohol and drug use disorders, associated physical and mental disabilities, treatment utilization, information on risk factors for substance use disorders, and on the economic impact of these disorders. This required a large sample and reliable diagnostic measures. Tables 1 and 2 show the design and assessment features of the NLAES.

As shown in Table 1, the sample was very large, exceeding 40,000 people. The size of the sample allowed analyses of alcohol and drug use disorders that were more refined than in previous surveys, for example, abuse and dependence categories within specific drug types. The diagnostic interview developed for the survey was the Alcohol Use Disorders and Associated Disabilities Interview Schedule (AUDADIS) (36). In the AUDADIS, substance dependence is not diagnosed unless symptoms cluster together chronologically. Although the NLAES was conducted prior to the publication of DSM-IV, the AUDADIS obtained the necessary information to make alcohol, drug, and

psychiatric diagnoses according to DSM-IV criteria (37).

Other fully structured diagnostic interviews have not been subjected to reliability testing on the grounds that, logically, subjects should always respond to fully structured questions with the same answers. However, if the questions in the interview are unclear, there is no reason to expect that the subjects will respond identically to questions in the first and second interviews of a reliability pair. The AUDADIS diagnoses were subjected to a test-retest reliability study of 473 urban community residents (from Newark, New Jersey and surrounding communities). The reliabilities *(kappa)* for these diagnoses ranged from 0.56 to 0.95 for current and past disorders (35). The AUDADIS was also subjected to a test-retest study in clinical settings where comorbidity was expected to be high (38). Reliabilities were similarly high in this study.

In the NLAES, the current (past year) prevalence of major depression for the full sample was 3.33%, while the lifetime prevalence was 9.86% (Table 3). Prevalences for current disorders were higher in women (about a 3:2 ratio), whites (also about a 3:2 ratio), and younger adults (e.g., 5.99% in adults aged 18–29 vs. 1.8% in adults 45–64 years old). Similar demographic patterns were observed for lifetime diagnoses, although between-group differences were not as large for lifetime diagnoses. The prevalence of current alcohol dependence was 4.38% in the total sample. Within population subgroups, the current prevalence of alcohol dependence was 6.33% in males and 2.58% in females. Differences between blacks and non-blacks were not as pronounced, but the discrepancy between younger and older adults was striking: 15.1% for adults aged 18–29 years, but only 2.1% for adults 45–64 years old. Table 4 shows the odds ratios for current and lifetime major depression among subjects with alcohol and drug use disorders. The confidence intervals for all odds ratios indicated a high level of statistical significance. As is shown, the odds ratios for all categories and time frames indicated a strong degree of association or comorbidity in this large survey of U.S. community residents. Odds ratios were higher for drug use disorders than for alcohol use disorders.

The material in Table 5 shows that the high level of association between alcohol and drug use disorders found in the NCS was also found in the NLAES. Given that this high level of association was found in the two more recent studies, despite their methodological differences, it seems warranted to conclude that drug and alcohol use disorders are more likely to co-occur within the same individuals than they were fifteen years ago. This is true both concurrently and on a lifetime basis.

When the association of current major depression with current alcohol dependence was broken down by population subgroup (39), males proved to have the strongest association, with an odds ratio of 5.54. The odds ratio for women was 3.78, somewhat lower than for males. Among different age groups, those in the 30–44 year age range had the highest association of current major depression with alcohol dependence, showing an odds ratio of 3.63. The association for current depression and alcohol dependence was considerably stronger among non-blacks (OR=4.48) than among blacks (OR=1.72), even though all odds ratios were statistically significant. Smaller subgroup differences were found for lifetime disorders. Males and females showed nearly equivalent associations of lifetime diagnoses of major depression and alcohol dependence (OR=4.33 and 4.28, respectively). Blacks and non-blacks also had similar associations when lifetime diagnoses were examined (OR=3.16 and 3.81, respectively). The association increased

with increasing age for lifetime diagnoses, starting at an odds ratio of 2.88 for adults of 18–29 years, and showing an odds ratio of 4.10 for adults 65 years and older. If the disorders are truly independent, then the extended period of "observation" in older individuals should not increase the odds ratio. Thus, some other process appears to have occurred. Again, due to the large sample size, all odds ratios were statistically significant, even when co-occurring conditions were rare.

Table 6 shows the association of major depression with alcohol, cannabis, and cocaine use disorders. As is shown, associations between major depression and the substance use disorders were stronger when dependence was considered, compared with abuse. Associations were stronger for current disorders than for lifetime diagnoses for alcohol and cannabis, although not for cocaine. Associations were also stronger for both of the drug use disorders and major depression than for alcohol use disorders and major depression.

One question raised in comorbidity research is whether major depression in alcoholics is simply a result of acute or extended withdrawal (40) rather than a distinct condition. One way to examine this is to determine whether the risk for major depression remains elevated among individuals who were formerly alcohol dependent, and who have not been drinkers or heavy drinkers for an extended period of time. The rationale for

Table 6 Comorbidity of Major Depression and Selected Alcohol and Drug Use Disorders in the NLAES Survey: Odds Ratios

	Timeframe	
Alcohol/drug disorder	Current	Lifetime
Alcohol abuse	2.2	1.7
Alcohol dependence	4.4	3.8
Any alcohol use disorder	3.7	3.6
Cannabis abuse	5.0	3.1
Cannabis dependence	12.5	7.1
Any cannabis use disorder	6.4	4.7
Cocaine abuse	4.4	4.5
Cocaine dependence	5.2	5.1
Any cocaine use disorder	4.9	5.0

this is that intoxication or withdrawal effects could no longer be considered the sole cause of depression among such subjects, suggesting the need to look further for causes. NLAES data proved a fruitful source of information on this subject because of the large sample size, which included 6050 former drinkers (41). Among the subsample of former drinkers, the risk of major depressive disorder was compared between those with a past history of DSM-IV alcohol dependence and those without such a history. Controlling for

confounders including demographic characteristics, alcohol abuse, smoking, and drug use, the risk of major depression was elevated by a factor of ~4 among the former drinkers who had a history of DSM-IV alcohol dependence. This suggested a relationship between major depression and alcoholism that is not explained by intoxication or extended withdrawal symptoms. What remains to be determined is whether there is a common cause for both disorders, even though they are separated chronologically, or whether lingering social or biological effects of former alcoholism place individuals at chronic increased risk for major depression.

Upcoming Epidemiological Developments

In 2001–2002, NIAAA conducted a second large-scale national survey similar to the NLAES. This survey, known as the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), included 43,093 individuals, including some important groups that had not been surveyed in the NLAES such as college students living in group quarters. The NESARC covered alcohol and drug use disorders and major depression, similarly to the NLAES. In addition, more complete coverage was added, including an expanded smoking history, nicotine dependence, bipolar disorder, anxiety disorders, personality disorders, and family history. Data are not available from the NESARC at this writing, but initial papers are planned for late 2003. Of considerable interest is that a follow-up survey of the entire sample is being prepared, which will take place in 2005. The NESARC would then become a longitudinal comorbidity study of unprecedented size.

THE CLINICAL EPIDEMIOLOGY OF COMORBIDITY

Over the last two decades, the prevalence of psychiatric disorders has been studied in many samples of patients at drug- and alcohol-identified treatment facilities. Various factors can affect the prevalence of psychiatric disorders in treated samples, including admission policies of treatment facilities, inclusion and exclusion criteria of studies, and differences in assessment methods and concepts of what constitutes a psychiatric disorder in heavy users of alcohol or drugs. Over time, several sets of diagnostic criteria have been used to assess psychiatric disorders in alcohol and drug patients, including Feighner criteria (42), Research Diagnostic Criteria (26), DSM-III (27), DSM-III-R (34), and DSM-IV (37). These criteria vary in how they treat the assessment of psychiatric disorders in substance abusers, particularly in the differentiation between expected intoxication/withdrawal effects, substance-induced psychiatric symptoms, and independent psychiatric symptoms. In addition, even when the same set of diagnostic criteria is used, it can be interpreted and applied differently between research groups (43). Despite these methodological issues, it is of interest to obtain an overview of the prevalence of psychiatric disorders among patients treated for alcohol and drug problems.

Information on the prevalence of affective, anxiety, and antisocial personality disorders is reviewed in Table 7. We included the disorders most commonly reported. Bipolar and psychotic disorders were uniformly very rare and are not reported. Nor were rates of

phobic disorders, which were very similar to rates from the ECA and NCS (12%–15%). To be listed in Table 7, studies had to 1) use explicit diagnostic criteria, 2) provide lifetime diagnoses, and 3) assess 50 or more patients.

Major Depression

As shown in Table 7, there was very wide variability in the lifetime rates of major depressive disorder. These varied from a low of 12% in two studies to a high of 88%. Almost all the treated samples reflect higher rates of major

Table 7 Prevalence of Lifetime Psychiatric Comorbidity in Alcohol and Drug Abuse Samples

		Type of disorder				
Author, year, type of sample, assessment	*N* (% male)	Major depression	Panic	Generalized anxiety	PTSD	Antisocial personality
(97) Fowler et al., 1980, veteran inpatient alcoholics, Feighner	169 (100%)	0.12	—	—	—	0.25
(98) Croughan et al., 1982, treated narcotic addicts, Feighner	200 (50%)	0.45	—	—	—	0.67
(99) Powell et al., 1982, veteran alcoholic inpatients, PDI, Feighner	565 (100%)	0.42	0.13	—	—	0.20
(100) Rounsaville et al., 1982, treated opiate addicts, SADS, RDC	533 (76%)	0.54	0.01	0.05	—	0.27
(101) O'Sullivan et al., 1983, inpatient alcoholics, Feighner	300 (100%)	0.27	—	—	—	—
(102) Fawcett et al., 1984, inpatient alcoholics, SADS, RDC	84 (88%)	0.88	—	—	—	—
(103) Hesselbrock et al., 1985, inpatient alcoholics, DIS, DSM-III	321 (72%)	0.38	0.10	—	—	0.41
(104) Khantzian and Treece, 1985, opiate addicts, structured interview, DSM-III	133 (71%)	0.56	0.02	0.05	—	0.35
(106) Woody et al., 1985, opiate addicts, RDC-	110 (100%)	0.35	0.02	0.17	—	0.45

DSM-III						
(107) Chambless et al., 1987, SADS, RDC	75 (61%)	0.31	0.09	—	—	—
(108) Hasin et al., 1988, alcohol rehabilitation patients, SADS, RDC	123 (70%)	0.67	0.10	—	—	—
(109) Ross et al., 1988, alcohol and drug patients, DIS, DSM-III	501 (52%)	0.24	0.10	—	—	0.47
(110) Abbott et al., 1994, methadone maintenance patients, SCID, DSM-III-R	144 (71%)	0.25	0,08	0.04	—	0.31
(111) Halikas et al., 1994, cocaine outpatients, DIS, DSM-III-R	207 (71%)	0.23	0.06	0.03	0.27	0.40

		Type of disorder				
Author, year, type of sample, assessment	*N* (% male)	Major depression	Panic	Generalized anxiety	PTSD	Antisocial personality
(112) Penick et al., 1994, veteran inpatient alcoholics, PDI, DSM-III	928 (100%)	0.36	0.10	—	—	0.24
(113) Ziedonis et al., 1994, cocaine patients, SADS-L, DSM-III-R	263 (69%)	0.34	0.03	0.07	—	0.33
(105) Windle et al., 1995, inpatient alcoholics, structured interview, DSM-III	802 (60%)	0.12	—	0.11	—	0.30
(114) Hasin et al., 1996, mixed alcohol and drug patients, PRISM, DSM-III-R	172 (52%)	0.52	0.16	0.01	—	0.25
(115) Milby et al., 1996, methadone maintenance patients, structured interview, DSM-III-R	102 (82%)	0.58	0.07	0.21	0.31	—
(116) Brooner et al., 1997, Methadone maintenance patients, SCID, DSM-III-	716 (53%)	0.16	0.02	0.01	—	0.25

R						
(117) Schuckit et al., 1997, alcohol inpatients and relatives with alcoholism, SSAGA, DSM-III-R	2945 (88%)	0.41	—	—	—	0.19
(118) Magura et al., 1998, methadone patients addicted to cocaine, SCID, DSM-III-R	212 (59%)	0.44	0.07	0.08	0.26	0.26
(119) Mason et al., 1998, methadone patients, DIS, DSM-III-R	75 (52%)	0.44	0.07	0.08	0.26	0.26
(120) Compton et al., 2000, drug treatment patients, DIS, DSM-III-R	512 (66%)	0.24	0.03	0.10	—	0.44
(121) Skinstad and Swain, 2001, substance abuse inpatients, DIS-quick, DSM-III-R	125 (100%)	0.22	0.04	0.10	0.14	0.22
(122) Hasin et al., submitted, substance abusing outpatients, PRISM, DSM-IV	285 (54%)	0.45	0.05	0.02	0.13	0.23

depression than the general population, as shown by comparison with the ECA, NCS, or NLAES. In 16 of the 26 studies listed, at least one-third of the sample had a current or past history of major depression. We know from the odds ratios of the third-generation studies that major depression is strongly and significantly associated with alcohol and drug use disorders among individuals in the general population. However, many of the treated samples show elevated rates substantially in excess of the increased risk for major depression in general population subjects with alcohol or drug use disorders. As noted above (and see Ref. 132), this association cannot be entirely attributed to intoxication or withdrawal effects mimicking psychiatric symptoms, and therefore the cause remains unexplained.

Anxiety Disorders

Table 7 includes panic, generalized anxiety, and post-traumatic stress disorder (PTSD). Panic disorder and generalized anxiety disorder were less common than major depression, generally occurring in less than 10% of the samples. PTSD was not assessed in earlier studies, which reflects an increased recognition of this disorder more recently. In the studies that included PTSD, the prevalence was most often about 25%.

Antisocial Personality Disorder

Rates of antisocial personality disorder in the studies shown in Table 7 were higher than the rates in the general population. As is evident from the table, these rates were also quite variable from study to study, with no obvious relationship to the gender balance in the samples as an explanation.

Table 7 shows lifetime rather than current rates of Axis I disorders (major depression and anxiety disorders) because few studies presented current rates of disorder. However (see below), disorders that are current when patients are in treatment may be more important predictors of outcome than lifetime diagnoses that may have occurred some time in the past. Current disorders are also amenable to treatment and thus of clinical interest, while the treatment implications of past disorders are less clear.

Direct Comparison Between Treated and Untreated Individuals with an Alcohol Use Disorder

The NLAES general population data were used to investigate differences in depression comorbidity between treated and untreated individuals with an alcohol use disorder (44). The NLAES data showed that about 9% of the subjects meeting the criteria for a current alcohol use disorder had current treatment (in the last 12 months). Treated and untreated subjects with an alcohol use disorder differed in a number of respects, one of which was a diagnosis of current (last 12 months) major depression. The treated group reported major depression more often, controlling for other factors, which suggests that depression in individuals with substance use disorders plays a role in treatment seeking.

Substance Use Disorders Among Patients with Psychotic Disorders

The high rate of concomitant substance use disorders among patients with psychotic disorders has attracted increasing public health attention in recent years. Regier et al. (32) estimated that individuals diagnosed with schizophrenia are 4.6 times more likely to have a comorbid substance use disorder than members of the general population. Moreover, the prevalence of substance use among schizophrenic patients has risen at a significantly higher rate than in the non-psychiatric population (45). According to Fowler et al. (46), the rates of lifetime stimulant abuse and lifetime alcohol abuse in schizophrenia have increased from between 11% and 22% in the 1960s and 1970s to between 25% and 50% in the early 1990s. Studies published since 1990 consistently indicate lifetime prevalences of comorbid substance use disorders and schizophrenia of 40–50% (47–55). In special patient populations the rates are even higher: 82% of homeless schizophrenic males and 92% of prison inmates with schizophrenia had a comorbid lifetime substance use disorder (32,56). Other than nicotine, the most commonly used substances in schizophrenia are alcohol, cannabis, and cocaine (45,47,48,57), with over 40% of schizophrenic users meeting criteria for two or more different types of substance use disorder (58).

LONGITUDINAL STUDIES ON THE EFFECTS OF COMORBIDITY ON SUBSTANCE USE DISORDERS

Information on Depressive Comorbidity from Treatment Studies

Treatment studies have addressed the efficacy of antidepressant treatment in cocaine, heroin, and alcohol abusers. Results have been mixed. Some of the disparities in treatment studies of substance users with depressed mood may be partially due to differences in assessing depression.

Reviews of early studies indicated that tricyclics had no effect in alcoholics (59,60). These studies used different indicators of outcome (alcohol or depression), and selected patients on the basis of cross-sectional assessment of depressed mood rather than diagnostic criteria for a depressive disorder. Early studies on the effects of tricyclics in depressed heroin addicts (61,62) (for a review see Ref. 63) showed inconsistent results and high placebo response rates. In most of these studies, depression was assessed using cross-sectional symptom scales instead of diagnostic interview procedures. Treatment studies of tricyclics used by cocaine abusers generally focused on cocaine use rather than depression as an outcome (64,65). Analyses of the depressed subgroups in some of these studies (64,66,67) suggested benefits in the depressed subsamples treated with tricyclics. Here again, depression was mostly identified through cross-sectional symptom assessment. Cross-sectional depressive symptoms in a patient actively using drugs or alcohol may often represent substance-induced or stress-related symptoms that are transient and not responsive to antidepressant medication treatment.

Recent placebo-controlled studies using longer treatment periods and more systematic assessment measures suggest that tricyclics are effective in improving mood in alcoholics with diagnosed depressive disorders, i.e., major depression or dysthymia (68–70). Studies of fluoxetine (71) and sertraline (72) assessed depression on an inpatient unit after detoxification and a period of enforced abstinence. Both studies found significant effects of medication in improving mood, and the fluoxetine trial also found an advantage for medication on self-report measures of drinking. A placebo-controlled trial of imipramine in depressed heroin addicts, where depression was assessed using standardized diagnostic procedures (73), found a low placebo response rate, a strong effect of imipramine in improving depressed mood, and significant (but less robust) effects on some measures of drug use. However, other recent studies, which also selected patients with depressive disorders using structured diagnostic assessment (74–76), had high placebo response rates and found no effect of fluoxetine on mood or substance use outcome.

Taken together, these studies suggest that treatment of comorbid depression may be a useful strategy in substance-dependent patients, but diagnostic methods may need improvement to select appropriate cases for controlled clinical trials. In particular, the data seem to suggest that depression, diagnosed after a period of abstinence, or with a careful psychiatric interview and diagnostic assessment, may be most likely to benefit from specific antidepressant treatment.

Naturalistic Studies

A number of longitudinal naturalistic studies have been conducted of the effects of mental disorder on alcohol and drug outcomes. Because antisocial personality disorder and major depression are so common in alcohol and drug patients, studies have tended to focus on these disorders.

Antisocial Personality Disorder

Concerning antisocial personality disorder, several major studies were conducted in the 1980s. These studies generally showed that antisocial personality disorder is associated with worse long-term outcome of alcohol or drug use problems (64,77,78), although not as consistently as might be expected (79).

Major Depression

Despite the inconsistencies in treatment studies, considerable clinical attention has continued to be paid to the relationship of major depression to the outcome of alcohol and drug use disorders. The studies can be divided into those focused on the effects of a *lifetime* diagnosis of major depression and those focused on *concurrent* or follow-up major depression. Table 8 summarizes the follow-up studies. To be included in this table, studies must have used a structured assessment procedure to evaluate specific diagnostic criteria and to report a follow-up response rate of at least 70%. The table is divided into two parts. The upper part of Table 8 shows studies that used *lifetime* diagnoses of depression to predict outcome at follow-up. The lower part of Table 8 shows studies that used diagnoses of depression that were *concurrent* at baseline, or that occurred *during follow-up*.

As shown in the top part of Table 8, studies focused on the effects of *lifetime* major depression generally did not show an adverse effect of a lifetime depression diagnosis on the longitudinal course of various alcohol or drug outcomes. This result did not appear to be related to the length of follow-up or to the assessment method.

The studies of *concurrent* major depression in the lower part of Table 8 present a different picture. These studies all showed that major depression at baseline or during follow-up predicted a worse outcome for alcohol or drug use or related problems. This was true regardless of the length of the follow-up period or the assessment method for depression, which ranged from the RDC to DSM-IV. The studies were conducted on a variety of treatment samples, including one study of female ECA subjects followed up one year later. Thus, although clinical trials show mixed results on whether pharmacological treatment for major depression improves the outcome of alcohol or drug use disorders, the naturalistic studies continue to indicate that a relationship exists. This suggests that treatment attention may be warranted, but that the optimal type or timing of treatment for major depression among alcohol or substance abuse patients (or possibly for subgroups of these patients) remains to be determined. This issue is of considerable interest to many clinicians, so

Table 8 Effects of Major Depression on the Outcome of Alcohol or Drug Abuse

Timeframe for major depression	Sample, *N*	Assessment	Length followed, response	Outcomes	Results
Lifetime					
(77) Rounsaville et al., 1987	Inpatient alcoholics, 266	DIS, DSM-III	1 year, 83%	Drinking and various drinking problems	Depression predicted worse outcome in men but not in women
(78) Powell et al., 1992	Inpatient alcoholics, 222	PDI, DSM-III	1 year, 92%	Drinking and various drinking problems	Depression unrelated to outcome
(123) Kranzler et al., 1996	Inpatient alcoholics, 225	DIS, DSM-III	3 years, 74%	Drinking days, drinks/day, alcohol symptoms	Depression related to lower drinks/day
(124) Sellman and Joyce, 1996	Inpatient alcoholics, 93	SCID, DSM-III-R	6 months, 94%	Relapse to problem drinking or dependence	Depression unrelated to outcome
(125) Rao et al., 2000	Female high school students, 150	SCID, DSM-III-R	5 years, 95%	Substance use disorder	Depression unrelated to outcome
Concurrent					
(126) Rounsaville et al., 1982	Opiate patients, 123	SADS, RDC	6 months, 78%	Heroin use and symptoms	Depression predicted poor outcome
(127) Kosten et al., 1986	Opiate patients, 268	SADS, RDC	2.5 years, 76%	Heroin use and symptoms	Depression in conjunction with life events predicted poor outcome
(128) Kosten et	Opiate patients, 268	SADS, RDC	2.5 years, 76%	Cocaine problems	Depression predicted poor outcome

al., 1987					
(129) Hasin et al., 1996	Depressed alcoholic inpatients, 127	SADS, RDC	5 years, 94%	Time to alcoholism remission, relapse	Depression during follow-up predicted delayed time to sustained remission of alcoholism and shortened time to relapse (poor outcome)
(130) Greenfield et al., 1998	Alcoholic inpatients, 101	SCID, DSM-III-R	1 year, 100%	Shortened time to first drink and alcohol relapse	Depression predicted poor outcome
(131) Dixit and Crum, 2000	Women from ECA, no prior alcohol history, 1295	DIS, DSM-III	1 year, 79.5%	Lifetime onset of heavy drinking during follow-up	Depressive syndrome predicted onset of heavy drinking (poor outcome)
(132) Hasin et al., 2002	Dual-diagnosis inpatients, 250	PRISM, DSM-IV	2 years, 91%	Time to remission from dependence, use, and relapse	Depression during follow-up predicted delayed time to sustained remission of alcoholism and shortened time to relapse (poor outcome)

further treatment studies appear to be warranted. These could include testing behavioral treatments specifically tailored for depression among substance abusers, in addition to continued study of pharmacological treatments.

DIRECTIONS FOR THE FUTURE

Large-Sample Survey Epidemiology

Future research on the epidemiology of substance abuse and psychiatric comorbidity in the general population is likely to reflect several important developments. First, availability of both NLAES and NESARC data will allow precise study of changes in the national prevalence of alcohol and drug use disorders as well as major depression between 1992 and 2002. Joint analyses of the two data sets will also allow investigation of changes over time in the comorbidity of alcohol and drug use disorders with one another and with major depression. Second, assessment of the additional DSM-IV Axis I and Axis II categories in the NESARC will expand the understanding of comorbidity in the general population to additional disorders. The large NESARC sample of over 43,000

individuals will allow study of less common disorders, and possibly study of the DSM-IV differentiation between primary and substance-induced psychiatric disorders. Third, the effects of comorbidity on the longitudinal course of alcohol and drug use disorders will be available from the follow-up component of the NESARC, which will be conducted in 2004–2005. This will be an unprecedented opportunity to learn more about the course of alcohol and drug use disorders in untreated as well as treated individuals. Further, comparisons will be possible in large, representative subsets of the sample. Comparisons can be made between the effects of lifetime and concurrent comorbidity on the longitudinal course of alcohol and drug use disorders. The information on the natural history of alcohol and drug abuse and dependence from the follow-up of the NESARC will also provide an empirical standard against which treatment effectiveness can be compared.

Genetic Epidemiology

Epidemiology is not only the study of the distribution of disease, but also that of its determinants. Psychiatric and substance use disorders are commonly acknowledged as having complex etiologies that include multiple genetic and environmental factors. Epidemiological studies of comorbidity will likely increasingly utilize the techniques of genetic epidemiology. Genetic epidemiology is not a new area of research, but epidemiological methods lend themselves well to the study of the heritability of psychiatric disorders and to gene-environment interaction. A great deal of this work to date has been conducted in twin studies (80). Studies of large population-based samples of twins have made it possible to estimate the heritability of psychiatric and substance use disorders by comparing concordance levels in disorders between monozygotic and dizygotic pairs of twins (81,82). Twin studies have also provided intriguing clues about whether disorders co-occur due to shared or unique inheritance (83). Twin studies may find an expanded use in the future through novel designs that capitalize on the unique genetic relationships of twin pairs to investigate specific genetic polymorphisms.

Techniques of genetic epidemiology can also be used to study the relationship of specific genetic polymorphisms to substance and psychiatric comorbidity. See Chapter 2 for a detailed discussion of the genetic basis of comorbidity. Genetic association studies have been viewed as important tools for gene mapping (84,85) and for studies of gene-environment interaction (86). Examples of research on specific genes in the substance abuse field include the studies of alcohol-metabolizing genes and drinking or alcohol dependence that were conducted in Asian (87) and Jewish samples (88–91). A methodological problem identified in gene-trait association studies in the mid-1990s was the problem of potential confounding due to population stratification (92). Fortunately, recent statistical developments have provided tools to test for population stratification in a given sample and control for it if necessary (e.g., 93–95). With these developments and the availability of large samples, specific genes may be investigated that appear to be specifically associated with comorbidity, such as the comorbidity of alcoholism and depression (96). Additional studies can be envisioned that dissect comorbidity by examining the association of psychiatric and substance use disorders while controlling for known genetic and environmental influences. Thus the epidemiological study of

comorbidity stands at an exciting point in time, when past research and techniques can provide a platform for a new generation of informative studies.

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2
Genetic Basis of Dual Diagnosis

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INTRODUCTION

Substance use disorders occur at higher than expected frequency among individuals with almost all other psychiatric disorders. This has been observed consistently both in large epidemiological surveys and in clinically ascertained samples (1–3). Particularly prevalent combinations are alcohol and drug dependence with affective disorder, alcohol and drug dependence with antisocial personality disorder (ASPD) among males, alcohol dependence with anxiety disorders among women, and schizophrenia with nicotine dependence (2,4–6). Comorbidity affects treatment, clinical course, medical sequelae, and prognosis (7,8). In general, the combination of substance dependence and a psychiatric disorder is considered particularly difficult to treat, and many medical centers have established teams that specialize in the treatment of dually diagnosed individuals.

Although greater than expected comorbidity between substance use disorders and other mental illnesses has been established in numerous studies, relatively little is known of the origin of this association. In particular, it is poorly understood whether this reflects shared liability for the co-occurring disorders, or whether a primary disorder increases risk of the secondary disorder. Examples of both etiological mechanisms can be found in other fields of medicine. For example, BRCA1 and BRCA2 genes predispose not only to breast cancer but also to ovarian cancer (shared liability) (9); diabetes predisposes to vascular disease (primary disease predisposes to secondary). It is conceivable that both etiological mechanisms play a role in the development of psychiatric dual diagnosis. Another ongoing debate in the field focuses on the distinction between primary and secondary disorders—i.e., are substance use disorders due to some other form of mental illness, or vice versa? One major problem in resolving these questions is that no specific tests, such as brain imaging, laboratory tests, or genetic tests, are available to study causal relationships objectively. Rather, these studies rely on recalled human experience, which is subject to biases and error. This is particularly true in those disorders, such as mood, psychotic, and substance use disorders, which affect insight to the presence of the illness or cause social stigma. On the basis of the available data, it appears that the relationship is bi-directional, i.e., substance abuse can lead to a mental illness and a mental illness can lead to substance abuse. Although this is a subject of intense debate, it is not known whether a disorder that is considered a primary disorder is somehow fundamentally

different if the same disorder arises after another mental illness or substance dependence. Prospective longitudinal studies may offer advantages in examining the patterns of causal associations. Unfortunately, these studies are often costly and always time-consuming.

One approach to disentangling etiological factors of dual diagnosis is a genetic approach. Family studies have shown that substance use and other psychiatric disorders co-aggregate in families (i.e., there is tendency of one disorder to be increased in the relatives of probands with another disorder). Twin studies have shown that a significant portion of the liability for several psychiatric disorders, including alcohol and drug dependence, is genetic. One large twin study that focused on disentangling genetic pathways that lead to dual diagnosis suggested that part of the genetic component for alcohol and comorbid mental illnesses is shared (10). In other words, there may be genes that are specific for predisposition to alcohol dependence and mental illness, and there may be non-specific genes that predispose to either disorder or their combination. An example of a genetic mechanism specific for predisposition to alcoholism may be the variants of the alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase (ALDH) genes (11,12). The variants of these genes can alter the metabolism of alcohol such that increased amounts of the toxic intermediate metabolite, acetaldehyde, accumulate in the body. Increased accumulation of acetaldehyde leads to an aversive reaction to alcohol and to a decreased risk, or even immunity to alcoholism. Finding the disease-specific and non-specific molecular genetic components that underlie predisposition would facilitate an understanding of how these disorders develop and co-occur in some individuals. For example, one could generate transgenic mice lines expressing the aberrant gene in order to study the neurobiological sequelae of the genetic defect more closely. One genetic variant may manifest itself in many different diagnoses, or in a combination of diagnoses. The treatment might then consist of restoring or diminishing the function of the gene product, which could benefit multiple conditions. Finding the genetic components of dual diagnosis may also help to develop environmental or pharmacological interventions to protect from the onset or exacerbation of the illness. For example, if the defective gene product is related to decreased stress tolerance, it may then be useful to identify those at greater genetic risk and educate them in effective coping strategies, or perhaps provide them with a particular medication. It should be pointed out that we currently have a very limited understanding of the molecular landscape of the genetic risk for psychiatric illnesses. For example, we do not know whether the total genetic risk is primarily due to a limited number of genes of major effect, or is composed of many genes of small effect. It is possible that many different types of genes will be discovered which cause varying degrees of increased risk.

In recent years, significant advances have been made in the identification of molecular genetic factors of both simple (i.e., Mendelian) diseases and complex traits. In psychiatric genetics, two genes for risk of schizophrenia (13,14) and a gene for risk of bipolar illness (15) have been identified. These studies are heralding a new era in identification of genetic risk factors for psychiatric illnesses. A great deal of this progress can be attributed to the development of techniques that allow rapid and high-throughput identification of single nucleotide and other types of polymorphism in large collections of DNA samples. For example, many academic research laboratories are nowadays equipped with techniques that allow completion of genomewide linkage scans in a matter

of a few months to 1–2 years. This time requirement will decrease in the near future. In fact, we may not be far from seeing the first sequencing-based genomewide scans in the identification of disease genes. Along with the development of molecular genetic methodologies, there has been a dramatic increase in our understanding of the human genome and its structure. This has allowed the development of new statistical methods, which are helping researchers to use available genetic research material more efficiently than before. For example, DNA samples from individuals with or without a disease (i.e., cases and controls) can now be used in large-scale mapping of genes (16,17); localization of unknown disease risk genes has until now relied upon genetic linkage, which requires the collection of large families or samples of sibling pairs for this type of analysis.

The goal of this chapter is to present an update of the findings from studies that focus on the genetic etiology of dual diagnosis. We will first review current methodologies in genetic epidemiological and laboratory research that are used to pinpoint genetic factors for predisposition to psychiatric dual diagnosis. We have chosen to review in detail the genetics of two common combinations: alcohol dependence with depression, and alcohol dependence with ASPD. Comorbidity between these disorders is among the most common dual diagnoses and most of the molecular genetic and epidemiological research so far has focused on these combinations. We aim to illustrate the approaches that are being taken to identify genetic factors for psychiatric dual diagnosis by examining past and current studies of these particular diagnostic combinations. The techniques and approaches presented in this chapter are applicable to the study of any comorbid constellations. The molecular genetic background of comorbid nicotine dependence and schizophrenia is another area of intense and interesting molecular work (18) and has been reviewed elsewhere (19). In this chapter, we will first introduce the reader to the current concepts of genetic epidemiology and genetic mapping. Evidence from family, twin, adoption, and population studies regarding shared or non-shared genetic etiology of the aforementioned comorbid combinations will be reviewed. We will not try to decipher causal or temporal relationships between alcoholism, depression, and ASPD (i.e., primary vs. secondary), but merely to determine whether a shared genetic etiology is suggested by the genetic epidemiological studies. We will then review data from studies that have attempted to identify actual molecular genetic factors affecting the risk for the dual diagnoses.

Molecular genetics of psychiatric comorbidity as a field of study is exceedingly young and only a limited number of studies are available. The majority of the molecular psychiatric genetic studies focus on primary disorders. The secondary disorders (or other comorbid disorders) are often disregarded, unless they are used as exclusion criteria. In some cases, the secondary disorder has been used to identify a subtype, the idea being to capture a putatively more homogenous form of the disease.

PRINCIPLES OF GENETIC METHODS TO IDENTIFY GENES FOR DUAL DIAGNOSIS

Family, Twin, and Adoption Studies

Family, twin, and adoption studies have as one of their goals to establish whether a disease has an identifiable genetic risk component. The most straightforward of these approaches is the family method, in which the researcher calculates the frequency of the disorder among the various classes of biological relatives of the probands. Prevalence of the disease in the general population or in control families is commonly calculated to assess more accurately whether the risk to the family members of the probands is increased. If the trait or the disease has a familial basis (some of which may be due to genes), an increased frequency of the trait should be observed among the close relatives of the proband as compared to the rate in distant relatives, the population prevalence, or the prevalence in control families. Co-aggregation of two separate disorders is observed in the same families if the diseases share etiological factors (i.e., there is a tendency of one disorder to be increased in the relatives of the probands with another disorder). This strategy has been used to elucidate pathways that lead to dual diagnosis (i.e., whether a disease is primary or secondary). If the etiology for two disorders is identical, then a proband with one disorder should have similar proportions of relatives with either of the two disorders. For example, if alcoholism and depression share an etiological background, then probands with either alcoholism or depression should have a similar number of both alcoholic and depressed family members. If the two disorders are etiologically related (i.e., one condition causes the other), then an increased prevalence of the primary disorder and the combination of the primary and secondary disorder would be observed in the family members of the probands with the primary disorder. No increase in the prevalence of the secondary disorder should be observed.

Family methods cannot distinguish between environmental and genetic factors, for which twin studies and adoption studies are more suitable. Twin studies are based on comparing the rates of the disorder in monozygotic (i.e., identical) and dizygotic (i.e., fraternal) twin pairs. Monozygotic twins are genetically identical, whereas dizygotic twins share, on average, 50% of their genes. Consequently, if the disorder has a genetic basis, then the percentage of monozygotic twins who both have the disorder (also known as concordance) should be approximately double the percentage of dizygotic twins who both have the disorder. Twin studies can also help to disentangle whether two disorders share a genetic basis. This can be done by calculating cross-twin cross-disease concordance rates (i.e., one twin with one disorder and the co-twin with another). If the disorders share a genetic background, then higher cross-twin, cross-disease concordance rates should be observed among monozygotic twins as compared to dizygotic twins. This relies on the assumption that co-twins, whether monozygotic or dizygotic, share their environments to the same extent.

Adoption studies may be the most accurate method in estimating the strength of a genetic component for a disease or a trait. In this method, the prevalence of a disorder among adopted-away children of biological parents with the disorder is estimated and

compared to the prevalence among adopted-away children whose biological parents do not have the disease. If the disease has a genetic risk component, then an increased prevalence of the disease should be observed among the biological offspring of a parent with the disorder. Information from the adoptive family is often used to estimate the influence of environmental factors on the risk for the disorder. Similar to that for twin and family studies, cross-disease transmission from biological parents to adopted-away children can be used to estimate whether two disorders share genetic risk factors. For example, increased somatization disorder was observed among adopted-away daughters of alcoholic criminal fathers in a large adoption study conducted in Sweden, suggesting that somatization disorder and alcoholism (Type II alcoholism) may have overlapping sex-specific genetic risk factors (20). One limitation of the family, twin, and adoption studies in identifying the magnitude of the genetic component for dual diagnosis is that it is often difficult to ascertain sufficient numbers of related individuals who are discordant for the two disorders being studied.

Genetic Mapping

Genetic mapping aims to identify those chromosomal regions that harbor genes that cause predisposition to a disorder. In general, genetic mapping of complex traits is divided into two broad strategic approaches: linkage mapping and linkage disequilibrium (LD) mapping. Although both strategies have the very same goal, they are founded upon different genetic principles and have distinct advantages and disadvantages. Linkage analysis using data from alleles that are identical-by-descent (IBD, alleles that are copies of the same maternal or paternal alleles) has been the preferred initial approach for finding genes for complex traits, such as alcoholism, if sufficient family material is available. IBD linkage techniques are based on observing deviations from the expected amount of shared alleles which are IBD. In other words, if a marker locus is linked to a trait locus, then increased sharing of alleles IBD is observed at the marker locus in the affected family members. Siblings are often used for IBD mapping, but information can also be derived from other forms of familial genetic relationships. These techniques provide a general solution to the localization of genetic susceptibility loci, as they do not require any previous information of the risk genes or their function.

Using a set of approximately 400 genetic markers and current genotyping technology, the entire human genome, which is approximately 4 billion base pairs in length, can be scanned for risk loci in hundreds of subjects in a matter of a few months to 1–2 years. Theoretically, when the regions containing the risk genes are discovered, the genes can then be identified using positional cloning. However, it has proven difficult to identify predisposing genes for complex psychiatric disorders using this strategy only. Because IBD linkage techniques derive information for gene localization from recombinations occurring in one or a few generations only, the regions identified by the IBD linkage methods are invariably long, often encompassing chromosomal segments that are 20–40 centimorgans [cM (about 20–40 million base pairs)], or even longer. In the case of a complex disorder, phenotypic heterogeneity, genetic heterogeneity, phenocopies, and incomplete penetrance make precise localization of the risk loci exceptionally difficult, because they make it impossible to identify individual genetic crossovers unambiguously.

Therefore, it is often the case that the more complex the trait, the longer the region identified by linkage. Considering that an average length of a gene in the human genome is about 30,000 base pairs, segments which are 20–40 cM long may easily encompass several hundred individual genes. The Collaborative Study on the Genetics of Alcoholism (COGA) is an example of a large concerted effort to identify genes for risk for alcoholism. Results from the COGA linkage analysis have been published and are reviewed below (21,22).

Techniques based on population LD have been advocated as alternative or complementary techniques to IBD linkage studies. LD refers to non-independence of alleles that are located on the same chromosome and usually in close proximity to each other. The decay of LD over many generations reflects "historical" recombination events between two alleles on the same chromosomal segments. Recombination is the major force that results in a "shuffling" of the alleles located on the same chromosome. However, this shuffling is not complete and alleles, especially if they are located close to each other, still tend to co-occur in unrelated individuals more often than would occur by chance. In other words, these alleles have been "fellow travelers in meioses" throughout generations.

To illustrate, suppose that allele *A* at locus 1 and allele *B* at locus 2 occur at frequencies *pA* and *pB* in the population. If the two alleles are independent, then we would expect to see the *AB* haplotype at frequency *pApB*. If the population frequency is either higher or lower than *pApB*, implying that particular alleles tend to be observed together, then the loci are said to be in LD (this example assumes, however, that there is random mating in the population). The length of a chromosomal segment where LD can be detected is related to the age of the population and historical events, such as population bottlenecks and genetic drift. In general, younger populations have longer LD segments. The length of a segment of preserved LD in the population, however, is always shorter than the length of an average IBD segment shared between affected siblings at a complex trait locus. LD-based studies can thus complement IBD linkage studies by allowing fine-mapping of the genomic regions that show genetic linkage to a particular trait.

The use of LD-mapping in genomewide searches for genetic risk loci has been limited by the length of the span of LD in the population and presence of multiple allelic variants that cause risk for the disease (allelic heterogeneity). In the U.S. population, the estimated average LD span is only 60,000 base pairs between two markers (23). Thus, to cover the entire genome would require hundreds of thousands of genetic markers (compared with about 400 markers that are required if linkage strategy is used). Although this is too strenuous a requirement for current technology, methods are being developed that will allow genotyping of such a large number of markers. In fact, an LD map of the entire human chromosome 22 was recently published (24). The first genomewide LD-based scan for genes predisposing to bipolar disorder was also recently reported (25). In this study, the researchers exploited the longer LD span that characterizes the recently founded Costa Rican (sub) population, in which LD can reach up to several million base pairs.

The major advantages of the LD-based methods are less burdensome recruitment efforts and increase in statistical efficacy, together with the ultimate ability to localize

risk loci more accurately than with linkage methods. For LD-mapping, suitable populations include individuals with and without the disease (i.e., cases and controls) or affected probands and one or both of their biological parents (for the transmission disequilibrium test). These types of samples are more accessible than are extended families and sibpairs, which are required for linkage-based studies. LD-based methods are also statistically more powerful than linkage and can, therefore, detect loci with smaller effect (26). This advantage is of particular importance in studies of diseases in which multiple genes exert small effects. Because of the many advantages LD-based methods provide, it is likely that they will gain increasing currency in research on complex genetic traits.

COMORBID ALCOHOL DEPENDENCE AND MAJOR DEPRESSION

Epidemiology

Alcoholism and depression co-occur in greater than expected frequency in clinical and epidemiological settings (27). Finding the causes and treatment for this phenomenon is important because the presence of the comorbidity changes the clinical course and complicates treatment (28). Three large population surveys conducted in the U.S., the Epidemiological Catchment Area (ECA) study, the National Comorbidity Survey (NCS), and the National Longitudinal Alcohol Epidemiological Survey (29,30), have established higher rates of alcoholism among individuals diagnosed with major depression and higher rates of depression among individuals with alcohol dependence (1,2,4). For example, in the ECA study, the rate of alcohol dependence among individuals diagnosed with major depression was 11.6% (population rate of alcohol dependence was 7.9% in this study) (2). Significant sex-specific differences in the rates of alcohol dependence, major depression, and their co-occurrence were observed in both of these studies. For instance, in the NCS study, women had an 8% lifetime prevalence of alcohol dependence, while men had a rate of 20%. Rates of lifetime diagnosis of major depression were higher among women (21%) than among men (13%). This sex difference was more evident among women and men diagnosed with alcohol dependence, for whom the rate of major depression was 48.5% and 24.3%, respectively. The vast majority (90%) of alcohol-dependent men reported the onset of alcoholism prior to the onset of depression, or their alcoholism occurred without co-occurring major depression. Women were more likely to have depression that preceded the onset of alcoholism (21%) or to have both alcohol dependence and major depression arise during the same year (5%) (1). These estimates are based on population surveys; the prevalence of comorbid alcohol dependence and major depression are even higher in clinically ascertained samples (27).

Family Studies

The most popular approach to studying the background of comorbidity between alcoholism and depression has been through studying families in which the proband has either alcoholism, depression, or both. Family studies do not differentiate genetic from

environmental components, but studying co-aggregation of two diseases in families may reveal patterns based upon which clues about the shared etiology of the diseases can be sought. Numerous studies on the familial transmission of alcoholism and depression have been conducted and many, but not all, demonstrate co-aggregation of alcoholism and depression (27).

Because of different proband selection, different diagnostic and interview schemata, differences in definition of primary vs. secondary alcoholism (see above), and different recruitment strategies, it is difficult to draw simple conclusions about the patterns of co-aggregation of these two disorders. One basic conclusion from the data may be made, which is that alcoholism and depression are not, in general, etiologically the same disorder. As mentioned above, if this were the case, then probands with either alcoholism or depression would have similar proportions of alcoholic and depressed family members. The majority of the studies suggest that this is not the case (27). Those studies that began with alcoholic probands show an increased risk for alcoholism and possibly increased risk for depression among female relatives (27,31,32). Studies that began with probands with primary depression have yielded mixed results; some studies show an increased rate of alcoholism among relatives (33), while others do not (27,34).

Twin Studies

Two large twin studies using monozygotic and dizygotic twins ascertained from the general U.S. population have addressed the degree to which alcoholism and depression share their genetic and environmental risk factors. In the study by Kendler et al. (35), 1033 female twin pairs were interviewed for the presence of psychiatric diagnoses, using the Structured Clinical Interview for DSM-III-R. In accordance with previous findings, both alcoholism and depression were found to be substantially heritable in this study. The cross-twin cross-disease correlations between major depression and alcoholism (e.g., depression in twin one and alcoholism in twin two, or vice versa) were much higher among monozygotic twins than among dizygotic twins, suggesting that shared genetic factors play a role in risk for depression and alcoholism. This was observed regardless of whether the disorder was defined in broad or narrow terms. For example, for DSM-III-R-defined alcohol dependence and major depression, the cross-twin correlations were 29% for monozygotic twins and 11% for the dizygotic twins. Bivariate model fitting of their data suggested that the genetic correlation between these two disorders in women was 50–60%. These analyses easily rejected models in which the genetic correlation was set to unity, which indicates that the two disorders clearly do not share an identical genetic etiology. In a large follow-up study, Kendler et al. analyzed 3755 male and female monozygotic and dizygotic twins (including 1408 opposite sex pairs) for concordance for major depression and various definitions of alcoholism (36). Once again, they found a significantly higher cross-twin cross-disease correlation between alcohol dependence and major depression among monozygotic twins (20%, both male and female monozygotic twins) than for dizygotic twins (7% for female dizygotic twins, 9% for male dizygotic twins). Cross-twin correlation between alcohol dependence and major depression was lowest for the opposite sex twin pairs. A correlated etiological model, in which the sources of liability for alcoholism and depression are overlapping but not identical,

provided the best fit for their data. They found no evidence for contribution of shared environmental factors in liability for depression and alcoholism, but all liability was due to genetic factors and individual-specific resources. They also found evidence that sex-specific processes contribute to the liability for comorbid alcoholism and depression, and that the risk factors are not identical between men and women (35,36).

Adoption Studies

To our knowledge, four adoption studies have been published which disentangled shared and non-shared genetic and environmental risk factors of comorbidity between alcoholism and affective disorders. Once again, simple conclusions are difficult to draw from these data because diagnostic methods, adoptee population, ascertainment strategies, and population size differ among the studies. Also, in some of these studies, the affective disorder group included individuals with both unipolar and bipolar affective disorder. Two of the four studies, including the one drawn from the largest population of adoptees, suggest co-aggregation of alcoholism and depression, and that a significant proportion of the liability for co-aggregation is due to genetic factors. The data also suggest that sex-specific mechanisms may be involved in risk for comorbid alcoholism and depression, which is in accordance with findings from the twin and family studies. Goodwin et al. (37) found an increased frequency of alcoholism among biological parents of male alcoholic adoptees (n=55), as compared to the biological parents of control adoptees (n=78). The biological parents of the control and alcoholic adoptees did not differ with regard to rates of other psychopathology, including depression. There were no significant differences in the rates of other psychiatric problems between the adoptive parents of the control and proband adoptees. Von Knorring et al. (38) studied the rates of psychiatric illnesses among the biological and adoptive parents of probands with affective disorders or substance abuse. They found a modest increase in the rates of alcohol or substance abuse among biological mothers of probands with affective disorder, suggesting the presence of shared genetic factors for these two classes of disorder (59 proband, drawn from a population of 2966 adoptees). Cadoret et al. (39) studied a population of 48 adoptees with major depression (drawn from a population of 443 adoptees) and their biological and adoptive relatives in an effort to study genetic and environmental contributions to risk of depression. They found positive, yet statistically non-significant, evidence for increased rate of depression among biological parents and other relatives of depressed adoptees. However, the rate of alcoholism among biological parents and other relatives was not elevated as compared to the biological parents of the adoptees who had no depression. Wender et al. (40) studied the rate of psychiatric disorders among the biological and adoptive parents drawn from a large pool of Danish adoptees (n=14,500). They identified 71 adoptees with affective disorder and 71 carefully matched controls with no record of psychiatric illness or substance abuse. They found a significant increase in the rate of alcoholism and substance dependence among biological relatives of the depressed probands (5% among biological relatives of probands vs. 2% among relatives of control adoptees). There were no differences in the rate of psychiatric disorders among adoptive parents of probands and control adoptees.

IDENTIFYING A GENETIC LOCUS FOR COMORBID ALCOHOL DEPENDENCE AND DEPRESSION

In an important genetic study on alcoholism and depression, Nurnberger et al. (41) followed up and extended the previous findings from a genomewide linkage scan for loci causing predisposition to alcohol dependence. A previous study by the Collaborative Study on the Genetics of Alcoholism (COGA) had presented data supporting the presence of a gene (or genes) causing predisposition to alcohol dependence on chromosome 1 (near the 120cM region of that chromosome) (21,22).

The COGA data were derived from two independently collected samples of families with high prevalence of alcoholism. The initial sample consisted of 105 alcoholic families with genotype data for 987 individuals. The replication sample consisted of 157 families with genotype data for 1295 individuals. Combined, this data set comprised 491 alcohol-dependent sibling pairs (259 pairs for which parental genotype information was available). The families were collected in the United States and the subjects were largely European-American. They tested for genetic linkage between the markers and phenotype using non-parametric linkage tests. As briefly reviewed above, these tests seek deviation from the expected degree of sharing of alleles that are identical by descent (IBD) between siblings. An allele is considered to be identical by descent if both members of a sibling pair have inherited the allele from the same parent. If there is no linkage between a marker and a trait, two siblings are expected to share 50% of their alleles that are IBD. For the alcohol dependence phenotype, the highest combined multipoint sibpair analysis LOD (logarithm of odds) score of 2.6 was obtained between markers D1S2614 and D1S1588 on chromosome 1 and a LOD score of 2.9 close to markers D7S821 and D7S1796 on chromosome 7. A LOD score of 3.3 or higher is commonly considered statistically significant (42). Therefore, these LOD scores can only be considered suggestive of linkage. However, evidence for the presence of an alcohol dependence predisposing locus in this region of chromosome 1 was obtained in both the initial and replication samples, which suggests that the finding was not due merely to chance. In the COGA study, the percentage of sharing of alleles IBD ranged between 57% and 59% at these loci on chromosome 1 and chromosome 7, using alcohol dependence as the phenotype.

Nurnberger et al. (41) reanalyzed the COGA data, allowing the affected phenotype to include not only alcoholism, but also depression, and comorbid depression and alcoholism. They defined depression as the presence of either DSM-III-R major depression or depressive syndrome (DSM-III-R major depression except for the exclusion criterion for organic causes, such as alcohol, which had initiated or was maintaining the disorder). Their combined data consisted of 224 sibling pairs with comorbid alcoholism and depression, 1359 pairs with alcoholism or depression (siblings with alcoholism only or depression only, or siblings with both alcoholism and depression), and 440 pairs with depression. As compared to the analyses using the alcohol dependence phenotype (see above), the increase in number of sibling pairs for the analyses was mostly due to inclusion of women with depression whose brothers were alcohol dependent. Their highest non-parametric LOD score of 4.66 for the phenotype of

alcoholism or depression was obtained at the same markers as for the phenotype of alcoholism. The broadening of the phenotypic definition thus resulted in an almost two-fold increase in the LOD score, which corresponds to a 100-fold increase in support for linkage. Maximum sharing of alleles IBD at this locus was 57%, not higher than the sharing for the phenotype of alcoholism. These results suggest that a gene (or genes) resides on chromosome 1 near the 120cM region that predisposes to alcoholism, depression, or both. This study was particularly important, as it was the first to identify a chromosomal region that harbors genes causing predisposition to two different psychiatric phenotypes: alcoholism or depression. The gene (or genes) in this locus may act in a sex-specific manner in predisposition to either depression, alcoholism, or both. This finding mirrors the previous genetic epidemiological studies which had suggested that there exist overlapping but sex-specific genetic risk factors for alcoholism and depression.

GENETICS OF ALCOHOL DEPENDENCE AND ANTISOCIAL PERSONALITY DISORDER

Epidemiology

Antisocial personality disorder (ASPD) co-occurs at higher than the expected (population) frequency among individuals with alcoholism and other substance dependence. The high rate of comorbidity between alcoholism and ASPD (or antisocial behavior) has been established by numerous studies in adolescent, clinical, and non-clinical samples. For example, the National Comorbidity Survey (NCS), which evaluated a sample of 8098 individuals, established a rate of ASPD of 17% among males with alcohol dependence (1). The rate of ASPD was estimated to be 6% among males in the general U.S. population. Among women, the corresponding rates of ASPD were 8% and 1%. A majority (63%) of those individuals who met criteria for ASPD also had alcoholism. These results are comparable to the findings from an earlier large population survey, the Epidemiological Catchment Area study (2). The odds ratios for an association between ASPD and alcoholism in these studies were 12 and 21 for NCS and ECA, respectively. In clinically ascertained samples, or in samples collected from forensic settings, the rates of comorbidity between alcoholism and ASPD are even higher (43,44). Similar to the association between depression and alcoholism, the interpretation of the direction of causality between antisocial behavior and alcoholism is difficult. ASPD is considered, by definition, to begin in childhood or early adolescence as conduct disorder. Therefore, it may be argued that antisocial behavior is conducive to the development of alcoholism. On the other hand, alcohol increases aggressiveness in laboratory studies. Furthermore, alcohol dependence and withdrawal causes irritability and depression, which may manifest as antisocial acts. Chronic alcoholism is also likely to impair judgment and insight, cause behavioral changes, and place the individual in dire social circumstances, all of which may predispose to criminality. However, none of these observations exclude the possibility of shared etiology.

Family Studies

We are aware of three recent large family-based studies, which focused on elucidating whether ASPD and alcoholism co-aggregate in families. All of the studies show moderate co-aggregation of alcoholism and ASPD. The relative rarity of ASPD and the high rate of comorbidity between this disorder and alcoholism have made it difficult to ascertain large numbers of phenotypically discordant individuals, which has limited the determination of causality between these two disorders. Matthew et al. studied the prevalence of psychiatric disorders among 408 adults ascertained through the ECA study who reported parental alcoholism (45). The number of antisocial symptoms was significantly higher among the children of alcoholics than among 1477 matched controls. Although a trend suggesting a difference in the prevalence of a DSM-III-R ASPD diagnosis between the adult children of alcoholics and adult children of unaffected parents was noted (1.2% vs. 0.4%), this difference did not reach statistical significance. Lynskey et al. examined the rate of conduct and oppositional defiant disorder among adolescent children of alcoholic parents (46). This study was particularly significant because the subjects were interviewed at the age of 15, prior to the age at which alcoholism commonly begins (although some of them had already begun to use alcohol or drugs and many more had been exposed). The rate of conduct disorder/oppositional defiant disorder was greatly elevated among the children of alcoholic parents as compared to the children with no parental alcoholism (25.6% vs. 9%). However, after adjusting for multiple demographic differences between biological and adoptive environments, the difference in the rate of conduct/oppositional defiant disorder between children with or without alcoholic biological parents was no longer significant (p=0.1). Kendler et al. examined the transmission of psychiatric diagnoses in the families of the participants of the NCS study. They found evidence for a relative specificity of transmission of major psychiatric diagnoses, including ASPD and alcoholism. Cross-disorder association odds ratios (parental ASPD and offspring alcoholism or vice versa) remained positive (odds ratios about 2), even after controlling for several demographic factors (47). Taken together, these studies suggest that ASPD and alcoholism show moderate co-aggregation in families and indicate that some of the etiological factors may be shared. Simple conclusions concerning the etiology or causal direction of this association are difficult to draw from these data.

Twin Studies

Two large twin studies show moderate support for a shared genetic liability to ASPD and alcohol dependence. Slutske et al. studied a sample of 2682 male, female, and opposite-sex monozygotic and dizygotic Australian twins, who were interviewed for the presence of DSM-III-R diagnoses using the Semi-Structured Assessment for Genetics of Alcoholism (SSAGA) (48). In accordance with previous studies, bivariate modeling of their data suggested significant heritability for alcohol dependence and conduct disorder (56–74% of the variance was identified as being due to genetics). In males, the cross-twin cross-disease correlation (conduct disorder in one twin and alcohol dependence in the other) was significantly higher in monozygotic twins (0.29) than in dizygotic twins

(0.05), suggesting a shared genetic component as an explanation for a part of the co-occurrence of the two disorders in males. This difference was not observed between female monozygotic and dizygotic twins, suggesting that among women environmental factors are more important in liability to alcohol dependence and conduct disorder. The correlation between the genetic sources of liability to conduct disorder and alcohol dependence was estimated to be 0.41 in males and 0.59 in females. Pickens et al. studied a twin sample of 63 monozygotic and 67 dizygotic twins who were ascertained through an alcohol-dependent twin (proband). Presence of other mental disorders in the proband and co-twin was assessed according to DSM-III criteria. Cross-twin cross-disorder comparisons in male twin pairs revealed significantly higher frequency of ASPD in the monozygotic co-twins of an alcoholic proband (0.63) as compared to the dizygotic co-twins (0.47) (49). Thus, according to these two twin studies, a proportion of the genetic liability for ASPD and alcoholism may be shared.

Adoption Studies

Adoption studies have played an important role in elucidating the genetic background of antisocial behavior and alcoholism. Furthermore, these studies have been important in identifying subtypes of alcoholism, which may hypothetically differ in terms of their heritability and genetic background. In their classic study, Cloninger et al. studied a cohort of 862 Swedish male and 913 female adoptees and their biological and adoptive parents through Temperance board, criminal, and other national registries (50). Using a discriminant function analysis, they identified two forms of alcoholism, Type I and Type II. Type II alcoholism was characterized by high heritability (90%), moderate alcoholism, earlier onset, and antisocial behaviors in the biological fathers and their sons (patrilineal transmission). In contrast, Type I alcoholism was associated with later onset, rapid progression to severe alcoholism, and lower heritability. More recently, the same group of investigators published a replication study from a similarly ascertained sample of Swedish male (n=577) and female (n=660) adoptees (51). The findings of the replication study were very similar to the original findings published in 1981. For example, in the original study, the 99 males with a Type II biological background had a seven times higher prevalence of Type II alcoholism than the rest of the adoptees (17.2% vs. 2.5%; OR 8.1). In the replication sample, the 84 alcoholic males with Type II biological background had five times higher prevalence of Type II alcoholism than the rest of the adoptees (10.7% vs. 2.0%; OR 5.8). Other studies have suggested the presence of certain characteristic personality traits, such as high novelty seeking and low harm avoidance, that underlie the risk for Type II alcoholism (52).

IDENTIFYING GENES RESPONSIBLE FOR COMORBID ALCOHOLISM AND ANTISOCIAL PERSONALITY DISORDER

Although there are reported association studies between candidate genes and biological and behavioral markers of ASPD (53,54), to our knowledge, only two studies with a large sample size have tested for an association between DSM-III-R-based diagnoses of ASPD,

alcoholism, and allelic variants of candidate genes (one of the studies is in fact a candidate chromosome study). Both of the studies are from the same research group, which is focusing on the genetics of alcoholism and antisocial behaviors in genetically isolated populations of Finns and Southwestern American Indians. Lappalainen et al. followed up on animal studies suggesting that the 5-HT1B gene (HTR1B) may play a role in predisposition to ASPD and alcoholism (55). Animals deleted for this gene showed increased aggressive behavior and elevated alcohol consumption. Furthermore, 5-HT1B is a serotonin autoreceptor and thus its variant function may lead to abnormal serotonin metabolism, including low 5-HIAA levels in cerebrospinal fluid. The sample included 640 Finnish subjects, including 166 alcoholic criminal offenders, 261 relatives, and 213 healthy controls, who were diagnosed according to the DSM-III-R criteria. A replication sample consisted of 418 individuals from a large multigenerational Southwestern American Indian family with a high rate of alcoholism. The results showed a weak, but significant, genetic linkage between the HTR1B G861C polymorphism and antisocial alcoholism (as defined by a comorbid DSM-III-R diagnosis of alcohol abuse or alcoholism with antisocial alcoholism or intermittent explosive disorder) in both the Finnish and Southwestern American Indian samples. A flanking genetic marker, D6S284, was also significantly linked to the same phenotype in both populations, supporting the finding between the G861C variant and antisocial alcoholism. Association analysis showed that the 861C allele was more common among the antisocial alcoholics in the Finnish sample. Given that G861C is not expected to change the function of the HTR1B gene, this finding suggests that the functional variant causing the predisposition to antisocial alcoholism resides close to this polymorphism and co-occurs predominantly in those chromosomes carrying the 861C allele. It is not known, however, whether the functional variant resides outside of the coding region of the HTR1B gene, in the regulatory region of this gene, or even in another gene located in proximity to the HTR1B. Similar association was not observed in the American Indian sample, which may have been due to lower statistical power in this sample that resulted from differences in the HTR1B allele distributions and LD patterns between the Southwestern American Indian sample and the Finnish sample (56). Although replication of this finding has not been attempted in a similar isolated and phenotypically extreme population, follow-up studies involving the phenotypes of suicidality, alcoholism, or ASPD have been largely equivocal (57–60).

Kittles et al. followed up on earlier findings from the Swedish adoption studies, which had suggested patrilineal transmission of Type II alcoholism (antisocial alcoholism, see above) (61). One possible genetic mechanism for a patrilineal pattern of transmission is through the Y chromosome, which they sought to test in this study. They studied a population of 359 unrelated Finnish males, including 154 criminal offenders remanded to undergo forensic psychiatric evaluation. Of this population, 136 individuals fulfilled the criteria for alcohol dependence, of whom 66 were also diagnosed as having ASPD. Most of the Y chromosome does not undergo meiotic recombination and it is therefore transmitted from fathers to their sons as a “block.” Thus, the interindividual variation in the non-recombining region of the Y chromosome results mainly from mutations. Kittles analyzed eight polymorphic markers spanning the non-recombining portion of the Y chromosome, which were used to identify the common haplotypes present in this

population and to construct the most parsimonious evolutionary cladogram (i.e., "evolutionary tree") of the Finnish Y chromosomes. Instead of using only haplotypes in their association analysis, they sought to test for an association between the position within the Y-chromosomal cladogram and diagnosis. In other words, they sought to test whether alcoholism and ASPD were more common in certain clusters of males connected to one another through a common male ancestor. They did identify three such clusters of Y-chromosome haplotypes which were associated with a higher prevalence of alcoholism. This suggested that a proportion of the genetic risk for alcoholism is inherited through the Y chromosome. However, since Y-chromosome haplotypes track male migration, it is also possible that these Y haplotypes marked a certain cohort of males and it is other aspects of their genetic background to which the observed phenotypes are attributable. No conclusive evidence for Y-chromosomal lineage specific for ASPD was discovered in this study. This was largely due to the fact that all males with ASPD were also diagnosed as having alcoholism. One Y-chromosomal haplotype was found only among those males who were diagnosed with both ASPD and alcoholism, but, due to the small number of males in this group, the finding did not reach formal statistical significance.

SUMMARY

One aim of genetic research is to identify genes for predisposition to illness and thereby to increase the chances of understanding the illness better, which may help to develop medications and other treatment strategies. Genes for predisposition to some complex disorder have already been discovered. Probably the first gene-discovery-based therapies for complex disease will be developed for breast cancer and Alzheimer's disease. Genes for some familial forms of breast and colon cancer and Alzheimer's disease have been identified- and treatment and prevention strategies are being developed on the basis of these findings (62,63). Although some of the genes and their variants are responsible for increased risk for the less common, early-onset familial forms of these diseases, through better understanding of the disease process it will also be possible to develop treatments and prevention strategies directed towards the non-familial cases. Psychiatric genetics is closing in on the first major genetic discoveries, as evidenced by the recent reports of identification of the first major genes for schizophrenia (13,14) and the localization of such a gene for bipolar disorder (15).

It has been difficult to understand the etiological basis for the higher than expected occurrence of more than one psychiatric disorder in the same individual. Unraveling the genetic basis of psychiatric disorders may identify genetic, biological, and environmental processes that lead to the aggregation of these disorders. In this chapter, we have reviewed major findings from genetic, epidemiological, and molecular studies on the comorbidity of depression and ASPD with alcoholism, which are among the most common diagnostic combinations in the U.S. Sex-specific differences in the prevalence of dual diagnosis have been observed; alcohol dependence and ASPD and their co-occurrence are particularly common among men, while major depression and secondary alcoholism are more common among women. Family, twin, and adoption studies have

identified overlapping, but not identical, genetic factors for the comorbidity of depression and ASPD with alcoholism. Some evidence also suggests that sex-specific genetic mechanisms play a role in the expression of alcoholism, major depression, or both.

The first steps towards identifying molecular genetic factors for the comorbidity of alcoholism with depression and alcoholism and ASPD have been taken. Of particular interest in this effort is the evidence for the presence of a gene (or genes) on chromosome 1, which predisposes to alcoholism or depression (or both) (41). This locus may have a sex-specific effect in the predisposition to either depression or alcoholism. Two positive candidate gene-based studies on ASPD and alcohol dependence have been published, although the proportion of the total variance in the risk for antisocial alcoholism that these genes (or chromosome) account for is likely to be quite low. Antisocial alcoholism is an attractive phenotype for genetic studies because of its proposed 90% heritability (51). No genomewide linkage screen for genes predisposing to antisocial alcoholism has been published as of today.

The molecular and epidemiological genetic studies reviewed above herald a new era in research on psychiatric dual diagnosis. We anticipate that revolutionary findings in this area will be made in the next decade. For example, we will soon have an answer to the question whether the majority of the genetic risk for psychiatric disorders and their higher than expected co-occurrence is caused by a limited number of genes of major effect—or is the risk primarily due to multiple genes of small effect? Another intriguing question is whether a particular combination of these genes is important in the risk for a disorder or whether a single gene is sufficient to trigger the disease in the presence of certain adverse environmental factors. Furthermore, it will be interesting to see what possible phenotypes are possible given a certain risk allele or a combination of alleles. This will eventually tell us about the specificity of psychiatric diagnoses. Identification of the risk-causing variants will help us to home in on the neural pathways that lead to a higher risk for a psychiatric illness. This may move the basis of psychiatric diagnosis and treatment from descriptive medicine to a pathophysiologic approach. Another interesting question that may be resolved by identification of genetic risk factors is the extent of population specificity: are the predisposition genes the same in populations of African, European, and Asian descent? Reports on the association between allelic variants of ALDH, ADH, and NPY genes and alcoholism suggest that, at least in these particular cases, human populations differ significantly in terms of their genetic make-up (11,12,41,64). Certain genes and their variants may account for varying amounts of the total genetic risk in different populations and parts of the world.

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3
Overview of Diagnostic Methods

Diagnostic Criteria, Structured and Semi-Structured Interviews, and Biological Markers

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INTRODUCTION

The problem of accurate diagnosis lies at the heart of the problem of psychiatric comorbidity in patients with substance use disorders. Epidemiological and genetic studies, reviewed in the first two chapters of this volume, depend on diagnostic criteria and structured interviews to define cases. Clinicians need diagnostic criteria and interview methods to decide whether to initiate specific treatment for psychiatric disorders in addicted patients. This clinical problem is an important focus of many of the upcoming chapters on specific kinds of comorbidity.

The validity of psychiatric syndromes in addicted patients, particularly anxiety and depressive disorders, is a longstanding source of controversy, because the acute or chronic effects of substance use can mimic symptoms of many other mental disorders, including disturbances of mood, sleep, appetite and cognition, autonomic symptoms, psychosis, and even antisocial behavior. The question becomes how to differentiate psychiatric symptoms that are "organic" and/or represent effects of acute or chronic substance use or withdrawal from those that represent an independent disorder.

The controversy grows, in part, from the more fundamental problem that all psychiatric disorders are "syndromes," i.e., patterns of symptoms with some proven clinical validity, rather than "diseases" with known pathophysiology and associated biological markers. The pathophysiology of psychiatric disorders has been under intensive study for decades. However, to date no markers exist with sufficient sensitivity and specificity to serve as a "gold standard" against which to compare measurements of diagnostic entities based on criteria sets and structured clinical interviews. Spitzer and colleagues (1) proposed the "LEAD standard" ("Longitudinal, Expert, All Data") as a kind of best estimate in the

absence of a gold standard. Given the controversy surrounding comorbidity, “experts” are likely to disagree or to apply idiosyncratic criteria, limiting their usefulness as criterion measures for validation. On the other hand, longitudinal and treatment response data have been some of the most useful in supporting the validity of comorbid syndromes.

This chapter reviews the development over recent decades of diagnostic criteria and of interview methods for psychiatric syndromes when they co-occur with substance use disorders. Criteria reviewed include the “primary/secondary” distinction first formalized in the Feighner criteria (2), the “organic/non-organic” distinction found in the Research Diagnostic Criteria (RDC) (3), DSM-III (4), and DSM-III-R (5), and finally the “primary” and “substance-induced” categories of DSM-IV (6). Fundamental aspects of reliability and validity are discussed, and evidence for the reliability and validity of the several systems for diagnosing comorbidity is presented.

The chapter concludes with a discussion of several areas expected to be of emerging importance in the diagnostic assessment of comorbidity. The first concerns alternatives to the predominant DSM system, including alternative or additional criteria, alternative typologies such as Types A and B (7) and Types 1 and 2 (8), composed of combinations of behavioral traits or dimensional measures of psychopathology. A related area concerns the promise and problems of biological markers, where there has been renewed interest in recent years in the hypothalamicpituitary-adrenal (HPA) axis, and in genetic markers and candidate genes. Biological tests that would “confirm” a comorbid diagnosis still seem far away or even, perhaps, overly simplistic. What may more likely emerge is a deeper understanding of how genetic and physiologic markers, and their associated behavioral traits, may combine to predispose to what we recognize as co-occurring psychiatric and substance use syndromes.

Finally, there is the question of how to apply the research findings in clinical practice. Community-based treatment programs, which are often constrained by limitations on time and other resources, are not likely to implement the detailed structured interviews used in research, and streamlined methods are needed to screen and diagnose comorbid psychiatric disorders in real-world clinical settings.

FUNDAMENTALS OF PSYCHIATRIC DIAGNOSIS

Although taken for granted today, the development of modern phenomenologic diagnosis in psychiatry, beginning in the 1960s and 1970s, was a major advance and has provided a foundation for most current psychiatric research. In order for meaningful research or clinical work to proceed, a diagnosis must be both reliable and valid, terms whose meanings are sometimes confused.

Reliability

Inter-rater reliability refers to the ability of independent raters to agree on whether or not a particular diagnosis is present. Reliability can be measured in a straightforward fashion by having two or more raters rate the presence or absence of a diagnosis either by independently rating the same patient at the same time (joint reliability) or at different

times (test-retest reliability). The results are expressed with the kappa statistic (9,10), which ranges from minus one to one and measures the degree of agreement, corrected for chance agreement. A value of kappa of 1.0 represents perfect agreement. Values of kappa that are greater than 0.75 are considered excellent agreement, while those between 0.40 and 0.75 are fair-to-good, and those less than 0.40 are poor. A value of kappa of 0.0 represents agreement at a purely chance level. Negative values of kappa up to −1.0 are theoretically possible, representing increasing levels of disagreement. A value of kappa of at least 0.60 is considered the minimum necessary for meaningful research or clinical work to proceed with a diagnostic entity. If a diagnosis or diagnostic method is not reliable, independent research groups, and even clinicians or diagnosticians within groups, will not be able to agree on which patients qualify for a particular study or benefit from a particular treatment, and reliable knowledge cannot develop.

Spitzer and colleagues identified several sources of variance that contribute to failure of reliability in diagnosis. Some sources of unreliability, such as the patient giving a different history to each rater, are difficult to avoid. However, two sources of unreliability that are amenable to improvement through efforts to refine diagnostic methods are information variance and criterion variance (11). Information variance results when two raters elicit and use different information to arrive at a diagnosis. Criterion variance results from raters using different diagnostic criteria. The use of standard criteria, based on directly observable behavioral symptoms, and incorporation of these into structured interviews, maximizes the extent to which the same information is elicited and applied to the same criteria to arrive at a diagnosis.

Prior to the 1970s, disorders were often defined in psychodynamic terms, which were difficult to operationalize and susceptible to both information and criterion variance. This terminology was reflected in DSM-I and DSM-II. Reliability was shown to be poor for most of these disorders (12). Modern phenomenologic diagnosis, which evolved from the Feighner criteria to RDC, DSM-III, DSM-III-R, and DSM-IV, represents a return to the Kraepelinian tradition of basing diagnoses on clusters of observable behavioral symptoms. With depression, for example, a description based on theoretical mental structures and conflicts, such as internalized anger or low self-esteem, is replaced with more directly observable symptoms, such as reported dysphoric mood, frequency of self-critical or guilty thoughts, sleep and appetite disturbance, etc. With modern criteria and semi-structured or fully-structured interviews, reliability for most diagnoses has been good or excellent. This is true for substance use disorders and their most common comorbid disorders, antisocial personality, mood disorders, and anxiety disorders (13). However, development of the modern criteria has focused mainly on discrete disorders, and only with DSM-IV has there been a major effort to grapple with diagnosis in the setting of comorbidity.

Ironically, a preference for theoretical concepts over observable symptoms in diagnosis has also plagued more recent efforts to study psychiatric syndromes when they co-occur with substance use disorders (14). For example, the “disease model” would hold that substance abuse is the predominant disease, and other symptoms, such as depression or anxiety, are often epiphenomena. Here, a sad alcoholic might be viewed as being in the process of “hitting bottom,” part of the natural course of addictive disease, and the prescription would be for more rehabilitation and counseling aimed at the addiction. An

opposing viewpoint is that substance use is a symptom of underlying psychological problems, perhaps an attempt to "self-medicate." Here, a sad alcoholic might be viewed as drinking in response to a mood disorder, and prescribed more psychotherapy or pharmacotherapy. Both theories are valid to a point, but over-subscription to either may result in premature closure on diagnosis and treatment, bypassing an attempt to define in phenomenologic terms the different types of sadness among substance abusers.

Validity

Validity refers to the meaning or significance of a diagnostic entity. Unlike reliability, it cannot be neatly expressed numerically. Reliability is a necessary, but not sufficient, condition for validity, hence the critical importance of developing reliable diagnostic distinctions. However, a criterion or diagnosis may be reliable, but lack validity. For example, despite considerable effort by our group to reliably identify chronological primary depression among substance abusers (15), this distinction has yet to predict antidepressant treatment response in clinical trials (16,17).

Among the several forms of validity that have been described, three are most useful for diagnostic purposes: face validity, concurrent validity, and, foremost, predictive validity. Face validity refers to the common sense meaning of a diagnosis or criterion. Thus, the term "primary" depression, defined as a depression with onset clearly prior to the onset of any substance use disorder, has face validity, in that it would seem clear that if it occurred first, common sense would suggest it to be an independent entity. Face validity is a useful starting point or source of nosologic hypotheses, but requires confirmation through evaluation of concurrent and predictive validity. Concurrent validity refers to the ability of a criterion or diagnosis to predict other current clinical characteristics, such as symptom severity, disability level, or family history. An example would be the association, frequently observed among groups of substance abuse patients, between depression and increased severity of substance use (18–23), or between depression in an index substance abuser and presence of depression in first-degree relatives (24–26). Most important from a clinical standpoint, predictive validity refers to the ability of a criterion or diagnosis to predict the natural course of illness or its response to treatment. For example, depression has been associated with poor clinical outcome in prospective longitudinal studies of samples of patients with substance abuse (27–34). The development of criteria for distinguishing which anxious or depressed substance-abusing patients will respond to specific anxiolytic or antidepressant pharmacotherapy represents a major ongoing challenge to the field, and an ultimate goal of much current nosologic and therapeutic research.

APPROACHES TO THE DIAGNOSIS OF COMORBIDITY

As presented in Chapter 1 of this volume, psychiatric diagnostic studies in samples of treatment-seeking substance abusers over the past three decades have produced widely divergent estimates of prevalence, particularly for mood and anxiety disorders. Some of this variation may be explained by sample differences, but it is likely that much of the

divergence occurs because of inconsistency in the criteria and methods used to differentiate psychiatric disorders from the acute and chronic effects of substance use.

Primary/Secondary Distinction

The terms “primary” and “secondary” have been commonly used throughout the literature to describe comorbid psychiatric syndromes in substance abusers. However, these terms have been defined in two ways, creating confusion. In medicine, primary and secondary are often used to describe a cause-effect relationship, usually based on a known pathophysiology (for example, peripheral neuropathy “secondary” to diabetes). Primary/ secondary has been used loosely in the psychiatric literature to imply cause and effect between substance abuse and co-occurring disorders. However, this has been more in the vein of describing a theoretical relationship, based on a clinician’s or a patient’s best guess. Since the pathophysiology of mental disorders is not sufficiently understood, no empirical method of determining primary from secondary in the causal sense is available.

Beginning with the Feighner criteria (2), primary/secondary has also been defined in a narrow sense to indicate the age at onset of disorders, the disorder with earliest age at onset being called primary. This is a simple distinction which can probably be measured reliably through standard structured interviews which elicit the age at onset of each of the disorders of interest (15,35). As mentioned, this approach has face validity in suggesting that the first disorder is independent of subsequent disorders. However, it is not helpful in distinguishing whether the second disorder is independent of the first, or how the disorders may be related. Psychiatric disorders tend to have characteristic ages of onset, with conduct disorder and attention deficit disorder (ADD) beginning in childhood, alcohol and other substance abuse beginning in early to mid-adolescence, and mood and anxiety disorders beginning in adolescence and adulthood. Thus, relative to substance use disorders, conduct/antisocial personality disorders and ADD will usually be considered chronologically primary, and mood and anxiety disorders chronologically secondary, merely on the basis of their natural histories.

Schuckit and colleagues have demonstrated concurrent and predictive validity of the chronological distinction by showing that alcoholics with secondary depression tend to resemble non-depressed alcoholics more than they resemble primary depressives, and their depressive symptoms remit after detoxification from alcohol (36,37). In contrast, depressive symptoms among primary depressives persist despite detoxification (38). However, both primary (39) and secondary (40) depressions in alcoholics appear to respond to antidepressant medication, and the primary/secondary distinction has not been useful in predicting medication response in a few studies where this distinction has been examined (16,17,41). Similarly, chronological primary/secondary distinctions among non-substance use disorders have not proved useful in predicting treatment response (42,43).

In summary, although the chronological primary/secondary distinction is simple and can be reliably measured, it may have limited validity in predicting treatment response.

"Organic"/"Non-Organic" Distinction

Beginning with RDC, and continuing through DSM-III and DSM-III-R, the problem of comorbidity of psychiatric and substance use disorders was handled by rating whether the psychiatric syndrome is of "organic" etiology, this being an exclusionary criterion for the non-substance psychiatric disorder. The term "organic" derives from classic psychopathologic nomenclature and indicates a mental disorder caused by some known physical condition such as a neurological or medical disorder or toxin. However, specific criteria for distinguishing organic from non-organic disorders were never provided in these nomenclatures. On the face of it, this terminology is little different from the loose version of primary/secondary in that it implicitly describes a cause-effect relationship without providing a way of evaluating it.

STRUCTURED DIAGNOSTIC INSTRUMENTS

The upcoming sections provide brief reviews of the major structured diagnostic instruments developed for use with three major pre-DSM-IV systems: RDC, DSM-III, and DSM-III-R. Detailed reviews of many of these instruments can be found elsewhere (13). Emphasis here is placed on the different approaches to structured diagnosis that each represent, and the attempts to operationalize the "organic" criterion critical to the evaluation of comorbidity.

RDC/SADS

The Schedule for Affective Disorders and Schizophrenia (SADS) (44) was originally developed to evaluate diagnoses based on Research Diagnostic Criteria (RDC) for the NIMH Collaborative Study on Psychobiology of Depression (45). The interview has been used extensively since that time in both epidemiologic and treatment research, and more recent versions have been modified to generate both DSM and RDC diagnoses. The SADS is a semi-structured interview intended for use by experienced clinicians. In the first step of its administration, items for current symptoms of schizophrenia, mood, and anxiety disorders, as well as items for substance use and antisocial symptoms, are rated. Structured questions are provided, and the symptoms are rated on multi-point (usually six-point) scales. Anchor points are also provided, though they require clinical judgment in their application. Next, lifetime symptoms are rated. Once all items have been rated, the interviewer reviews the items scored positive and makes current and lifetime diagnoses according to the criteria. Diagnoses reported have often been based on "best estimates" made by clinicians who consider data from the SADS as well as clinical narratives, medical records, and collateral informants (46).

Instructions provided with the RDC and the original SADS are vague in terms of how to apply the organic exclusion, stating simply that disorders are diagnosed "only when there is no likely known organic etiology" (44). In more recent efforts to study substance-abusing populations, more instructions are provided to interviewers, for example

directing that comorbid disorders are diagnosed only if they occurred either in the absence of substance use or during a period of stable substance use (47). The rationale here is that, during periods of increasing or decreasing substance use, psychiatric symptoms would be more likely to represent toxicity or withdrawal, respectively. This represents one of several recent efforts to operationalize the "organic" distinction by gathering and applying detailed information about the temporal relations between substance use and psychiatric syndromes.

SADS diagnoses, particularly depressive disorders (31,33), antisocial personality disorder (48), or combined non-substance use disorders (49), have been shown to have predictive validity, in that their presence is associated with poorer clinical outcome in treatment-seeking samples with a variety of substance use problems. Most of these studies used the approach of diagnosing "non-organic" disorders only during periods of abstinence or periods of stable, rather than increasing or decreasing, substance use. Nevertheless, test-retest reliability of non-substance psychiatric use diagnoses made with this system has not always been high (47). Further, at long-term follow-up, major depression has been found to be rather impermanent, with different sets of patients manifesting the syndrome at different follow-up points (27). This could reflect variance due to subject reporting, which cannot be corrected by diagnostic methods. Alternatively, depression in this population may be a transient phenomenon, related either to substance toxicity or to the stress of life crises which these patients frequently encounter.

DSM-III/DIS

The Diagnostic Interview Schedule (DIS) was developed originally to make DSM-III diagnoses in large-scale community surveys (50). It is a fully structured diagnostic interview, designed for use by non-clinician interviewers, hence no clinical judgement is required to rate the items. Once all items have been queried, a computer program generates DSM and RDC diagnoses. The DIS was used in the Epidemiologic Catchment Area study and has also been used in clinical investigations. Interviewers read the structured questions for each item verbatim. If the subject responds affirmatively to the opening question about whether a particular symptom is present, the interviewer follows a probe flow sheet to determine how to rate the item. The flow sheet asks whether the symptom resulted in treatment-seeking (to a doctor or other professional), treatment (e.g., taking medication), or interference with daily activities. If the subject's verbatim answer is "yes" to at least one of these, the symptom is considered to be of sufficient severity or significance to meet the criterion.

The organic/non-organic distinction is handled next in the probe flow sheet, relying ultimately on the opinion of either the subject or a physician consulted by the subject. The subject is first asked whether the symptom was ever a result of illness, or related to the use of medication, drugs, or alcohol, and, if "yes," is asked if it was always a result of one of these. If either the "ever" or the "always" item is scored "no," the symptom is rated non-organic. If the "always" item is scored "yes," the symptom is rated as organic. If a physician was consulted about the symptom, then that physician's diagnosis about the relation of the symptom to drugs or alcohol is queried.

Comparison of SADS and DIS Approaches to Organicity

The SADS relies on the interviewing clinician's judgement to determine whether a syndrome is "organic," i.e., due to the effects of substance use. In contrast, the DIS relies on either the subjects' attributions or the opinions of physicians they consulted as to whether substance use caused each symptom. Further, in the DIS, organicity is queried symptom by symptom, whereas in the SADS the judgement about organicity is made at the syndromic level. Perhaps not surprisingly, agreement between these approaches has been inconsistent. One study found poor agreement between the DIS and clinicians' diagnoses (51). Hesselbrock et al. (52) found good agreement between SADS and DIS in a sample of alcoholics, although in that study clinicians, not the computer program, assigned the DIS diagnoses.

Hasin and Grant (53) also compared the SADS and the DIS. They found poor agreement between the interviews, explored reasons for disagreement, and compared validity of the two approaches. One hundred and twenty-nine patients in an inpatient rehabilitation unit for drug and alcohol problems were interviewed twice with the SADS and the DIS, administered by clinically experienced and lay interviewers, respectively. Prevalences of major depression (RDC or DSM-III) and dysthymia (DSM-III dysthymia or RDC intermittent depression) in the sample were much higher by SADS (major depression 66%; dysthymia 33%) than by DIS (major depression 20%; dysthymia-intermittent 14%), and agreement was poor, with kappa ranging from 0.11 to 0.18, barely above a chance level. Restricting SADS diagnoses to major depression which was chronologically primary reduced the proportion diagnosed to 31%, close to the proportion diagnosed by the DIS (20%), but did not improve agreement (kappa=0.06). However, when the DIS diagnoses were rescored ignoring the organicity questions in the probe flow chart (where subjects' or their physicians' attributions are elicited), agreement improved to a kappa of 0.43, which is fair. Examination of the limited available external validators showed that, compared to the DIS diagnosis, a SADS diagnosis of major depression was more strongly associated with a history of antidepressant medication treatment or hospitalization for depression, with non-significant trends in the same direction for a history of suicide attempts and several family history variables.

The widely divergent proportions diagnosed, and the poor agreement, suggest that the DIS, the SADS, or both are flawed. Better agreement was achieved once subjects' attributions were removed from DIS diagnoses, and the limited validity data favors clinician's judgement as exercised in the SADS. This suggests that, in the effort to improve structured interview methods for comorbidity, semistructured interviews involving clinician judgement may be preferable.

DSM-III-R/SCID

The Structured Clinical Interview for DSM-III-R (SCID) (54), like the SADS, is a semi-structured interview, designed for use by experienced clinicians. The SCID is convenient to use and comes naturally to clinicians because of its modular format, which "skips out" of questioning about associated features of a disorder if the essential criteria are not met.

For each criterion, standard initial questions are suggested, and there are follow-up questions to be asked if the initial question does not yield a clear answer. The interviewer is prompted to incorporate the patient's own words for key symptoms such as depression or anxiety and may also word his or her own questions, if needed, to clarify an item.

After establishing the presence of a syndrome by working through its module of semistructured questions, the interviewing clinician is asked to make a judgement about substance use and organicity, based on a simple exclusion criterion: "it cannot be established that an organic factor initiated and maintained the disturbance." DSM-III-R provides a table of substances likely to produce various organic syndromes (mood, anxiety, etc.), but, other than this, DSM-III-R is no less vague than RDC, and the SCID provides no further guidance to the interviewer on how to make the organic distinction.

Again, not surprisingly, test-retest reliability in samples with substance abuse has been inconsistent. In the multi-site SCID reliability study, one site was a substance abuse treatment program. In this sample, reliabilities for lifetime psychiatric diagnoses were acceptable, but reliability was poor for many current disorders, including major depression (kappa=0.37) (55). In another sample of current drug users, drawn from several of the sites, reliability for both current and past major depression was again fair to poor (56). Another test-retest study with the SCID in a sample of substance abusers found poor reliability for most psychiatric diagnoses. When the data were explored further, disagreement over the "organic" rule-out items was found to contribute to poor reliability (57). Similarly, for SCID diagnoses of personality disorders (SCID, Axis II version) in substance-dependent patients, reliability has been found to be poor (58), but it improved when substance-related symptoms were operationalized and counted toward personality disorder diagnoses (59).

In a study of the validity of the SCID (60), research technicians (not clinicians) administered the SCID to a series of substance abuse patients. Major depression and antisocial personality demonstrated moderate concurrent validity, anxiety disorders demonstrated poor concurrent validity, and all three demonstrated poor predictive validity. Taken together, these results again suggest that structured interviews need to be improved, and that one important step involves providing clinician-interviewers with clearer guidelines for making the "organic" distinction. In another study utilizing the SCID, interviewers were instructed to inquire whether symptoms of depression had occurred only while either high or withdrawing from substances, and such substance-related symptoms were not counted toward a diagnosis of depression. This was a randomized trial of standard therapy versus relapse prevention therapy for patients with cocaine dependence. Here, a lifetime diagnosis of major depression had prognostic significance, suggesting that the effort to operationalize criteria for counting symptoms toward a depressive diagnosis in the setting of substance abuse may have been helpful (61).

SCID-Substance Abuse Comorbidity Version (SCID-SAC)

The Structured Clinical Interview for DSM-III-R-Substance Abuse Comorbidity Version (SCID-SAC) was developed as a tool to select substance-abusing patients with mood or anxiety disorders for antidepressant treatment trials (15). In the SCID-SAC there is no

attempt to rate the "organic" criterion per se, and the corresponding item in each diagnostic module is removed. Instead, semi-structured questioning guides the interviewer to evaluate an expanded version of chronological "primary," which is rated if a mood or anxiety syndrome began before the onset of regular (at least three times per week) substance use, emerged or persisted during a period of at least six months of abstinence, or both. Syndromes not meeting these requirements are rated as "secondary." SCID-SAC has proved easy to administer, and its "primary/secondary" distinction has shown acceptable reliability in methadone-maintained patients (15). The SCID-SAC and its forerunners were used to select patients in a series of clinical trials which demonstrated favorable effects of antidepressant medications in depressed outpatients actively abusing substances (14,39,41,62,63). In analyses to date, antidepressant medications have been equally effective in "primary" and "secondary" depressives (16,17,41), which suggests that this distinction, as rated with the SCID-SAC, has little predictive validity. However, the larger implication is that "secondary" depression appears to respond to antidepressant treatment.

In a related effort, reliability and concurrent and predictive validity of comorbid diagnoses were examined, using criteria similar to those applied in the SCID-SAC (64). In a sample of mainly hospitalized substance-dependent patients, diagnoses of DSM-III-R major depression and anxiety disorders were made by experienced clinicians and divided into "independent" versus "substance-induced" categories depending upon whether the comorbid disorder was chronologically primary or had persisted during a six-month abstinent period. Test-retest reliability of comorbid diagnoses was fair to poor, and there was little evidence of concurrent or predictive validity of the "independent" versus "substance-induced" distinction. Interestingly, however, at six-month follow-up, patients with a "substance-induced" depression scored higher on depressive symptoms, measured by the Beck Depression Inventory, again suggesting the clinical significance of comorbid syndromes rated as "secondary" or "substance-induced."

Designed to be brief and convenient for clinical use, the SCID-SAC may gather too little chronological information to be of predictive utility. Other modifications of standard instruments have been developed which ascertain the relative time-course of substance use and other psychiatric disorders in more fine-grained detail. For example, one version of the SADS used in epidemiologic studies maps each syndrome onto a timegrid covering the patient's entire lifetime (65). Timelines for substance use disorders and comorbid disorders can then be superimposed, although the reliability and validity of patterns generated from such data have not been reported.

AUDADIS

The Alcohol Use Disorders and Associated Disabilities Interview Schedule (AUDADIS) is a structured interview for DSM-IV, developed for use by lay interviewers in the National Longitudinal Alcohol Epidemiologic Survey (NLAES). It focuses on alcoholism and associated disabilities, including major depression, drug abuse, smoking, and medical problems (66). Other common comorbid disorders, such as anxiety disorders or antisocial personality, are not included. Unlike its fully-structured counterpart, the DIS, the

AUDADIS requires the requisite symptoms of disorders to cluster in time in order for a diagnosis to be met. Likewise, age at onset of disorders is operationalized as onset of the full syndrome for substance dependence diagnoses, rather than onset of first symptoms. If a depressive syndrome is met, a series of questions is used to ascertain whether alcohol or drugs are taken to feel better, suggestive of "self-medication," and how the depressive syndrome relates to periods of either increased substance use or withdrawal. This inquiry takes place at the syndrome level, rather than for each individual depressive symptom as is done in the DIS. Reliability of major depression in a sample of substance abusers was acceptable (kappa=0.60–0.65), although separate values for kappa for chronological subtypes of depression ("primary/secondary") are not reported (67,68). AUDADIS does not diagnose "substance-induced" disorders.

Age at onset data from AUDADIS in the NLAES were used to generate the first analysis of concurrent validity of the "primary/secondary" distinction in a large-scale community sample (68). Cases of lifetime major depression were classified into an expanded primary/secondary scheme that included a third group, "concurrent," if major depression and alcoholism both began at the same age. Contrary to previous findings from smaller clinical samples, subjects with secondary depression did not closely resemble subjects with alcoholism only. Instead, the three comorbid depressed groups (primary, concurrent, and secondary) resembled each other in showing slightly more severe alcohol use disorders than the group with alcoholism alone, more severe depressions than the group with major depression alone, and a greater likelihood of other drug use disorders than both the alcoholism-alone and major depression-alone groups. Primary depressives did differ from the other groups in having more severe depressive symptoms and greater likelihood of suicidal thinking and attempts. Thus, the validity of chronological "primary" depression as the most severe form of depression in alcoholics was affirmed in this study. However, these findings are also reminiscent of findings from drug-dependent samples, where most major depression would be classified as chronologically secondary due to the early onset of drug abuse, but depression is nevertheless associated with greater severity of illness and poor prognosis (69).

SSAGA

The Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) (70) was developed for a multi-site genetic linkage study of alcoholism (COGA) and borrows features from SADS, DIS, SCID, and others. This instrument places emphasis on comorbidity, based, as for various "primary/secondary" schemes, on the relative chronology of disorders. For example, comorbid depression and alcoholism is evaluated by organizing ages at onset and offset of both disorders, abstinent periods, etc., into a timeline, and then classifying depression as "independent," "completely co-occurring," or some mixture of the two. Test-retest reliability studies yielded kappas of 0.65 and 0.74 for lifetime major depression in two separate samples (70). Reliability data for chronologic subtypes were not reported. Analyses from the COGA study have begun to emerge which bear upon the validity of psychiatric disorders diagnosed with SSAGA in treatment-seeking alcoholics and their relatives. Concurrent validity of the "independent"

versus "substance-induced" distinction was supported by an analysis showing participants with independent major depression to have less drug involvement and more suicide attempts and more family history of mood disorder than those with substance-induced depression (71). A study of predictors of suicide attempts over a five-year follow-up found that substance-induced psychiatric disorders (specifically depression, mania, and panic disorder) at baseline were predictive of subsequent suicide attempts, while both substance-induced and independent depressions at the follow-up point were predictive of suicide attempts. Here, disorders were called "independent" if they showed prior onset or had persisted during at least a three-month abstinent period (72). Again, the implication seems to emerge that carefully diagnosed substance-induced psychiatric disorders have clinical significance.

PRISM

The Psychiatric Research Interview for Substance and Mental Disorders (PRISM) was designed to overcome reliability problems in the diagnosis of comorbid psychiatric disorders in substance-abusing samples. Developmental work on the PRISM was based on psychometric theory, previous research with the SADS-L and DIS (53), and systematic review of the audiotapes of discordant cases from the SCID test-retest reliability study (55) in order to pinpoint sources of unreliability. The PRISM was initially developed and tested for DSM-III-R criteria and used many aspects of the SCID as a starting point. Significant new features of the PRISM include the following: 1) the substance use disorders section was moved to the beginning of the interview, so that the interviewer began the modules for mood and other mental disorders with a thorough knowledge of the subject's patterns of substance use; 2) items in the mood and other mental disorder modules were expanded to include more anchor points to reduce criterion variance, and more suggested probe questions; 3) the organic item was clarified with more instructions and anchor points, and separate items were added for alcohol, drugs, and prescribed medications.

Two reliability studies were conducted with the PRISM, one in 75 non-patients with a history of heavy drinking, and one in 172 patients from an inpatient dual diagnosis unit and an outpatient drug clinic (73). The kappa for current "primary" major depression was 0.81, substantially better than other diagnostic interviews in substance-abusing samples. Kappas for other affective disorder diagnoses were all greater than 0.60 in both samples, as well as for most other comorbid disorders (e.g., panic disorder) for which the prevalence was sufficient to yield meaningful tests. These findings suggest that the effort to reduce criterion variance and better anchor the "organic" criterion resulted in improved reliability compared to the previous experience with the standard SCID.

The DSM-IV Approach

Responding to increasing recognition of the prevalence of comorbidity in both the general population and treatment-seeking samples, DSM-IV placed more emphasis on comorbidity, focusing especially on the combination of depression and substance abuse,

and replacing the dichotomous "organic" vs. "non-organic" distinction with three categories: "primary," "substance-induced," and "expected effects" of substances. In contrast to prior diagnostic systems, DSM-IV provides guidelines for distinguishing depressive syndromes in the setting of ongoing substance use.

Specifically, primary major depression is diagnosed if one or more of the following criteria is met: 1) "persistence of mood symptoms for a substantial period of time (i.e., about a month) after the end of Substance Intoxication or acute Substance Withdrawal"; 2) "the development of mood symptoms that are substantially in excess of what would be expected given the type or amount of the substance used or the duration of use"; or 3) "a history of prior recurrent primary episodes of Major Depression" (6).

"Substance-induced" disorders are diagnosed when: 1) symptoms of the disorder are present, having developed during or within a month of substance intoxication or withdrawal; 2) the requirements for "primary," stated above, are not met; but 3) the symptoms are "in excess of those usually associated with the intoxication or withdrawal syndrome and when symptoms are sufficiently severe to warrant independent clinical attention." If neither "primary" nor "substance-induced" criteria are met, then the syndrome is diagnosed as simply substance intoxication or withdrawal (6).

Thus, DSM-IV expands on the older notion of "chronologically primary" to include persistence during abstinence, or a syndrome occurring in conjunction with substance use but which is too clinically significant to be attributed to substance effects. Further, there is a recognition, through the intermediate "substance-induced" category, that mood or other psychiatric syndromes may have clinical implications even though they are chronologically secondary. These developments seem well grounded, given the findings, reviewed above, that suggest that depressions which previously would have been called "secondary" or "organic" may have prognostic significance, either by influencing severity or outcome of addiction treatment, or by being responsive to antidepressant medication.

However, the system continues to present challenges for diagnostic precision and for the development of structured instruments. Particularly in those commonly encountered patients with chronic substance use dating to an early age, the differential diagnosis between categories of depression will often hinge on interpretation of the terms "substantially in excess" and "in excess" of the "expected" effects of substance use. These are not further defined and are thus left to clinical judgment.

SCID (DSM-IV Version)

The DSM-IV version of the SCID provides for diagnosis of "primary" or "substance-induced" depression, but furnishes no more specific guidelines than those stated in the criteria. Reliability data for the SCID-IV in substance-abusing samples are not yet available. However, in the absence of clear guidelines, this would seem to predispose to the same poor reliability encountered with prior criteria sets and diagnostic interviews, as reviewed above. The predictive validity of SCID-IV diagnoses of primary and substance-induced depression was supported in a sample of substance-dependent patients seeking treatment at an outpatient program. Both primary and substance-induced depression had a similar prognosis, being associated with better outcome compared to patients without

depressive disorders, a result which may have reflected the strong psychiatric component of the program, such that patients' comorbid disorders were addressed as part of the treatment (74).

DIS and CIDI

The Diagnostic Interview Schedule (DIS), reviewed above in its DSM-III form, has been updated for DSM-IV. It has been used to examine the primary/secondary distinction based on age of onset (75). The Composite International Diagnostic Interview (CIDI) was developed along similar lines to the DIS. It is a fully structured interview which, like the DIS, includes probes to establish whether co-occuring psychiatric disorder symptoms are caused by substance use, in which case the syndrome can be classified as "substance-induced" in the DSM-IV sense. This feature has been used to compare cross-sectional characteristics of patients with "independent" vs. "substance-induced" disorders, and within independent disorders to compare those which are "primary," in terms of prior age of onset, to those which are "secondary" in terms of onset only after the onset of the first substance use disorder (76). Few differences were found between groups, which calls into question the significance of the distinctions, although the data are limited by their cross-sectional nature.

PRISM (DSM-IV Version)

To address the changes in the DSM-IV and to provide diagnoses of "primary" and "substance-induced" disorders, the PRISM has been updated and revised. The PRISM-IV now assesses 20 DSM-IV Axis I disorders and two Axis II disorders. A substance-induced specifier is provided for those diagnostic categories, whose symptoms mimic intoxication and withdrawal symptoms. These include major depression, dysthymia, mania, psychotic disorders, panic disorder, and generalized anxiety disorder. To standardize the diagnosis of substance-induced disorders, the PRISM requires the same duration and number of symptoms as are required for the corresponding DSM-IV primary disorder. Questions are provided in the mood and psychotic disorders sections that ascertain the temporal relationship of mood or psychotic symptoms and substance use.

Guidelines that are provided for the interviewer operationalize "substance-induced disorder" when a mood syndrome occurs in the context of active substance use. This depends upon identifying mood disorder symptoms that are "in excess" of what would be expected to be produced by the substance or substances being concurrently abused, and distinguishing symptoms that are merely "expected effects" of the concurrently used substance. To operationalize this distinction, the subject's own pre-depressed, substance-using state is considered the baseline or frame of reference. Any onset or exacerbation of psychiatric symptoms is evaluated against this state. Information is provided for each item regarding whether the psychiatric symptom reflected in the item may represent expected effects of alcohol or particular drugs (for example, that cocaine intoxication may produce insomnia, or cocaine withdrawal may produce a depressed mood). Although this line of inquiry is more painstaking than that used in other instruments, it does reduce the level of judgement involved on the part of the diagnostic interviewer. While the

DSM-III-R version of the PRISM was quite long, other changes in the DSM-IV version of the PRISM reduced the interview to a more feasible length. Probes were shortened to decrease administration time, and the alcohol and drug sections were combined to streamline administration. A computer algorithm is available which derives diagnoses from item-level responses.

Special attention was given in the PRISM-IV to Major Depressive Disorder (MDD), a particular source of diagnostic controversy in earlier research (77). By using the PRISM, two distinct types of primary MDD can be diagnosed, reflecting a refinement of DSM-IV. The first, "prior-onset" MDD, is defined as beginning prior to the initial onset of substance use disorders. This corresponds to the "primary" diagnosis found in the Feighner criteria (2). An "abstinence" MDD can also be diagnosed that occurs during periods of sustained abstinence or remission from substance use disorders. DSM-IV "substance-induced" MDD is diagnosed by the PRISM when a full-syndrome episode of MDD is met, meeting all duration and symptom criteria for DSM-IV Major Depression (again, as noted above, symptoms judged to be merely "expected effects" of substances are not counted toward the syndromal diagnosis), but the syndrome occurs entirely during a period of substance use. Table 1 lists essential features of the PRISM-IV.

The revised PRISM has been subjected to a test-retest reliability study (n=285) in patients treated in inpatient and outpatient substance abuse, dual diagnosis, and mental health settings. All subjects were current users of

Table 1 Essential Features of the PRISM, DSM-IV Version

1. Obtains overview of lifetime psychiatric treatment history
2. Obtains history of heavy drug and alcohol use prior to other diagnostic sections
3. Obtains lifetime timeline of periods of heavy substance use and abstinence
4. Assesses lifetime and current psychiatric symptoms and disorders
5. Provides guidelines to assist in differentiating substance-induced symptoms, primary symptoms, and symptoms that are "expected effects" of intoxication and withdrawal
6. Provides guidelines to assist in determining the temporal relationship of psychiatric symptoms and substance use
7. Allows for interviewer or computer diagnosis

alcohol, cocaine, and/or heroin. Initial analysis indicates good to excellent reliability (kappa for current primary major depression=0.75; current substance-induced major depression=0.68; current primary psychotic disorder=0.86; current substance-induced psychotic disorder=0.75). The mean administration time in the test-retest study was 2.33 hours, with a minimum of 42 minutes, depending on the complexity of the psychopathology involved.

A comparison of the concurrent validity of the PRISM and SCID was conducted in 105 drug abuse patients in Spain (78). In this study, diagnoses from both instruments were compared to LEAD diagnoses, the standard used in psychiatric validity studies in the

absence of a "gold standard" (1). Agreement was substantially higher between PRISM and LEAD diagnoses than between SCID and LEAD diagnoses for many of the major psychiatric disorders assessed, suggesting the validity of the PRISM procedures. Predictive validity of the categories of prior-onset, abstinence, and substance-induced Major Depression was supported by a study (34) in which the PRISM was administered to 250 patients in a dual-diagnosis inpatient unit, who were then followed for up to two years with the PRISM-L, a modification for longitudinal studies, which documents onset and offset of syndromes since the last evaluation point. Prior onset and substance-induced depression were found to reduce the likelihood of remission from substance dependence, while abstinence depression during a period of remission in the follow-up was found to predict subsequent relapse to substance use disorder. The effects were found to be similar when alcohol-, cocaine-, and opiate-dependent patients were examined separately (79). All three depression types were also found to predict various measures of suicidal behavior over the follow-up period (80). Taken together, these studies suggest that both DSM-IV primary and substance-induced depressions, carefully operationalized, have prognostic significance. This is consistent with the DSM-IV concept that substance-induced depression, while it cannot be established to have occurred independently of substance abuse, nevertheless represents more than merely toxic effects of substances and warrants clinical attention. These latter studies are among the few that have examined the predictive validity of primary vs. secondary or primary vs. substance-induced distinctions by means of detailed longitudinal follow-up.

Summary of Approaches to Diagnosis of Comorbidity

Approaches to the diagnosis of co-occurring psychiatric disorders among substance-dependent patients have evolved from the simple approach in Feighner and RDC criteria of distinguishing primary from secondary disorders by age at onset, and from the more theoretically based but poorly defined and operationalized notion of "organic" disorders in DSM-III. The latest DSM-IV approach integrates aspects of these prior systems, but shows promise of being an improvement over them. It defines "primary" comorbid disorders as those that have been independent over time (either with prior onset or occurring during a substantial abstinent period), and, among those that are not temporally independent, distinguishes "substance-induced" disorders as those with symptoms in excess of what would be "expected effects" of substance intoxication or withdrawal. Contemporary diagnostic instruments, including the DIS, CIDI, SSAGA, SCID-SAC, SCID-IV, and PRISM, incorporate methods for making such distinctions, although the methods differ across instruments.

The differences between instruments reflect, in part, differences in how each instrument operationalizes the DSM-IV categories, which are defined in broad, conceptual terms, leaving the designers of instruments or studies to grapple with erecting more specific criteria that will perform reliably and make valid, clinically useful distinctions. For example, the SCID-SAC requires a six-month period of abstinence during which a co-occuring disorder can be rated as primary, SSAGA has been implemented using a three-month abstinence criterion, and the PRISM requires at least one month of abstinence, while other applications have left the definition of the abstinent

period vague. To varying extents, the DIS, CIDI, SSAGA, SCID-IV, and PRISM all ask the interviewer to judge whether symptoms represent expected effects of substances. The PRISM goes the farthest in providing guidelines and anchor points for interviewers in distinguishing expected effects of substances from mood symptoms which are in excess of what would be expected from the concurrent substances and would count toward a "substance-induced" diagnosis. PRISM divides DSM-IV primary depression into "prior onset," consistent with RDC primary, and "abstinence" categories.

In examining the approaches that various instruments take to implementing the DSM-IV typology, several issues emerge which should inform future research. First, DSM-IV really represents a three-level typology: primary psychiatric syndrome, substance-induced psychiatric syndrome, and symptoms that are expected effects of substance use. Instruments and studies tend to operate with only two levels, ignoring the expected effects (e.g., depressive syndromes that are judged to be expected effects are simply ruled out and lumped among non-depressed cases) or not clearly distinguishing between substance-induced and expected effects categories. This points to a somewhat awkward aspect of the nomenclature, namely that the term "substance-induced" suggests symptoms that are merely effects of substance use, whereas "substance-induced" in the DSM-IV sense indicates a syndrome that is in excess of what would be expected from the toxic effects of the substance alone.

Second, relatively few studies, to date, have examined the validity of the DSM-IV typology, especially in terms of predictive validity. The DSM-IV system will be clinically useful, ultimately, to the extent that it can help clinicians to identify more precisely those substance-dependent patients with comorbid syndromes who would benefit from specific psychiatric treatment. Thus, more studies are needed that examine the longitudinal course of primary and substance-induced disorders, as well as of symptoms or syndromes representing "expected effects," and their relationship to outcome of substance use and response to substance abuse treatment. Studies are also needed of treatments for specific psychiatric syndromes among substance-dependent patients, and whether their efficacy is moderated by primary vs. substance-induced vs. expected effects categories. However, the limited studies of predictive validity that are available suggest that both DSM-IV primary and DSM-IV substance-induced depressive disorders (or similar categories applied with earlier diagnostic systems) have prognostic significance and should be considered as targets of treatment efforts.

FUTURE DIRECTIONS

Biological Markers

As alluded to in the introductory comments, psychiatric disorders are actually syndromes or symptoin-clusters with clinical validity but unknown pathophysiology. In contrast, for many diseases encountered elsewhere in medicine, pathophysiology and symptom production are understood, and this usually means that biological markers of high sensitivity and specificity are available, such as antibody titers, organisms grown in culture, or radiological or histopathological findings. Needless to say, biological markers

would be enormously helpful in differentiating between psychiatric disorders and the effects of substance use, providing a "gold standard" for validating clinical diagnoses and a way to confirm a diagnosis prior to initiating specific treatment. Such markers do not yet exist, although several examples are reviewed with potential relevance to co-occurring psychiatric and substance use disorders. At the current stage of development of the field, biological markers may be more useful in elucidating pathophysiologic mechanisms of substance use and other psychiatric disorders and their relationships than in serving as diagnostic markers per se.

Biological Markers as Diagnostic Tools

The finding of abnormal dexamethasone suppression test (DST) results in many patients with depressive disorders generated considerable excitement and investigation, including a flurry of studies examining whether the DST could be used to differentiate different types of depression in substance abusers. The DST turned out to have very poor specificity, with positive results obtained in many other conditions including physical and psychological stress, starvation, eating disorders, and alcoholism (with or without depression). Although there were some promising reports (81–84), most studies of the DST in substance abuse samples did not support its utility as a marker for depression (85–91). However, growing interest in the role of stress in engendering addictions and psychiatric disorders has reinvigorated the study of the hypothalamic-pituitary-adrenal (HPA) as a window into the pathophysiology of these related disorders.

Panic disorder can be mimicked by the effects of alcohol, sedative or opiate withdrawal, or by acute stimulant intoxication. Among individuals without substance use disorders it has been shown that panic attacks can be provoked by either sodium lactate infusion or carbon dioxide (CO_2) inhalation, and that these tests are relatively sensitive and specific. Both procedures suggest that abnormal respiratory physiology may be involved in the etiology of panic disorder, perhaps an abnormal sensitivity of the suffocation alarm response, which is normally triggered by rapidly increasing CO_2 levels during suffocation (92). Several small studies have shown that infusion of lactate provokes panic attacks in alcoholics with panic disorder (93–95). It has also been hypothesized that alcohol and other drugs, especially cocaine, may "kindle" panic attacks. If chronic substance use itself predisposes to the provocation of panic attacks in response to lactate or CO_2, then the challenge tests might, as with the DST, turn out to be too non-specific to be useful as a diagnostic test. However, relatively few subjects have been studied and more research in this area would seem warranted. Specifically, further study is indicated into whether lactate or CO_2 provocation of panic attacks is specific to substance abusers with typical panic-agoraphobic histories and whether this susceptibility correlates with other validators, including clinical course (e.g., persistence of panic after abstinence from substance use), presence of agoraphobia (which would not be an expected result of panic-like attacks induced by substances), family history of panic disorder, and, ultimately, response to antidepressant medication or cognitive-behavioral therapy.

Biological Markers to Advance Etiologic Models

Psychiatric syndromes are likely to be biologically heterogeneous, such that clinical syndromes that are observed represent common final pathways for numerous different underlying pathophysiologies, each of which would theoretically have unique markers (96). Given this heterogeneity, findings of biological studies will be inconsistent, because samples will vary in the proportion of patients with the marker of interest, and large studies with adequate statistical power will find that only some fraction of a larger clinical syndrome is associated with a given marker or mechanism. Patients with a given marker may then be considered to belong to a putative subtype, which will lead to investigations of how they may differ clinically or biologically from patients without the marker and from normal subjects (96). The markers discussed in the previous section could be applied in this way. Thus, depressed substance-dependent patients with a positive DST may be approached as a putative subtype with derangements in the HPA axis (97), and anxious substance-dependent patients with a positive response to CO_2 or lactate challenge may be approached as a putative subtype with derangement of respiratory physiology (92).

While the delineation of pathophysiology has classically advanced through study of selected samples with a relatively pure form of some disorder, studies of comorbid samples may also be useful for teasing apart underlying mechanisms. This relates to a general argument in favor of studying comorbidity (98). Since substance use disorders and mood disorders present many of the same symptoms at cross-section, such as euphoria, dysphoria, irritability, impulsivity, insomnia, etc., such symptoms are probably final common paths for complex chains of pathophysiologic events. A biologic study in psychiatry, comparing ill patients with normal subjects, may find a marker associated with symptoms, but cannot distinguish whether the marker reflects activity at the final common pathway or earlier in the pathophysiologic chain. The addition to this design of a group of remitted patients distinguishes state from trait markers. The addition of a group of psychiatric controls addresses the specificity of the marker. However, unique information might be garnered by comparing, for example, patients with depression only with psychiatric controls who are substance abusers with 1) depression which persists after abstinence, or 2) “substance induced” depression, or 3) depressive symptoms representing “expected effects” of substance abuse. A biological marker observed in all these groups likely reflects events in the common final pathway that produces depressive symptoms. Markers unique to each group would reflect earlier events in distinct pathophysiologic chains leading to depression.

Advances in genetics, including the identification of genetic markers and candidate genes, promise to hasten the delineation of biological subtypes of addictive disease and its co-occurring psychiatric syndromes. For example, common genetic contributions to substance use disorders and major depression have been identified in twin studies (99–101), the latter (101) suggesting that antisocial personality disorder mediates the shared genetic risk of substance abuse and depression. Recently a marker locus on chromosome 1 has been identified that is associated with either alcoholism or depression (102). It has been well known that disruptive disorders in childhood and adolescence represent a strong risk factor for subsequent addiction, although only a subgroup of patients with substance use disorders manifest this developmental pathway. More recently, genetic studies have revealed multiple alleles for components of the dopamine and serotonin

systems (103), which have begun to be studied for their functional and clinical significance. For example, alleles of the dopamine transporter and various receptors have been associated with attention deficit hyperactivity disorder and behavioral traits such as novelty seeking, which are associated with disruptive disorders and with substance abuse and dependence (104). Low levels of dopamine D_2 receptors have been associated with addiction, possibly representing a link between allelic variations in the dopamine system and clinical manifestations (105). Deficits in serotonin system functioning have been implicated in depression and pathological aggression (106–114). Reduced sensitivity of serotonin receptors was suggested in a study of d-fenfluramine challenge in opiate-dependent patients (115). Relatedly, an association of an allele of the promoter region of the gene encoding the serotonin transporter, which results in reduced expression of transporters, was reported to be associated with alcoholism and antisocial personality traits (116). Comorbidity, broadly defined, occupies a central role in these lines of research (117), as genetic markers are gradually linked to behavioral traits and syndromes underlying risk for addictions and co-occurring conditions.

Exploration of Alternative Nosologies

The DSM and its predecessors have served a critical function in the development of psychiatric research, and the DSM-IV approach to classifying comorbid psychiatric disorders in the setting of substance abuse represents a clear advance, which is just beginning to be subjected to tests of validity. However, it is important to bear in mind that the DSM diagnostic categories are at the level of hypotheses, and that it is important to consider alternatives, both alternative definitions of categories and alternative approaches to classifying psychopathology (118).

The DSM-IV system for classifying comorbid syndromes emphasizes the time course and severity of psychiatric symptoms relative to substance use. However, it is not uncommon for patients to present with a chronic history of both substance dependence and psychiatric symptoms, such that chronological distinctions are hard to make. Other features or dimensions might be explored by examining their validity in comparison to the current DSM-IV system. For example, the pattern of symptoms within a psychiatric syndrome, or the presence of specific distinctive symptoms, might help to indicate the presence of an independent disorder requiring treatment. This is, to some degree, implicit in DSM-IV, since many psychiatric symptoms are not “expected effects” of substance use in that they do not appear on the list of criteria for intoxication or withdrawal. For example, panic attacks might resemble alcohol withdrawal, but agoraphobia is not a recognized symptom of either alcohol intoxication or withdrawal, and its presence would suggest the presence of a “true” panic disorder. Similarly, suicidal ideation or a history of suicide attempts might suggest the presence of a true mood disorder. A problem with this approach is that effects of chronic substance use often go beyond those listed as symptoms of toxicity or withdrawal in DSM-IV. For example, chronic alcohol use can produce a depressive syndrome of substantial severity which resolves rapidly with abstinence, and suicidal ideation might be a part of this. Cocaine use can produce anxiety and autonomic symptoms which resemble panic attacks, or paranoia, which can be confused with agoraphobia. The chronicity of psychiatric symptoms might also be

important (15,119). Psychiatric symptoms that are toxic effects of substance use might be more likely to wax and wane with variations in substance intake, as is suggested by many studies that show that depressive symptoms abate after abstinence or treatment entry (27,29,82,90,120–127). Independent disorders might be more persistent over time. It is also theoretically possible that some psychiatric syndromes caused by the toxicity of substance use may become chronic, as in, for example, the debated syndromes of protracted abstinence (128). The treatment implications (e.g., response to pharmacotherapy) might be the same as for independent disorders. In non-substance-abusing outpatients, chronic depression (major depression or dysthymia of at least two years' duration) has been associated with lower placebo response rates in pharmacotherapy trials (129). Chronicity of depression has been part of the working criteria used to identify medication-responsive depression among alcohol- (63), cocaine- (14), and opiate-dependent patients (41). Measures of chronicity are suggested in those studies, but research is needed on such measures in substance-abusing samples.

Family history has often been used as a validator in nosologic research, and it also might be considered as a diagnostic indicator. For example, a clear-cut history of primary major depression in a first-degree relative might be used to contribute to a diagnosis of either "primary" or "substance-induced" depression in cases that are otherwise ambiguous.

Another alternative diagnostic strategy would be to place more emphasis on dimensional measures of psychopathology rather than categorical diagnoses. Dimensional measures may be more powerful by reflecting severity, and may more accurately reflect underlying traits that represent part of a continuum. Further, such scales are brief and easy to administer and thus have the advantage of low cost and ease of implementation, which are substantial advantages that will be revisited in the final section below on clinical recommendations for procedures to be used in community-based treatment settings. However, the predictive validity of such scales in selecting treatment-responsive substance abusers with mood or anxiety disorders has been mixed. A number of placebocontrolled clinical trials of antidepressant medications for treatment of substance abusers, particularly those conducted prior to the 1990s, used cross-sectional dimensional measures, such as the Beck Depression Inventory, to ascertain depression at baseline. These studies generally failed to detect antidepressant effects, and often had high placebo response rates (for reviews see Refs. 130, 131; for more recent negative trials see Ref. 132). More recent studies identifying depressed cases with clinical history and DSM syndromal diagnosis have demonstrated medication effects, supporting the importance of syndromal diagnosis in identifying treatable mood disorders among substance abusers (14,39–41,63,133–136). Nevertheless, some studies using simple cross-sectional scales to identify depressed anxious cases did demonstrate antidepressant effects (137–142), while some medication trials using syndromal depressive diagnosis have been negative and additionally plagued with high placebo response rates (143–146). The inconsistency in these findings highlights the need for further nosological research to identify better criteria for selecting treatable comorbidity.

Biological and genetic studies, such as those considered briefly above, may indicate more precise subtyping of existing diagnostic categories, and may also lead the way to alternative typologies. For example, alcoholics have been classified into two types

(Cloninger's Type 1/Type 2 (7) and Babor's Type A/Type B (8)) based on family history and clinical features and course. Type 1 or Type A drinkers have later onset and variable and less severe course with less associated psychopathology and a better prognosis overall. Type 2 or Type B drinkers have early onset more associated psychopathology such as sociopathy and depression, and worse prognosis. These subtypes have demonstrated reliability and discriminative validity (147). Further, two recent placebo-controlled clinical trials (140,146) suggest that serotonin uptake inhibitor antidepressants are effective in improving drinking outcome in Type A (uncomplicated alcoholics) but may actually worsen drinking outcome in Type B (complicated or poor prognosis) alcoholics. This finding is counterintuitive, given the preponderance of depressive symptomatology in the Type B group and the expectation that an antidepressant should help this group, and it serves to highlight the importance of considering such alternative typologies for co-occurring psychopathology in substance dependence.

Another example of an alternative psychopathological category is that of the "reward deficiency syndrome" (148). This concept is suggested by genetic and biological studies that implicate a deficiency in the functioning of the brain reward system, and specifically in its dopaminergic pathways, underlying a range of disorders from substance dependence to Tourette's disorder, attention deficit hyperactivity disorder, and personality characteristics such as novelty seeking and sociopathy. Putative biological phenotypes such as this may form the building blocks of more sophisticated models of psychopathology, based on interactions of biological and environmental factors, eventuating in clinical syndromes such as those now reflected in the DSM.

Evaluation of such alternative nosologic schemes would require a highly detailed current and lifetime diagnostic evaluation, such as that afforded by the PRISM-IV, supplemented by other measures of chronicity, family psychopathology, and dimensional scores, as well as biological measures and/or measures reflective of alternative typologies. Such evaluation, conducted at the outset of epidemiologic studies or clinical trials, would allow comparison of the predictive validity of various systems and development of improved systems. This would require a strong commitment to nosologic inquiry on the part of both investigators and funding agencies, since it involves more training and effort per subject, as well as large samples.

Clinical Recommendations for Community-Based Treatment Providers

Clinicians should be encouraged to use the DSM-IV system to categorize mood, anxiety, and other psychiatric syndromes in their substance-abusing patients. Training and use of a semi-structured diagnostic instrument such as the SCID-IV or PRISM should be encouraged. In the potentially confusing history of a substance abuser, such instruments provide a disciplined approach to establishing whether a psychiatric syndrome, for example major depression, is present, and whether the disorder is "primary" or "substance induced." Even if the instruments themselves are not used routinely in clinical practice, the training and approach will generalize to routine history-taking and sharpen diagnostic acumen. At the same time, clinical judgment remains essential to integrate the many rich sources of data that are available in a clinical history into an overall evaluation of a comorbid psychiatric syndrome and a decision on how to proceed with treatment.

A larger problem for the field is that most substance abuse treatment programs lack sufficient access to psychiatric consultation, or to clinicians of any stripe trained in recognition of common co-occurring psychiatric disorders, such that most programs are poorly equipped to identify and treat such patients (149). The Drug Abuse Treatment Outcome Study (DATOS), among the most comprehensive naturalistic studies of treatment outcome, collected data on typical community-based treatment programs (150). Overall, the study sampled 96 programs with a variety of levels of care, serving over 10,000 patients. Analysis of the services provided by those programs showed that only 53% of them administered any kind of psychological assessment to their patients. Most importantly, the assessments were generally unidimensional (such as the isolated use of the Beck Depression Inventory or Michigan Alcohol Screening Test) or consisted of psychological inventories of limited value in guiding treatment decisions, such as the MMPI. Only 7 (7.3%) of the sampled programs conducted assessments that evaluated the presence or absence of more than one disorder (149).

Another likely factor contributing to underdiagnosis is the limited time available for clinical encounters with patients, driven by limited funding for care, burdens stemming from documentation and other paperwork, and the need to tend to the presenting substance use problems. Detailed structured clinical interviews such as the SCID or PRISM may be too lengthy to be realistic in most clinical settings, which suggests a need for reliable and valid screening and/or diagnostic instruments that clinicians can use quickly and efficiently to assess comorbidity. Fully structured instruments such as the DIS and CIDI are suitable for lay interviewers, and clinicians with little psychiatric training could be trained to administer them, but they too are lengthy. Symptom severity scales such as the Beck Depression Inventory screen for only one disorder. The ideal instrument would need to target the most common disorders in the population under study and place minimal demands on patients and clinicians. A precedent for such an effort exists in the setting of primary medical care, which faces similar barriers to recognition of psychiatric syndromes and where screening programs for depression, implemented in conjunction with appropriate interventions, have been shown to improve patient outcomes (151–154).

Brief screening diagnostic instruments, developed mainly for primary care settings, are beginning to emerge, and research on application of such instruments in substance abuse treatment settings is needed. Examples of such instruments include the Psychiatric Diagnostic Screening Questionnaire (PDSQ) (155,156) and the Patient Health Questionnaire (PHQ) (157). The PDSQ consists of 126 questions assessing the symptoms of 13 disorders in five areas: eating disorders, mood disorders, anxiety disorders, substance use disorders, and somatoform disorders, and has demonstrated good psychometric properties (156). One potential disadvantage of the PDSQ is that all items are filled out, and diagnoses are then based on cutoff scores on subscales, such that completion takes about 20 minutes. Some disorders that are common among substance abusers, including pathological gambling and attention deficit disorder, are not covered; modules for these would be needed if the instrument were to be applied in substance abuse treatment settings.

The PHQ is a self-administered version of the Primary Care Evaluation of Mental Disorders (PRIME-MD) (158). The PRIME-MD was a brief clinician-administered

diagnostic screening instrument which represented an earlier step in the effort to develop a brief diagnostic instrument. The PHQ consists of a four-page questionnaire that can be entirely self-administered by the patient (it can also be read to the patient if necessary). The clinician then scans the completed questionnaire, verifies positive responses, and applies diagnostic algorithms that are abbreviated at the bottom of each page. The entire process takes less than 10 minutes (157,159), and both patients and clinicians have reported high levels of satisfaction with the use of the PHQ in primary care settings (157). The PHQ currently assesses four DSM-IV diagnoses (major depressive disorder, panic disorder, other anxiety disorder, and bulimia nervosa), and four subthreshold syndromes (other depressive disorder, probable alcohol abuse/dependence, somatoform, and binge eating disorders). In published studies, the PHQ sensitivity ranged from 61% (for "any mood disorder") to 89% (for "panic disorder"), while its specificity ranged from 92% to 99%, using a modification of the SCID as the comparison criterion. Kappa values between the PHQ and the SCID for the diagnoses ranged between 0.54 and 0.84 (157). There appear to be no significant differences in specificity, sensitivity, and kappa statistics between the PHQ and the clinician-administered PRIME-MD (157,159). The PHQ has more recently been applied outside of primary care settings, including inner city and uninsured populations (160–164).

In summary, brief instruments such as the PHQ appear promising for application in community-based treatment settings. Modules for several disorders common among substance-dependent patients, such as post-traumatic stress disorder, pathological gambling, and attention deficit hyperactivity disorder, would need to be added, and evaluations of reliability and validity would be needed in substance abuse treatment settings. Such instruments, at present, do not make distinctions between primary and secondary disorders. Ideally, their role would be one of screening, to be followed up by expert consultation and detailed psychiatric evaluation. However, it remains an empirical question as to the extent to which such brief instruments may successfully compete with more detailed instruments and evaluations at selecting treatable comorbid disorders among substance-dependent patients.

CONCLUSION

Research on comorbid psychiatric and substance use disorders has reached an exciting stage. Improvements in nosology and in the design of structured diagnostic instruments have culminated in the DSM-IV criteria, reflecting a consensus in the field, supported by emerging empirical data, that psychiatric disorders such as depression can be reliably diagnosed among substance-dependent patients, and that "primary" and "substance-induced" categories can be distinguished reliably and may have prognostic implications and warrant clinical attention. Advances in psychiatric genetics and biological psychiatry have begun to suggest pathophysiologic processes and related behavioral traits that may underlie addictions and co-occurring disorders such as sociopathy and depression. More research is needed in all of these areas, particularly to examine the implications of diagnostic categories, as well as biological findings, for treatment planning. More research is needed, as well, on efficient methods for identifying comorbid disorders in

community-based substance abuse treatment settings, and on optimal methods for integrating treatment for co-occurring disorders into the fabric of substance abuse treatment.

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4
Overview of Treatment Modalities for Dual-Diagnosis Patients

Pharmacotherapy, Psychotherapy, and 12-Step Programs

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INTRODUCTION

For the past 15 years, interest in developing and implementing new treatments for patients dually diagnosed with substance use disorders and coexisting psychiatric disorders has grown significantly (1–4). One major reason for this attention has been the fact that this patient population has traditionally had poor outcomes; when compared with individuals with either disorder alone, dually diagnosed patients have an increased rate of hospitalization, medication non-compliance, homelessness, criminality, and suicide (5–8). Research in the early 1980s by McLellan et al. (9,10) demonstrated the ineffectiveness of certain forms of traditional substance abuse treatment for psychiatrically ill substance abusers; this served as an impetus for clinicians and researchers to develop treatment approaches that are specifically suited to dually diagnosed patients.

In this chapter, we will present an overview of these treatment methods. Since the treatment of many specific subpopulations of dually diagnosed patients will be discussed in detail later in this book, we will not present in depth the full scope of the work being done in this field. Rather, we will focus on some of the major themes that have dominated this subject area, and will discuss issues that continue to present particular difficulty to clinicians and researchers in the field.

THE IMPORTANCE OF HETEROGENEITY AMONG DUALLY DIAGNOSED PATIENTS

One unfortunate byproduct of the interest in patients with coexisting psychiatric illness and substance use disorders has been the fact that the term “dually diagnosed patient” has often been used as if this were a discrete category of patients, requiring “dual-diagnosis treatment.” Our group (11) has previously discussed the problems inherent in this categorization; one would never find a ward in a general hospital strictly for patients with two *medical* disorders. It is similarly important to recognize the heterogeneity of patients dually diagnosed with both a substance use disorder and a psychiatric illness. Thus, in

devising a treatment plan for a dually diagnosed patient, one should consider the specific substance use disorder(s), other Axis I and/or Axis II disorder(s), and coexisting medical conditions. The clinician then needs to evaluate all of the various disorders as well as their interactions. Consider, for example, the case of a diabetic patient with a narcissistic personality disorder who develops chronic pain as a result of a peripheral neuropathy. The patient is prescribed opiates for pain relief, and abuses them by taking more than the prescribed dose. He eventually feels discouraged by the pain and his illness, and becomes severely depressed. This "dually diagnosed" patient is then referred for evaluation and treatment. Which are the "two" diagnoses? Clearly, this patient has six important diagnoses, namely diabetes, peripheral neuropathy, chronic pain, depression, narcissistic personality disorder, and opioid use disorder. Only by performing a careful evaluation and attending to the interaction of these disorders, as well as to other important phenomena such as presence or absence of family support, employment, and stable housing, can one formulate an appropriate comprehensive treatment plan.

Different psychiatric disorders may have highly varied relationships with specific substance use disorders. For example, Brown et al. (12,13) found symptoms of depression and anxiety to abate quite dramatically over the course of one month and three months, respectively, in male alcoholics treated in a VA setting. Conversely, there are some reports that women with coexisting posttraumatic stress disorder (PTSD) and substance use disorder may experience an exacerbation of their PTSD symptoms upon attaining early abstinence (14–16). Therefore, in devising a treatment strategy for a dually diagnosed patient, it is critical to understand the relationship between that individual's two disorders, including the impact of improvement or worsening of one disorder on the other.

Drug choice may also vary according to psychiatric diagnosis, although there are conflicting findings in this area. For example, in a study that our group conducted, 37% of 350 patients hospitalized for drug dependence had a concurrent Axis I psychiatric disorder other than substance dependence (17). Cyclothymic disorder was significantly more common among cocaine-dependent patients, while generalized anxiety disorder and panic disorder were more prevalent among those dependent upon sedative-hypnotic drugs. Moreover, "harder drugs" such as cocaine and opioids consistently show a higher association with trauma and the diagnosis of PTSD than do marijuana or alcohol (which are presumably "less severe" substances) (18). Other studies, however, have not demonstrated a clear link between specific drug preference and psychiatric symptoms or diagnosis. A recent study by Aharonovich et al. (19), for instance, showed that, while a sample of treatment-seeking individuals diagnosed with cocaine or opioid dependence had high levels of depression and anger, subjects diagnosed with heroin dependence were more likely to have depression and subjects diagnosed with cocaine dependence were more likely to have difficulties with anger. This finding could be seen as contradicting the hypothesis (20) that a sedating drug such as heroin would be preferred by patients with higher levels of anger and that a stimulating drug such as cocaine would be preferred by patients with higher levels of depression. Indeed, Mueser et al. (21) found little correlation between drug of choice and psychiatric diagnosis among 263 psychiatric inpatients. Rather, these investigators argued that sociodemographic characteristics (e.g., gender, age) and drug availability were more important than diagnosis as determinants of

substance use among psychiatrically ill patients.

Integrated vs. Parallel or Sequential Treatment

One of the fundamental clinical and research issues that arises in the treatment of dually diagnosed patients is the question of whether a patient with coexisting substance use disorder and psychiatric illness can and should simultaneously receive treatment for both illnesses from the same staff in the same setting (i.e., integrated treatment), or whether the patient should initially be treated for the problem that is more acute, and then begin treatment for the other problem (i.e., sequential treatment). A third option is "parallel" treatment, in which patients concurrently receive treatment in two settings, e.g., a mental health center and a drug abuse clinic, each staffed by different clinicians. The difficulties inherent in the parallel treatment system have been well described (22,23). One of the major problems with parallel or sequential treatment is the fact that psychiatric and substance abuse treatment programs frequently have different philosophical orientations. Psychiatric programs often downplay substance use, or see it as merely a secondary problem or as a form of "self-medication" that will resolve with treatment of the psychiatric disorder. In some psychiatric settings (particularly for patients with psychotic disorders), substance use disorders frequently go undiagnosed (24–27).

Staff in substance abuse programs, on the other hand, are frequently confrontational about substance use and might, conversely, attribute too many psychiatric symptoms to substance use. For example, depression or lack of motivation may be seen as a manifestation of self-pity or a lack of effort to resolve one's substance abuse problem. Manic irritability may similarly be misinterpreted as willfulness and denial of substance use. Thus, confrontation may extend beyond substance use to psychiatric symptoms. In some substance abuse treatment settings, certain psychiatric symptoms, such as those that occur following trauma, are neglected. Clinical staff may be reluctant to deal with psychiatric symptoms or may be ill informed about the assessment of disorders such as PTSD (25,28).

Patients may therefore receive different treatment experiences in a parallel or sequential treatment model, on the basis of initial routing to a substance abuse or a psychiatric treatment setting. Moreover, as described above, patients who receive parallel or sequential treatment in different settings are likely to receive different feedback from the staff members who treat them. This can be quite confusing, particularly if communication between the two programs is infrequent and not well organized. Unfortunately, this state of affairs is quite common, and patients are likely to suffer as a result.

Although many clinicians and researchers have long advocated an "integrated" approach to the treatment of patients with substance use disorders and coexisting psychiatric illness, no single method is agreed upon to accomplish this goal. Integrated models have been developed primarily for patients with schizophrenia (29–38), but also for patients with bipolar disorder (39,40), personality disorders (41,42), posttraumatic stress disorder (43–45), and depression (46). These models provide integrated treatment in a variety of ways. Strategies include discussing commonalities between the disorders; alternating between sessions focusing on psychiatric issues and sessions focusing on

substance use issues; providing intensive case management; and stressing the importance of compliance with medication.

Several studies in the 1980s and early 1990s suggested that certain forms of integrated treatment of patients with dual disorders could improve outcome. Kofoed et al. (47) developed an outpatient program for severely mentally ill patients and found that patients who stayed in the treatment program experienced a reduction in hospital occupancy. Hellerstein and Meehan (48) also reported a substantial decrease in hospital days among patients who entered a weekly outpatient therapy group for individuals with schizophrenia and substance abuse. Ries and Ellingson (49) found that integrating psychiatric and substance abuse treatment on an inpatient psychiatric unit was also beneficial, as patients who attended substance use discussion groups were more likely to be abstinent during the month following discharge from the hospital. Drake et al. (50) showed dramatic long-term results from an integrated dual diagnosis treatment approach; over 60% of chronically mentally ill patients enrolled in their program had achieved stable abstinence at four-year follow-up. One negative study of integrated treatment from that era was reported by Lehman et al. (51), who found no reduction in substance abuse among dually diagnosed patients in an integrated program after a year.

Although the majority of studies have shown favorable outcomes from an integrated approach, many published studies of integrated programs have consisted of reports from pilot projects, with small sample sizes and/or no control groups. Hellerstein et al. (36), however, conducted a prospective study that compared an integrated model of treatment for 23 patients with schizophrenia and substance use disorder to a non-integrated (parallel) treatment model (N=24). They found treatment engagement and retention to be significantly better in the group receiving integrated treatment. Similarly, Drake et al. (34) compared treatment outcomes for 159 homeless adults who received integrated treatment (IT) for severe mental illness and a co-existing substance use disorder to 59 homeless adults who received parallel treatment (called standard treatment or ST) for the same psychiatric conditions. When compared to the ST group, the IT group had greater numbers of days in stable housing, fewer days in an institutional setting, greater progress toward recovery from substance abuse (measured by the stage of substance abuse treatment), and greater improvement in their alcohol use disorders. Moreover, descriptions of other integrated treatment approaches for schizophrenia (29–33,37,38,52), posttraumatic stress disorder (43–45), personality disorders (41,42), bipolar disorder (39), and depression (46) have also been published. While the initial results of studies of integrated treatments for dual disorders with small sample sizes are encouraging (29–33,36,40,43,53,54), further empirical research of integrated treatment of dually diagnosed patients, using control groups and larger samples, are needed to demonstrate which specific integrative strategies are most successful for which populations. In the remainder of this chapter, we will review some of the major findings of pharmacologic, psychotherapeutic, and self-help approaches that have been used in the treatment of dually diagnosed patients.

PHARMACOTHERAPY

The use of pharmacotherapy for the dually diagnosed patient has generally been targeted to treat the patient's psychiatric illness rather than the substance use disorder. Such an approach has several goals. First, it is hoped that the medication will be effective in treating the disorder for which it was designed. Moreover, with the relief of psychiatric symptoms, it is posited that the patient will experience a reduction in substance use as a result of having improved mood, less anxiety, better judgment due to fewer psychiatric symptoms, and increased ability to engage in and profit from psychosocial treatment. Many practicing clinicians, however, are reluctant to prescribe psychoactive medications for patients who are actively abusing substances. Reasons for this include: 1) fear of a toxic interaction between a patient's drug(s) of abuse and prescribed medication; 2) fear that patients who are actively abusing drugs or alcohol are unlikely to experience improvement in their psychiatric disorders because of the deleterious effects of substances of abuse on mood, anxiety, cognition, or psychotic symptoms; 3) a fear of "enabling" the patient, accompanied by the hope that issuing an ultimatum (e.g., "I won't prescribe you an antidepressant until after you have stopped drinking") will motivate the patient to abstain; 4) a fear of being manipulated by a substance-abusing patient, even if the clinician is unclear about the patient's potential ulterior motive; and 5) an impression that the patient's psychiatric symptoms are substance-induced, and that medication is thus unnecessary.

Research findings from studies of the pharmacotherapy of dually diagnosed patients should alleviate some of the concerns described above. Specifically, Saxon and Calsyn (55) found, by conducting psychiatric evaluations on patients entering an outpatient VA substance abuse program and then pharmacologically treating coexisting psychiatric disorders, that outcome at the end of one year was as favorable for the dually diagnosed patients as for the patients with substance use disorder alone. Moreover, a number of double-blind, placebo-controlled studies of patients with substance use disorders and coexisting mood or anxiety disorders have shown a beneficial effect of the medication on the disorder for which the medication is targeted (e.g., improvement in depressive symptoms among patients receiving an antidepressant), and a less dramatic (but not countertherapeutic) effect on substance use (56,57). In one study, however, treatment with desipramine improved major depression secondary to alcohol dependence, and also prolonged abstinence from alcohol (58). In addition, untreated major depression has been shown to be associated with negative drinking outcomes. A study by Greenfield et al. (59) found that, while hospitalized patients dually diagnosed with alcohol dependence and major depression relapsed three times more quickly following discharge than did those without a depression diagnosis, those with major depression who were not prescribed an antidepressant at the time of discharge relapsed more quickly than those with depression who received antidepressants at the time of discharge. The treatment of co-occurring psychiatric disorders, therefore, is an important component of the overall treatment of patients diagnosed with substance use disorders; failure to treat the psychiatric disorders may result in poorer substance use outcomes for patients with dual disorders.

The effect of pharmacotherapies on dually diagnosed patients has been studied most thoroughly for depression. This literature is well summarized by Nunes and Quitkin (60), whose group has studied the treatment of depression in patients dependent on alcohol (61) and opioids (62). They reported similar findings in both instances—specifically, a relatively good antidepressant effect and a more modest effect on substance abuse. Studies of the safety and effectiveness of antidepressants in the treatment of individuals with depression and coexisting substance use disorder are important because they address some of the central concerns of practitioners who treat these dually diagnosed patients. Specifically, these studies help to allay concerns about the futility of treating depression in patients who are using drugs that may adversely affect mood. Moreover, they address the important question of whether prescribing psychotropic medications for patients who are abusing substances represents a form of "enabling." Although the use of antidepressants for depressed patients does not generally lead to substantial improvement in their substance use, it does not *worsen* substance use, as would be the case if this were a form of "enabling" behavior. In fact, studies of fluoxetine in depressed alcoholics (63–65) and venlafaxine in depressed, cocaine-dependent individuals (66) have shown improvement in depressive symptoms as well as reductions in alcohol and cocaine use, respectively. One study by Pettinati et al. (67), however, found that a lifetime diagnosis of major depression in alcoholics was associated with a poorer response (as measured by drinking frequency during the 14-week study period) to sertraline than to placebo. The conflicting findings between the study of sertraline (67) and the studies of fluoxetine (63–65) and venlafaxine (66) emphasize the importance of further study of antidepressants for the treatment of substance use disorders and coexisting major depression to determine which medications may be most efficacious for specific subgroups of dually diagnosed patients.

Even if antidepressant treatment of depressed alcohol-dependent patients does not result in a reduction in drinking behavior, improvement of depression (with its attendant morbidity and mortality) is itself an important goal, analogous to the appropriate treatment of coexisting medical illness. It is unthinkable, for instance, that anyone would recommend withholding treatment for pneumonia from a drug-dependent patient on the grounds that the treatment would enable the patient's addiction. Properly diagnosed depression and other psychiatric illness should be treated similarly.

There has been very little research on the pharmacological treatment of patients with bipolar disorder and substance use disorders; we are aware of only three small open trials with this population: two with lithium (one positive, one negative) (68,69), and one with valproate (70). The latter report was relatively encouraging in that nine patients in the trial tolerated valproate well and showed improvement in both mood and substance use. In one double-blind, placebo-controlled study of lithium in adolescents with bipolar disorder and substance dependence, Geller et al. (71) found that treatment with lithium was effective for both disorders. However, the open nature of three of these trials and the small sample sizes of all four studies are significant limitations.

Research involving patients diagnosed with both substance use disorders and anxiety disorders is also sparse. Although Quitkin et al. (72) long ago reported a successful trial of imipramine in a small group of patients with coexisting substance abuse and panic disorder (both drinking and panic attacks improved), little research has since been

conducted with this subgroup of dually diagnosed patients. Two studies of patients with generalized anxiety disorder and substance use disorder revealed a beneficial effect of buspirone on anxiety (73,74). However, drinking behavior did not improve in one of the studies, and substance use was not assessed as a treatment outcome measure in the other study. A double-blind, placebo-controlled study by Kranzler et al. (75) showed the potential benefits of buspirone in a group of 61 anxious alcoholics (i.e., they scored 15 or higher on the Hamilton Anxiety Rating Scale (76) after a week of abstinence from alcohol). Patients who received buspirone were more likely to remain in the 12-week treatment trial and had lower levels of anxiety (although only among a subgroup with the highest pretreatment anxiety levels), a slower return to heavy drinking, and fewer drinking days during the 6-month post-treatment follow-up. Finally, a recent 8-week, double-blind, placebo-controlled study of paroxetine for patients with social anxiety disorder and coexisting alcohol dependence demonstrated significant reductions in symptoms of anxiety for patients treated with paroxetine (77). However, no significant differences in alcohol use outcomes between the paroxetine and placebo groups were found.

Few issues generate as much controversy as the use of benzodiazepines for patients with an anxiety disorder and a coexisting substance use disorder (78). Indeed, some authors (79) assert that this class of medications is contraindicated in substance-dependent patients except during detoxification, since benzodiazepines can cause physical dependence, be abused, and serve as a trigger for other substance use. Other authors (80–83), however, have argued for the judicious use of these medications in patients who cannot take other pharmacological treatments or who fail to respond to them. Additionally, a study of the treatment of PTSD with benzodiazepines for VA patients with coexisting substance use disorders revealed both a decrease in PTSD symptoms and utilization of outpatient health services, without demonstrating an increase in substance abuse (84). These findings, however, apply to a specific patient population with PTSD and substance use disorders, and may not apply to other patients with the same disorders or to patients with other anxiety disorders. More systematic studies of this topic are needed, since clinicians often encounter substance-abusing patients who are currently being prescribed clonazepam or another benzodiazepine, most commonly for an anxiety disorder. The decision regarding whether to continue the benzodiazepine is a complicated one; factors to consider include the level of certainty of the diagnosis, the adequacy of previous trials of alternative pharmacological treatments, and whether psychological treatment approaches alone could allow the patient to cope with his or her anxiety.

Another highly controversial topic is the treatment of patients diagnosed with both attention deficit hyperactivity disorder (ADHD) and substance use disorders. Several case reports (85,86) have supported the potential efficacy of stimulants in the treatment of patients with these coexisting disorders. In their 12-week, open-label trial of sustained-release methylphenidate in 12 patients with ADHD and cocaine dependence, Levin et al. (87) demonstrated significant improvement in both symptoms of ADHD and cocaine use. One must be concerned, however, about the potential abuse of stimulants in a drug-dependent population, particularly among those patients who are not diagnosed with ADHD (88) or who receive that diagnosis mistakenly. Because of its low abuse potential,

bupropion may prove to be a promising alternative to stimulants for patients with ADHD and substance use disorders. A recent single-blind study of bupropion for the treatment of cocaine dependence and adult ADHD reported decreases in both cocaine use and symptoms of ADHD (89). Larger, controlled clinical trials will be necessary to assess its efficacy in this patient population. In addition, the recent approval by the US Food and Drug Administration of atomoxetine, a selective norepinephrine reuptake blocker, for treatment of ADHD, may offer another option in the treatment of the disorder among patients with substance use disorders.

Research investigating pharmacological treatment of patients with coexisting schizophrenia and substance use disorders has expanded with the introduction of atypical antipsychotic agents. Previously, most studies of these patients had focused on psychosocial treatment, with patients receiving standard neuroleptic pharmacotherapy. One randomized pharmacotherapy study with this population was conducted by Ziedonis et al. (90), who compared the combination of desipramine and antipsychotic agents to antipsychotic medications alone for patients with schizophrenia who were abusing cocaine. Patients who received desipramine had significant fewer cocaine-positive urine drug screens during the third and final month of the trial.

More recently, a number of studies have focused on the potential utility of atypical antipsychotic medications for treating patients diagnosed with schizophrenia and substance use disorders. Treatment with clozapine has been shown to decrease craving for cocaine (91) and reduce substance use (92–96). A retrospective chart review study by Zimmet et al. (96) showed that clozapine reduced both overall clinical symptoms and substance use in a sample of 43 patients diagnosed with coexisting schizophrenia or schizoaffective disorder and a substance use disorder. At the present time there are no published randomized, clinical trials examining the efficacy of clozapine for the treatment of patients with schizophrenia and coexisting substance use disorders.

In their 12-month, prospective, open label trial of olanzapine, Littrell et al. (97) reported significant reductions in psychopathology and substance use in 30 patients diagnosed with either schizophrenia or schizoaffective disorder and a coexisting substance use disorder. Similarly, a 6-week, open-label study comparing risperidone to standard neuroleptics in 18 patients diagnosed with schizophrenia and cocaine dependence found that treatment with risperidone resulted in significantly less cue-elicited cravings and fewer relapses at the end of the study period (98). The results of studies of atypical antipsychotics for treatment of substance use disorders in schizophrenia must be viewed with caution because of small samples and a lack of control groups. More studies are necessary to determine whether atypical antipsychotic medications will be effective in treating coexisting substance use disorders in patients with schizophrenia.

While most medication studies involving patients with schizophrenia and substance use disorder primarily target schizophrenia, a small 8-week, open-label, prospective trial of naltrexone administered three times per week to individuals diagnosed with schizophrenia and coexisting alcohol abuse or dependence demonstrated reductions in both psychotic symptoms and alcohol use (99). The greatest reductions in alcohol use were seen among those patients with higher levels of baseline drinking. Naltrexone may play a role in the treatment of schizophrenia and alcohol dependence, but randomized,

clinical trials with larger samples are needed to determine its efficacy in this patient population. Furthermore, the degree to which improvement in schizophrenia symptoms is directly due to reduced drinking should also be examined.

In summary, pharmacological treatment of dually diagnosed patients is generally helpful for the targeted psychiatric disorder, and is sometimes (although generally less robustly) beneficial for the substance use disorder. In general, the fears that many clinicians harbor regarding the prescription of psychotropic medications for this population have not been borne out by empirical studies. However, more well-designed clinical trials are needed in this area.

PSYCHOTHERAPY

Currently, there is substantial interest in the development of psychotherapies for dually diagnosed patients. Indeed, interest in psychotherapy for substance abuse per se is itself a relatively recent phenomenon. For most of the 20th century, therapists did not attend to substance abuse, and saw psychotherapy for this population as contraindicated.

However, as drug abuse attracted increasing attention as a public health problem, and as attempts to develop effective pharmacotherapies (particularly for cocaine dependence) were disappointing, interest grew in the development of new psychotherapeutic treatments (100). Recent years have seen the adaptation of psychodynamic approaches for substance abuse patients (101,102). These include the seminal cognitive-behavioral work by Marlatt and Gordon (103) that launched the area of relapse prevention, the development of motivational enhancement therapy (104), and several creative behavioral treatments for substance abuse, such as contingency management (105–107) and cue exposure (108,109). A natural outgrowth of such developments has been their application to dually diagnosed patients with schizophrenia (29–38,52,110), PTSD (43–5), personality disorders (41,42,53), depression (46), and bipolar disorder (39,40).

Preliminary studies of psychotherapies for dual disorders have shown some promising results. Brady et al. (43) found that a combination of exposure therapy to treat PTSD and cognitive-behavioral techniques to treat cocaine dependence resulted in significant decreases in PTSD symptoms and cocaine use both during treatment and over a 6-month follow-up period. Similar decreases in psychiatric symptoms and substance use have also been reported in studies of a modified dialectical behavioral therapy (DBT) for borderline personality disorder (53), social skills training and motivational interviewing for schizophrenia (29,31,36,37), and cognitive-behavioral therapy for PTSD (54) and bipolar disorder (40). However, it is important to note that, while these initial results are promising, much more remains to be achieved. Many of these studies represent early-stage work that needs refinement (e.g., elucidation of the impact of external treatments, application to larger samples, and comparison to randomized control conditions).

The use of psychotherapy becomes particularly important when other treatments are either ineffective or contraindicated for particular dually diagnosed patients. Consider the case of a patient with severe borderline personality disorder who abuses cocaine. There is currently no standard psychopharmacological treatment for either borderline personality disorder or cocaine dependence. While 12-step self-help groups may be useful, they are

unlikely to resolve many of the patient's problems such as poor interpersonal relationships and self-destructiveness. Psychotherapy may be particularly helpful for such a patient. In contrast, some alcoholic patients with major depression might be successfully treated with a combination of disulfiram or naltrexone, an antidepressant, and Alcoholics Anonymous meetings. The extent to which a particular dually diagnosed patient needs psychotherapy must therefore be assessed on a case-by-case basis, particularly since resources for treatment are often scarce. In short, psychotherapy should be neither automatically eschewed ("just send them to Alcoholics Anonymous") nor uniformly prescribed.

Psychotherapy may be helpful to a variety of dually diagnosed patients. Those patients with long-standing psychiatric disorders for whom functional deficits remain even after resolution of acute psychiatric or drug-related symptoms may benefit from having such problems as poor socialization or employment difficulties addressed in supportive psychotherapy. Psychotherapy may also be helpful for patients who are at risk for an exacerbation of psychiatric symptoms during early abstinence (e.g., patients with PTSD), those with erratic medication compliance (111), and those with psychiatric illnesses that make it difficult for them to appreciate the severity of their substance use problems (112).

Although empirical research on the psychotherapy of dually diagnosed patients is still relatively sparse, certain common principles have emerged from descriptive reports of psychotherapeutic approaches with chronically mentally ill substance abusers (30,113–115). First, such treatment needs to proceed in stages, using a longitudinal, long-term perspective. Although substance abuse treatment settings generally emphasize the importance of abstinence as an immediate (as well as long-term) goal, many patients with severe mental illness and substance use disorder do not even perceive substance use to be problematic. Moreover, they often react negatively to the type of confrontation that is common in substance abuse treatment settings. For these reasons, the psychotherapeutic approach to the dually diagnosed patient should be informed by knowledge of Prochaska and DiClemente's five stages of readiness to change substance use behaviors: precontemplation, contemplation, preparation, action, and maintenance (116). Thus, for patients who are contemplating whether substance use is a problem, the goal of treatment is to discuss their ambivalence rather than to practice drug refusal skills. The latter is important in the action phase of treatment when the patient's central question is *how*, not *whether* to get sober.

Osher and Kofoed (114) have divided the psychotherapy of dually diagnosed patients into four phases, which are consistent with a longitudinal approach. In *engagement*, the therapist tries to make a connection with the patient, and attempts to convince him or her that treatment may offer something beneficial. During *persuasion*, the goal is to convince the patient that substance use is a problem, and that he or she should therefore try to abstain. This stage of therapy consists primarily of motivational interventions based on the work of Miller and Rollnick (104), including a) expressing empathy, b) pointing out discrepancies between the patient's goals and his or her current behavior, c) avoiding argumentation, which generally increases resistance to change, d) rolling with resistance, rather than challenging it, and e) supporting self-efficacy by expressing confidence in the patient's ability to make changes. A recent small study by Martino et al. (117) indicates some promise for the use of motivational interviewing techniques with dually diagnosed

patients.

During the stage of persuasion, providing education about the negative consequences of substance use and the potential benefits of abstinence can be very important. Since severely and persistently mentally ill patients are frequently demoralized, they may feel that they have nothing to lose by using substances to gain a few hours of escape. A thorough discussion of potential adverse consequences of substance use (e.g., physical damage, medication non-adherence, worsening psychiatric status, estrangement from friends and family) may help persuade a patient of the potential benefits of abstinence. This stage of treatment may be quite lengthy and needs constant reinforcement, since the desire to resume substance use can return at any time.

A*ctive treatment* is most familiar to clinicians in the substance abuse field, since it focuses on techniques to achieve abstinence: learning drug and alcohol refusal skills, recognizing and avoiding high-risk situations, dealing with craving, and beginning to establish a drug-free lifestyle. Self-help group attendance is generally most beneficial if begun during this phase.

Finally, *relapse prevention* attempts to solidify the gains made during the previous stages of treatment. During this stage, the patient identifies relapse triggers and ways of dealing with them, learns about the abstinence-violation effect, and develops positive coping behaviors to deal with risky situations, including “lapses” and “slips.”

Throughout the process, the therapist needs to search for areas of common ground with the patient. For example, if the patient does not see substance use as a problem in its own right but is worried about depression, the therapist may stress the adverse effects of substance use on mood. Thus, one may help enhance motivation for substance abuse treatment by linking the substance use to an issue that the patient *does* want to change (e.g., depression). Finally, dually diagnosed patients often need concrete training in social skills, both to help them attain abstinence (e.g., drug refusal skills) and to aid them in other life areas, such as job interviews and social relationships.

Psychotherapy with dually diagnosed patients presents special challenges for the therapist. For example, as one disorder improves or worsens, it is likely to affect the other, often in unpredictable ways. Abstinence may exacerbate PTSD symptoms (15,16) while making depressive symptoms better (12). Similarly, substance use may have a variety of effects on symptoms of the other disorder, depending on the substance, the diagnosis, and the individual patient. The etiological relationship between the two disorders may also vary widely (118). Some patients may be “self-medicating” their psychiatric symptoms, while others will have developed substance abuse first, predisposing them to other psychiatric illnesses. Still other patients will have two disorders that are not clearly related. Such variability may have implications for psychotherapeutic treatment by suggesting alternate interventions for the therapist to pursue (e.g., taking a harm reduction approach rather than an abstinence-oriented stance with a patient whose other psychiatric disorder worsens with abstinence).

In conducting psychotherapy with dually diagnosed patients, therapists must learn to compensate for whichever side of their training is weaker. Most clinicians are more experienced and adept in either substance abuse or mental health, and relatively few receive extensive training in dual diagnosis treatment. The therapist who is relatively less skilled in substance abuse treatment must learn to obtain detailed information about

substance use at each session (e.g., amount, type, and frequency). Obtaining urine drug screens and/or breath alcohol tests is often unfamiliar to psychiatrically oriented clinicians, and may be resisted on the grounds that it conveys distrust of the patient. However, such monitoring provides the most powerful method of accurately monitoring substance use and is quite common in substance abuse treatment settings. Learning the psychobiology of substance use (such as withdrawal and habituation), the language ("craving," "enabling," slang terms for drugs), the lifestyle (e.g., sex-for-drug exchanges, needle-sharing), and the extraordinary ways in which substances come to dominate patients' lives beyond all other concerns may also be new to such a therapist.

The therapist new to substance abuse must learn the need for stabilization before in-depth psychotherapeutic work can begin, and the importance of delaying insightful interpretations and exploration of painful effects in favor of containment and support. There is a need to continually reassess which symptoms are substance-induced and which genuinely reflect another disorder. The therapist also learns the limits of methods that work on single-diagnosis patients. For example, flooding, which is widely promoted for PTSD, may be dangerous for a patient with this disorder who is also prone to a substance abuse relapse.

Clinicians who are more familiar with substance-dependent patients may similarly require new learning. The confrontational approach used in many substance abuse treatment programs may be deleterious for dually diagnosed patients, for whom such interventions may precipitate increased psychosis, depression, anxiety, or other symptoms. Moreover, this approach may increase resistance to substance abuse treatment, leading to an early departure from treatment. The emphasis on 12-step programs may also need to be modified, as is described below in the next section. The therapist may need to become skilled in new treatment interventions, e.g., exposure therapy for obsessive-compulsive disorder, "grounding" for PTSD symptoms, and a motivational, long-term approach for psychotic patients. Knowledge of medications for psychiatric illness, their potential side effects, and their interactions with substances of abuse is also important. On a more subtle level, the therapist will need to acquire a sensitive understanding of how substance use may hold dynamic meanings within the context of another disorder. In a depressed patient, substance use may represent a "reward" for long-term suffering; in a patient with bipolar disorder, it may represent a desire to precipitate euphoric mania; in a patient with PTSD, it may represent retaliation against an abuser. Exploring the patient's past may also take up more of the session to understand how the substance use and psychiatric illness have intertwined to affect the patient's development. Progress may be slower than in patients with a single disorder; setting realistic treatment goals may mean giving up immediate expectations of abstinence and thinking of treatment as a long-term endeavor. Outcome assessment is thus likely to become more complex, comprising a broader array of domains.

An integrated treatment model requires integration within the person of the therapist, as well as in the structure of the treatment program. The therapist who can fluidly move between the worlds of substance abuse and mental health is likely to be most effective. Such a therapist is also willing to take on tasks not previously emphasized within the domain of psychotherapy: case-management work such as helping the patient locate housing, calling to set up an HIV test for the patient, helping the patient to obtain public

assistance, making oneself increasingly available outside sessions, and carrying out an involuntary commitment to prevent violence. On an emotional level, the therapist may need to face strong counter-transference issues such as viewing a substance abuser as a "low-life," a "morally weak" person, or "manipulative" (119). In turn, therapists sometimes view patients with other psychiatric illnesses as "hopeless" or "making an excuse for substance use." Developing an optimistic, compassionate stance in treating the dually diagnosed patient (48) may take considerable effort.

In conclusion, the future development of psychotherapies for dually diagnosed patients should draw on the advances in both individual and group treatment models as well as the understanding of the skills that therapists should possess in order to enhance patient care.

12-STEP PROGRAMS

The use of 12-step, self-help or mutual-help programs such as Alcoholics Anonymous (AA) for dually diagnosed patients is a subject of great interest and some controversy. It is in this area that a parallel treatment approach can be most problematic. Although many dually diagnosed patients find self-help groups enormously helpful because of their structure, role modeling, practical advice, and optimism, some of these very characteristics may make a number of patients, particularly those with more severe mental illness, feel more alienated (120).

A patient with a longstanding history of depression and alcohol dependence was asked about his opinion of AA. He said, "I hate it." When asked why, he said, "It's too upbeat. I don't want to hear about people's job promotions and hear about the 'joys of recovery.' I don't want to see pictures of people's grandchildren and hear how their lives have been turned around. I'm miserable, and I want company."

This quotation echoes a common theme among patients with psychiatric illness, some of whom find it difficult to relate to the degree of life improvement that so many AA members experience as the result of abstinence. Indeed, some individuals who remain depressed despite their sobriety are sometimes accused of wallowing in self-pity ("sitting on the pity pot") by other AA members. Some psychiatrically ill patients are criticized for taking medication, despite official AA publications to the contrary. When dually diagnosed patients heed the advice of well-meaning but misguided AA members who suggest that they stop their medication, disaster may ensue.

Another problem that frequently arises when dually diagnosed patients attend self-help meetings is the fact that the clinicians treating them often have unrealistically lofty expectations of self-help meetings. Psychotic patients who have long been socially withdrawn may be expected to relate to AA members in a way that they have been unable to relate with anyone else in recent memory. Integrated dual-diagnosis treatment programs may help to alleviate these difficulties, since the staff is familiar with both the psychiatric illness and the characteristics of self-help meetings. Patients who are helped to review and process what happens at 12-step meetings may benefit much more from them.

Paying attention to a patient's motivation for treatment is also critical in helping to advise him or her regarding 12-step meetings. Ziedonis and Fisher (52), for example,

have written about a longitudinal treatment program for schizophrenic substance abusers, based on the "readiness to change" model described above. Since self-help groups are part of the "action" stage, it is important to recommend them for patients who are most likely to be receptive, since the goal in having patients attend AA or other self-help meetings is for them to attend them *regularly*, not just once. The likelihood of regular attendance is enhanced if a patient's initial experience with AA is positive. Thus, it is less helpful to have patients attend such meetings if they are at only the precontemplation or even the contemplation stage. A study by Jerrell and Ridgely (121) compared a 12-step recovery approach (i.e., patients were taken to or referred to AA meetings, received help with finding a sponsor, and received ongoing supportive counseling to help manage the 12-step recovery process) with two other treatment models—behavioral skills training and intensive case management—for 132 patients with substance use disorder and severe psychiatric illness. Patients receiving the 12-step approach fared considerably worse on measures of psychosocial functioning and symptom changes than did the other two groups. It is important to note, however, that 12-step meetings such as AA are "programs of attraction," and are thus designed to help only a subgroup of patients. It is quite possible that blending aspects of a 12-step model into an overall integrated dual-diagnosis program that includes pharmacotherapy, behavioral skills, and case management may yield better results.

Recent evidence has suggested that 12-step groups that are specifically designed for psychiatrically ill individuals may be quite helpful. With the development of Double Trouble in Recovery (DTR), a 12-step self-help group for persons diagnosed with a substance use disorder and mental illness, dually diagnosed patients have a forum where they can discuss their psychiatric illness without fear of criticism from other group members. Recent research has demonstrated that participation in DTR may increase the likelihood of compliance with psychotropic medications. Magura et al. (122) found that patients who attended weekly DTR meetings had better self-reported compliance with their medications than did those patients who attended DTR less frequently. While these findings are promising, more research on DTR will be necessary to validate them with objective measures of compliance and to determine whether this 12-step self-help group will be beneficial for larger groups of dually diagnosed patients.

SUMMARY

The development of treatments for dually diagnosed patients is an exciting and productive area of psychiatric research. Both pharmacological and psychological treatment approaches to specific subgroups of dually diagnosed patients have been formulated, empirical testing is proceeding, and outcomes have been quite promising. The future of dual-diagnosis treatment is likely to include the continued refinement of these treatments; better integration of psychological, pharmacological, and self-help therapies; more controlled outcome studies; improved training of clinicians; and new standards of care.

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5
Multiple Substance Use and Multiple Dependencies

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INTRODUCTION

It is surprising that so little attention has been paid to what has long been known: most drug misusers take a range of different substances. This simple fact is known to all who work with drug misusers. Yet, perhaps due to the large number of potential combinations of substances and routes of administration, multiple substance use has seldom been the specific topic of research investigations, and its implications have only occasionally been explicitly discussed in the addictions literature. The issue of multiple substance use is more problematic, more complex, and more interesting than is usually assumed.

A useful way of understanding its complexity is to conceptualize it as being represented in terms of three dimensions. These are:

consumption behaviors;
problems (e.g. health, social functioning);
dependence.

These dimensions can be regarded as being conceptually distinct and separate. In reality, they tend to be related in a number of ways. This chapter begins with a discussion of commonly reported patterns of multiple substance misuse. It examines the ways in which different drugs, including alcohol, are actually used, and questions traditional conceptualizations of these issues. The chapter moves on to consider in more detail the implications of the distinction between consumption behaviors, dependencies, and problems. It also gives further attention to the implications of this distinction, especially with regard to the assessment and treatment of multiple dependence. The realities of multiple substance use and multiple dependencies require that these issues be more explicitly addressed in the investigation and treatment of substance misuse disorders.

PATTERNS OF MULTIPLE SUBSTANCE MISUSE

The first dimension refers to the behavioral parameters of drug taking. The most obvious features of drug consumption behavior involve frequency and quantity of drug use. Many misunderstandings arise through a failure to distinguish between infrequent, frequent, and

regular patterns of use, or between low-dose and high-dose use. Different drug consumption behaviors are related to different types of risks and problems.

Since the 1960s, heroin has consistently been the most frequently reported "main" problem drug among drug misusers in treatment in the United Kingdom. However, cocaine, amphetamines, and benzodiazepines are also widely misused by drug users seeking treatment for heroin dependence (1). Heroin use almost never occurs in isolation. The extent of multiple substance misuse (including heavy drinking) is shown in Fig. 1. Almost two-thirds of the drug misusers in this British sample (64%) were current users of three or more substances during the period prior to admission to treatment, and more than one-third were using stimulants on a frequent basis. The most commonly used stimulant among these drug misusers seeking treatment for heroin dependence was crack cocaine.

The prominence of cocaine as a "main" drug among drug users in treatment services in the United States increased greatly between the early 1970s and the early 1990s (2). Cocaine is currently one of the most frequently reported "main" drugs, as well as the most prevalent supplementary drug among methadone maintenance patients in the United States (3), and in many other countries cocaine is one of the more prevalent secondary drugs used by opiate-dependent patients in addiction treatment programs. A rapid increase in the use of crack cocaine by opiate addicts in London occurred during the 1980s (4).

Benzodiazepines are infrequently used as a "main" drug, but they have often been used as part of a pattern of multiple drug misuse and dependence in many countries since the early 1980s. Among heroin addicts treated at the Maudsley Hospital in London, the percentage who were regular users of benzodiazepines doubled between 1988 and 1991. In 1991, about

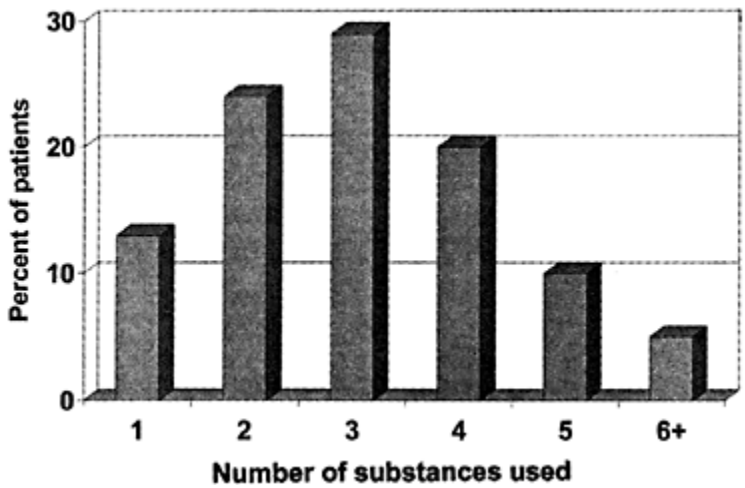

Figure 1 The rates of use for seven substances among patients admitted to drug misuse treatment services in England (25,77). The substances were: heroin, non-prescribed methadone, crack cocaine, cocaine powder, amphetamines, non-prescribed benzodiazepines, and alcohol (heavy

drinking defined as more than 10 units or 80 g of ethanol per drinking day).

one-third were regular users of benzodiazepines, and about half of the regular users were physically dependent, requiring detoxification for a benzodiazepine withdrawal syndrome (5).

Other drugs may also be described as "secondary" drugs. However, the traditional categorizations of drug misusers according to a single drug type are not consistent with contemporary patterns of drug use and abuse. Terms that imply single substance use, such as "heroin addict" or "cocaine user," can be misleading. It is questionable whether it is adequate to classify drug takers according to a primary or "main" drug of preference, with other types of drugs being seen as "secondary." Such drugs may or may not be seen as being problems by the users themselves, but the combined use of several substances can increase the risk and severity of problems, and the use of multiple substances can complicate treatment in various ways.

Other drugs may be used concurrently or sequentially, and there may be several different reasons for multiple drug use. These include:

- *Drug enhancement.* Several drugs may be used at the same time to enhance the psychoactive effect the drug misuser achieves. The combined use of opiates and benzodiazepines, for example, may be intended to increase overall levels of sedation.
- *Modification of effect.* Different drugs may be combined to counteract the adverse or unwanted effects of one or more drugs. Cocaine and heroin may be used together so that either the heroin takes away some of the unpleasant overstimulation and anxiety caused by the cocaine, or the stimulant offsets the sedation of the heroin.
- *Substitution.* The user may take a different drug as a substitute for the preferred drug if it is not available. For example, some heroin users take alcohol in this way. Substitute drugs are sometimes used to self-medicate withdrawal symptoms. Some heroin users take benzodiazepines for this purpose.
- *Social.* For some drug misusers, multiple drug use is largely determined by the social behaviors of their peers. The psychoactive drugs that are available are the ones that are used. This may be reflected by a generalized pattern of multiple drug abuse in which a wide range of substances is taken in what appears to be an indiscriminate manner.

The use of illegal drugs may be the most conspicuous problem among drug addicts, but many of the people who seek treatment for drug dependence also have problematic patterns of drinking. Between 20 and 50% of drug misusers in treatment in the United States are problematic drinkers (6,7). In a national study of drug misusers in the United Kingdom, more than one-third of those who were drinking at intake to treatment reported problematic patterns of alcohol consumption (8). Most of the heavy drinkers were drinking every day, or almost every day, and more than one-third were regularly drinking 30 units (an approximate ethanol content of 240 g) or more per drinking day. Many reported high levels of dependence upon alcohol. Using the Research Diagnostic Criteria for alcoholism, current and overall lifetime rates of alcoholism among opiate addicts in a U.S. program were found to be 4% and 35%, respectively (9). In a U.K. sample of methadone maintenance patients, 41% were found to meet DSM-IV criteria for alcohol dependence in the past 12 months (10).

Drinking may also be linked to the use of different types of drugs. In some circumstances, there may be an inverse relationship between the frequency of use of alcohol and drugs (11,12). Alcohol-dependent drug misusers have been found to be less frequent users of heroin and crack cocaine and more frequent users of stimulants such as cocaine powder and amphetamines and of non-prescribed benzodiazepines (7,13). High rates of cocaine problems have been found among alcohol-dependent drug misusers (14). Some drug misusers may substitute alcohol for drugs after treatment, though this occurs less frequently than has sometimes been suggested (15,16). Where substitution of alcohol for drugs occurs, it is unclear whether this is due to a deliberate choice to replace one substance with another, or whether it represents a gradual generalization of substance misuse patterns in which additional substances are incorporated within the drug-taking repertoire. The drift towards increased use of alcohol among drug misusers is also age-related, with increased use of alcohol among older drug misusers (8).

Drug dependence, including multiple dependence, may also be found among the elderly. The use of multiple prescriptions, and combined use of prescription drugs with heavy drinking, may put elderly people at increased risk of accidents and adverse reactions (17). Where drug taking is excessive, or where drug interactions, including drug-alcohol interactions, lead to drug-related delirium or dementia, this can be wrongly seen as indicative of Alzheimer's disease.

A further important parameter of drug consumption behavior involves the route of administration. This is related to the effect experienced by the user, to dependence liability, to the risk of overdose, and to the risk of infections and other health problems. Where multiple drug use occurs, different routes of use may be involved.

Routes of drug administration which are commonly used by drug misusers are:

oral (i.e., tablets, liquids);
intranasal/snorting/sniffing (e.g., cocaine powder, heroin powder);
smoking (e.g., cannabis, opium);
inhalation (e.g., "chasing the dragon," volatile substances);
injection (i.e., intravenous, intramuscular, subcutaneous/skin popping).

Patterns of drug taking are sensitive to social, environmental, and interpersonal influences. As a consequence, there can be marked geographical differences in the types of drug being used, the amounts taken, or in routes of administration. Patterns of drug taking can change with great rapidity, as is shown by the growth of crack cocaine misuse in the United States during the 1980s (18) and the spread of heroin addiction in Pakistan during the 1980s (19). In the 1960s, all, or nearly all, heroin users in the United Kingdom injected it; currently, almost all heroin users in London start to use heroin by "chasing the dragon" (20). Typically, heroin chasing is done by placing heroin on a piece of tinfoil and heating it until it liquefies, when the user inhales the fumes that are given off from the liquefied mixture.

Changes in routes of cocaine use occurred in many countries during the 1980s. In the United Kingdom, those who first took cocaine before 1986 typically started to use the drug by snorting (65%) or injecting (30%), with only 6% having first used it by smoking (4). Between 1987 and 1989, snorting remained the most common route of first cocaine

use, though about one-quarter of new users were smoking cocaine. After 1990, smoking was the most common route of first use. Similar changes occurred in other countries. In Brazil, the percentage of cocaine users who smoked cocaine increased from 5% to 65% between 1986 and 1997 (21).

Currently, the two predominant routes of heroin administration among regular users in the United Kingdom are injection and chasing the dragon. Although some users report heroin snorting, this is not common and is rarely reported as a primary route (22). Intranasal use of heroin has been described as being more common among heroin users in New York (23). Concern has more recently been expressed about changes in route of administration, with increasing numbers of young people in the United States using heroin by snorting rather than injecting (24).

Preferred routes of drug administration may change. Although only two routes of heroin administration tend to be used in the United Kingdom, more than two groups of heroin users can be identified (22). These include heroin users who first took the drug by injection and who continued to inject (stable injectors); those who first used by chasing and continued to take heroin in this way (stable chasers); those who moved from chasing to injecting; and those who had previously been injectors and who moved to chasing. When compared to initial chasers who had made a transition to injecting, stable chasers were less involved with the heroin-using subculture, they had more social contact with non-users, and they were much less likely to have friends who were heroin injectors. The transition from intranasal use to injection has been described among heroin users in New York (23).

Once a drug user has started to take any drug by injection, this route of administration is likely to be used with other types of drug. There is a greatly increased likelihood that those polydrug users who inject heroin will also take other drugs by injection (25). In a study of drug misusers seeking treatment at programs across England, among those who were current users of both heroin and crack cocaine, heroin users who took the drug by injection were found to be almost 50 times more likely also to have injected crack during the previous 3-month period. (This is an unusual but worrying practice: although crack is not water soluble, it can be converted into an injectable mixture by the addition of acids.) Similarly, they were more than 30 times more likely to have also injected illicit methadone, nearly 20 times more likely to have injected benzodiazepines, and 10 times more likely to have injected amphetamines (see Fig. 2).

Among drug users recruited from treatment services across England, rates of injecting varied between 5% and 58% according to the specific drugs being used (24). Rates of injecting were highest for heroin, and, as in other studies (22), heroin users were approximately evenly divided between injectors and chasers. There were marked regional variations across

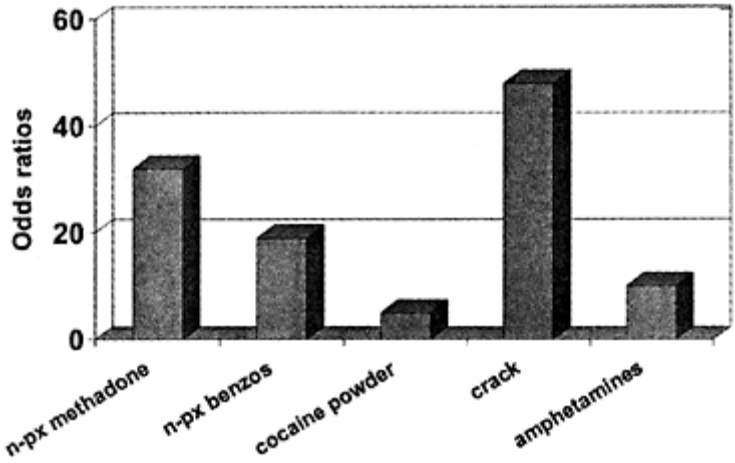

Figure 2 The increased probabilities (odds ratios) of heroin injectors also taking other drugs by injection (25). n-px=non-prescription; benzos=benzodiazepines.

England with regard to the main routes by which heroin, non-prescribed methadone, non-prescribed benzodiazepines, cocaine powder, crack cocaine, and amphetamines were used (24). The geographical variations in drug-taking practices raise questions about the wisdom of talking in general terms about "national" drug problems. It has been suggested that "there is not truly a 'national' problem…[but] a series of local and regional difficulties" (26).

MULTIPLE SUBSTANCE MISUSE, DEPENDENCIES, AND PROBLEMS

Drug *dependence* has traditionally been the most frequent reason for drug or alcohol misusers presenting to treatment services. A clear distinction should be made between dependence upon drugs, and the specific problems that may be associated with the consumption of drugs or alcohol (27).

Drug and alcohol problems may be of many different sorts, and may involve physical health, mental health, social functioning, and criminal behavior. Many people experience social, legal, psychological, and health problems as a result of their drinking without being dependent. Examples might include the individual who is not a regular drinker but who on one occasion gets drunk and becomes involved in a motor vehicle accident because of impaired driving performance. Serious harm may follow from even a single episode of drug injection. There is an increased likelihood of sharing injecting equipment among inexperienced injectors. First-time injectors are especially likely to share injecting equipment. Many drug takers become infected with viral hepatitis or HIV within the first few weeks of starting to inject drugs, at a time when they are unlikely to be seriously

drug dependent. Less severely dependent heroin users have been found to be more likely to inject in social settings, and to share injecting equipment with people they do not know well (28).

Dependence is a learned behavior disorder. The essence of dependence is that the relationship between the user and their drug is altered. With the development of dependence, the person becomes increasingly preoccupied by drugs and feels some degree of compulsion to use them. The initial reasons for taking drugs may or may not still be present. However, with the development of dependence the habit disorder becomes self-perpetuating and new factors are added which increase the likelihood, intensity, and persistence of drug taking.

The risks associated with multiple drug use can be cumulative. This can lead to a wider range and greater intensity of problems, though relatively few studies have investigated multiple substance use with specific attention to severity of dependence upon more than one substance.

Some drug users may become dependent upon drugs without experiencing significant harm. More often, there is an association between drug dependence and negative consequences from using drugs. Health problems and psychiatric comorbidity are prevalent among people with substance misuse and dependence disorders (29,30). Substance-related problems and substance dependence are correlated, even after controlling for such consumption behaviors as quantity of consumption (31), and the frequently observed relationship between problems and dependence seems to exist independently of the quantity of consumption.

Heroin-dependent patients who are also dependent upon alcohol tend to have poorer physical and psychological health than those dependent on heroin alone (13). The greater psychiatric problems of alcohol-dependent drug misusers may be related to their excessive use of alcohol, or to pre-existing psychological health problems. Among intravenous drug users, the most severely dependent drinkers were more likely to have had problems related to their injecting behavior, including abscesses, scarring, and overdoses (13).

Multiple drug use and multiple dependencies can coexist in complicated ways. In a study of a cohort of over 1000 clients admitted to treatment programs for drug misuse problems, pre-admission patterns of opiate use were not related to psychiatric symptoms among those opiatedependent patients who had relatively low levels of polydrug use. However, there was a positive association between opiate use and psychiatric symptoms among those opiate-dependent individuals who were concurrent and frequent users of stimulants, benzodiazepines, and/or alcohol (32).

Another study of stimulant misusers found that problems of mental health, general health, and social functioning were worse among amphetamine users who also took benzodiazepines (33). In addition, a community sample of stimulant users who also used opiates and/or benzodiazepines were found to be more likely to report adverse effects than drug users who used stimulants only (34).

The observation that cannabis use by opiate addicts in treatment is common has been well documented. Studies have reported that 45% of a group of methadone maintenance patients were consistently positive for THC (35), and that 78% of a treatment sample were cannabis users (36). Among opiate addicts in methadone treatment programs in

London and Edinburgh, 40% used cannabis every day, and more than three-quarters of the daily users were smoking more than four joints every day (37). The regular use of such large amounts of cannabis is not trivial, and may itself be associated with cannabis dependence problems.

Opiate users in methadone programs who were also daily users of cannabis were less likely to use either heroin or crack cocaine than those who had not smoked cannabis in the previous month; they were also less frequent drinkers than opiate users who did not smoke cannabis (37). This is consistent with studies of methadone maintenance patients in the United States, where patients who consistently tested positive for cannabis have been found to be less likely to use other illicit drugs (35). Reductions in the frequency of use of heroin, crack, and alcohol are positive treatment outcomes for methadone maintenance treatment, and in this respect there is an apparently paradoxical finding that daily cannabis use among opiate addicts in treatment may be associated with positive outcomes in terms of reduced use of alcohol and other drugs (37). On the other hand, daily cannabis use among opiate addicts was found to be associated with worse outcomes in terms of higher levels of anxiety and depression, as well as poor appetite (37).

Heavy drinking and, in particular, alcohol dependence is an important and often underrated problem in the treatment of drug users. Excessive alcohol use may aggravate other drug-related and health problems, and may adversely affect outcomes after treatment. Dependence upon alcohol is related to differences in patterns of illicit drug consumption. Alcohol-dependent drug misusers tend to be less frequent users of heroin and crack cocaine and more frequent users of cocaine powder, amphetamines, and non-prescribed benzodiazepines (7,13,14). Alcohol use among drug users has also been linked to increased levels of criminal activity (38).

Multiple drug use and dependence may affect drug-dealing activities. Most illicit drug sellers use the types of drugs that they sell. Many drug sellers, especially of heroin and crack cocaine, report purchasing drugs for their own use (39). Multiple drug sellers tend to be multiple drug users.

Drug overdose continues to be one of the most frequent causes of death among drug misusers. The annual mortality rate of the drug misusers in the National Treatment Outcome Research Study (NTORS) was 1.2% (40). This is substantially greater (about six times higher) than for a general, age-matched population. In a Scottish study conducted in 1989, more than 90% of deaths among drug misusers were due to drug overdose or suicide, and only 2% to HIV/AIDS (41).

Heroin is frequently implicated in fatal overdoses. This is generally attributed to respiratory depression mediated by inhibition of medullary centers. However, overdoses that are commonly attributed to the use of opiates are seldom due to the use of opiates alone. Overdoses are more likely to involve the combined use of opiates and alcohol or other sedatives (42,43). Opiate use with additional polydrug (including alcohol) use is especially likely to increase the risk of death subsequent to the direct depression of respiration. Death may also be due to secondary effects where blockage of the airways by saliva, mucus, or vomit leads to a reduction in respiratory capacity.

Multiple substance use may produce various sorts of interaction effects. The nature of the interaction is influenced by the specific drug combination, and the presence of more than two substances can be expected to produce complex interactions. Drug-alcohol

interactions can occur at the biochemical, pharmacological, and physiological level. Alcohol has the capacity and potential to inhibit the biotransformation of some drugs through the inhibition of hepatic microsomal enzymes (44). In many cases, the mechanisms related to pharmacodynamic interactions are poorly understood, but the combination of alcohol with other CNS depressants generally produces greater sedation than when either substance is taken on its own. The use of alcohol with other sedative-type drugs produces at least additive effects, while some drug combinations have also been reported to result in synergistic interactions. Opioid drugs, for example, can interact synergistically with alcohol. Alcohol appears to reduce the mean lethal dose through a potentiation of its respiratory depressant actions.

Benzodiazepines and alcohol have frequently been detected during post mortem examinations of the deaths of opiate misusers (40). In the majority of cases, more than one drug was detected. Indeed, a single substance was found after death in only about one in five of the cases. In more than half of the overdose deaths, three or more different drugs were detected. The most common drug combinations associated with death involved opiates and alcohol, opiates and benzodiazepines, or a mixture of all three of these drugs. Polydrug use in general, but this sort of mixture of substances in particular, was found to lead to a significant increase in the risk of mortality. The most risky combination of all involves a mixture of all three of these substances (opiates, benzodiazepines and alcohol), and this was detected in one-fifth of the overdoses. A study in Austria found that, whereas 30% of the overdose deaths involved a single drug, 56% involved more than one substance (45).

Where drug misuse involves the careless or reckless use of more than one substance, the risks of overdose are increased. Although it cannot be known how many drug overdoses are taken for the purpose of causing death, it is possible that some overdoses are taken with suicidal intent. About one-third of the drug misusers in the NTORS sample reported thoughts of killing themselves at the time of admission to treatment (32).

The issue of multiple substance use complicates the recording of causes of death. In the United Kingdom, there appears to be no standardized way in which the causes of death are entered on a death certificate, particularly with regard to the involvement of drugs. It seems unsatisfactory that it should be left to the coroner’s discretion as to what information is included or omitted. In many situations it is not possible for a coroner/pathologist/ toxicologist to say with certainty which drugs were a cause of death. This is especially true when a variety of substances has been consumed. Under such circumstances, preconceptions about the “dangerousness” of particular drugs may lead to over-reporting or under-reporting of different substances which had been used prior to death. The recording of overdose deaths is liable to a high degree of misclassification by coroners (46). The accuracy of death certification would be improved by routinely recording all of the multiple substances detected during toxicological examination.

THE ASSESSMENT AND TREATMENT OF MULTIPLE DEPENDENCE

Various attempts have been made to define what is meant by dependence. A World

Health Organization working group suggested that dependence should be regarded as a syndrome which includes various cognitive, behavioral, and physiological effects (27). According to this formulation, no single item is sufficient to define dependence, and the assessment of a dependence upon drugs or alcohol must rely upon multiple criteria.

The Criteria for Substance Dependence, as specified both by DSM-IV (47) and by ICD-10 (48), are very similar, and both identify a substantially similar dependence construct (49). Within both nosological systems, dependence is seen as involving three (or more) of a specified list of symptoms within a 12-month period. The criteria are well known and include:

tolerance (using increased amounts of the substance to achieve intoxication or desired effect, or diminished effect with continued use of the same amount of the substance);

w*ithdrawal* symptoms when the substance is discontinued;

e*scalation* (using larger amounts or for longer periods than was intended);

i*mpaired control* (persistent desire, or unsuccessful efforts to cut down or control substance use);

s*alience* (a great deal of time is spent in activities necessary to obtain or use the substance, or to recover from its effects);

n*eglect* of personally important social, occupational, or recreational activities because of substance use;

p*ersistence* with substance use despite awareness of problems associated with it.

In day-to-day clinical practice, an assessment of dependence is needed to guide decisions about when and how to prescribe medications within treatment programs. For these purposes, assessment seeks to determine the presence of physical dependence and, more specifically, levels of tolerance or the likelihood of clinically significant withdrawal symptoms after discontinuation of a drug. For such purposes, severity of physical dependence (tolerance and withdrawal) is generally assessed by reference to drug consumption behaviors. The indicators used in this assessment are primarily dose, and frequency and duration of use.

One of the best indicators of the extent of physical dependence to a particular drug is the current drug-taking behavior. Information about this is usually obtained by history taking. Self-report remains an essential tool, and in many circumstances it is the most practical way or the only way to obtain information. Despite the suspicions that have been voiced about the use of self-report data from drug users, a substantial literature points to the reliability and validity of such information in most circumstances (50,51).

Several problems arise in the measurement of multiple drug use. It may be more difficult for the patient to remember details about multiple quantities and frequencies of substances used than to remember details about the use of a single substance. Also, the traditional separation of treatment services for “alcoholics” and “drug addicts” increases the probability that a patient’s substance misuse history may be inaccurately obtained and/or evaluated by personnel who have not been properly trained to deal with polydrug users. The patient’s anxieties about being excluded from an alcoholism treatment service

may lead alcoholics who use multiple drugs to under-report or deny the use of illicit drugs (52). Multiple substance use may also lead to increased problems of intoxication. Intoxication at the time of assessment may seriously reduce the reliability and validity of self-reported information (53). Where issues concerning the validity of self-reported drug use are of special concern, information may be sought from other sources, or by laboratory tests such as analysis of urine samples.

The assessment of tolerance is most often required when a patient is first prescribed a drug, such as at the start of a methadone maintenance program. In some circumstances, and especially where the patient's history is uncertain, it may be necessary to require that the initial doses are taken under observation in a clinical setting. The miscalculation of tolerance levels can have serious consequences if relatively high doses of a drug are prescribed to a non-tolerant drug user.

Drug users seeking treatment frequently present with dependence upon several drugs which require medical detoxification. The most common multiple dependencies which require clinical management during withdrawal involve combinations of two or more of the opiates, benzodiazepines, alcohol, and stimulants. This issue of multiple dependencies and multiple detoxification treatments is one that confronts clinicians every day. However, there is little in the literature to indicate how detoxification from multiple drugs should be managed. The clinician may wonder whether normal treatment procedures should be modified, or whether treatments for different drugs should be delivered simultaneously or consecutively. In view of the importance of these questions, additional research in this area is needed.

Few patients with a primary dependence upon alcohol require medication with a benzodiazepine for more than two or three days, and withdrawal regimes of longer than 7–10 days are rarely necessary for uncomplicated alcohol withdrawal (54). However, a complicated withdrawal is likely when individuals are dependent on two or more substances.

Unless there are good reasons to do otherwise, a good general principle is to withdraw the less problematic drugs first, and subsequently to tackle the more problematic drug. For instance, stimulant withdrawal can generally be done first. Similarly, when a heroin addict is also dependent upon alcohol, it is reasonable to withdraw the alcohol first, using symptom-triggered chlordiazepoxide doses as needed, and then to withdraw the opiates. On the other hand, when a heroin addict is also dependent upon benzodiazepines, the opiates are withdrawn before the benzodiazepines. The benzodiazepine withdrawal syndrome may manifest itself over relatively protracted periods of time and may involve increased risk of seizures. When the patient must be detoxified from alcohol, opiates, and benzodiazepines, the drugs are withdrawn in that order, starting with alcohol.

When patients are dependent upon different types of drugs there can be interference between different medications. For instance, among patients who are dependent upon both cocaine and opiates and require pharmacological management of withdrawal responses to both types of drugs, this creates problems due to the opposing pharmacological effects of tricyclic antidepressants and the alpha-2 adrenergic agonists (such as lofexidine and clonidine). Tricyclic antidepressants and alpha-2 adrenergic agonists have opposite effects upon the noradrenergic system which may interfere with, or even cancel, the effectiveness of either or both types of drugs (55).

An inpatient setting is often required for drug users who are dependent upon more than one substance that requires detoxification. This allows more intensive medical supervision to better manage the risks of complex drug and withdrawal interactions. Often, re-evaluation and adjustment of detoxification regimens are necessary (56). Treatment of withdrawal in an inpatient setting is also more likely to lead to abstinence (57), not only for the "main" drug of dependence but also for other drugs (including alcohol) upon which the patient may be dependent. An inpatient setting can also provide a useful first phase of an integrated treatment program in which patients are returned to outpatient care in a drug-free state and ready for relapse prevention treatment.

Dependence upon sedative hypnotics may be found as part of a pattern of polydrug use, often with co-dependence upon heroin or other opiates. Typically, dependent users take very high doses of sedative hypnotics. During the 1970s, barbiturates and methaqualone were the drugs of choice for many addicts seeking treatment (58). Barbiturate dependence is currently seen infrequently, but benzodiazepines are widely used by many drug users who present to treatment (59).

When the patient presents with dependence upon both benzodiazepines and alcohol, detoxification can be managed by substituting and gradually reducing doses of a long-acting benzodiazepine such as chlordiazepoxide. For patients who are dependent upon both benzodiazepines and alcohol, withdrawal responses tend to be similar to those of benzodiazepine dependence rather than alcohol dependence (60). Sometimes detoxification from benzodiazepines and alcohol proves difficult. In such cases, phenobarbital substitution can be used to withdraw those who are dependent on multiple sedative-hypnotics including alcohol. Phenobarbital, rather than a benzodiazepine, is typically used for barbiturate withdrawal, whether or not alcohol dependence is present.

Withdrawal seizures are one of the most severe physical problems that can occur during alcohol withdrawal. These are usually encountered 12–48 hours after alcohol abstinence, or in association with a sharp decline in the blood alcohol level. When the user is dependent upon alcohol and benzodiazepines or related drugs, the risk of seizures is increased and may be more difficult to manage. When patients who have had alcohol withdrawal seizures present in acute and severe withdrawal, an intramuscular injection of phenobarbital may be administered (61).

For many years, tolerance and withdrawal were seen as the twin pillars that supported the concept of addiction. In earlier classification systems, they were seen as essential characteristics of drug dependence. DSM-III stated that "the diagnosis requires the presence of physiological dependence" (62). However, it is now generally accepted that these neuroadaptative processes are just part of the cluster of factors that may go together to create the dependence syndrome. For theoretical and research purposes, less emphasis is usually given to tolerance and withdrawal.

Although less theoretical weight is now attached to neuroadaptation, its clinical significance should not be underestimated. For the individual who is physically dependent upon a drug, the prospect of withdrawal may provoke serious anxiety (63). Also, the discomfort of withdrawal symptoms may interfere with treatment interventions and may lead to the patient dropping out of treatment. For these reasons, it remains important to monitor and reduce the distress and discomfort caused to the patient by withdrawal symptoms.

However, detoxification is only the immediate and most visible manifestation of the treatment for multiple drug dependence. As with single substance dependence, the successful management of drug withdrawal is necessary but not sufficient for recovery. There remains a further need to tackle the problems of psychological dependence which can lead to relapse after detoxification or even after prolonged periods of drug-free functioning. In these respects, the central features of dependence can be seen to involve the desire or compulsion to use drugs. It has been suggested that, of the dependence criteria, "the sense of compulsion would seem to be an essential ingredient. It contradicts our understanding of what we mean by an 'addiction' that someone could be said to be addicted to something but not experience a strong need for it" (1, p.2).

Dependence on multiple drugs complicates both the theoretical conceptualization of substance misuse problems and the assessment and treatment of these disorders. One may ask a number of questions. For example, where dependence on several substances occurs, does this constitute a single problem or a collection of problems? Are these problems directly related, indirectly related, or unrelated? Is the overall degree of dependence established by the more severe of the two dependencies? Does the user have a more severe dependence problem than if he or she took only one drug? Is severity of dependence upon each drug additive, or is it interactive?

Where a user is dependent upon two similar types of drugs (e.g., crack cocaine and amphetamines), to what extent is it clinically and practically useful to regard this as a generalized "stimulant dependence" disorder? Where the user is dependent upon two drugs of different types (e.g., heroin and crack cocaine), can this also be regarded as a generalized "drug dependence" disorder? Or should it be seen as two separate dependence disorders? If the latter condition is seen as constituting two separate disorders, to what extent do these require separate treatment interventions? One may propose various possible, and plausible, answers to these questions. But these issues have not received the systematic investigation that they deserve.

DSM-IV suggests that the dependence syndrome may be present for a specific substance (e.g., heroin or alcohol), for a class of substances (e.g., opioid drugs), or for a wider range of different substances (as for those individuals who feel a sense of compulsion regularly to use whatever drugs are available and who show distress, agitation, and/or physical signs of withdrawal upon abstinence). ICD-10 states that clinicians should record "as many diagnoses as are necessary to cover the clinical picture. When recording more than one diagnosis, it is usually best to give one precedence over the others by specifying it as the main diagnosis." (p.6). This assumes that the precedence given to the "main diagnosis" can be used to guide further treatment interventions. However, it does not adequately deal with the questions raised above. By what criteria should the clinician or researcher decide whether there is one generalized dependence disorder or there are two (or more) separate dependence disorders? If there are several dependence disorders, these may be directly related, indirectly related, or independent.

Substance use at intake to treatment has been found to be related to substance use after treatment, with pre-intake types and levels of substance use often relating to subsequent outcomes, and it could be expected that the same association would be found for multiple substance dependencies (64,65). However, the interrelationships between substance use outcomes may vary. The treatment outcome for each substance may be independent, or

associated with the outcomes for other misused drugs. This association may be either positive or negative. Drinking outcomes have often been found to be poor among drug misusers, with many continuing to report problematic patterns of alcohol consumption after drug misuse treatment (6,7). In a study of multiple substance dependencies, no association was found between severity of dependence upon alcohol and drugs (13). This lack of association between these two forms of dependence is interesting in view of the fact that the sample was composed of multiple drug misusers with a wide range of severe and often longstanding drug-related and other problems. In such a sample, it might have been expected that the possibilities of a general predisposition towards a "chemical dependency" would have been more evident. The results provided no support for a generalized dependence upon both alcohol and drugs.

When drug misuse continues despite treatment for multiple drug dependencies, there may be an increased risk of a range of adverse effects among multiple substance misusers. Chronic alcohol abuse has been identified as an important cause of medical complications during methadone treatment (66). Drug-dependent patients who are also dependent upon alcohol have been found to be more likely to have a wider range of health problems, and to have more severe health problems than other (non-alcohol dependent) drug misusers (13). The poorer physical and psychological health of alcohol-dependent drug takers is shown in Fig. 3. Severity of drug dependence has also been found to be related to involvement in prostitution (28). Among both the women and men who had sex with men, the heroin users who were more severely dependent were more likely to have been involved in sex-for-money transactions.

Improvement in health represents an important treatment goal for patients with substance misuse disorders. Continued heavy drinking among drug misusers with liver disease is a cause for serious concern because of the high rates of hepatitis C infection among drug misusers (67). Heavy

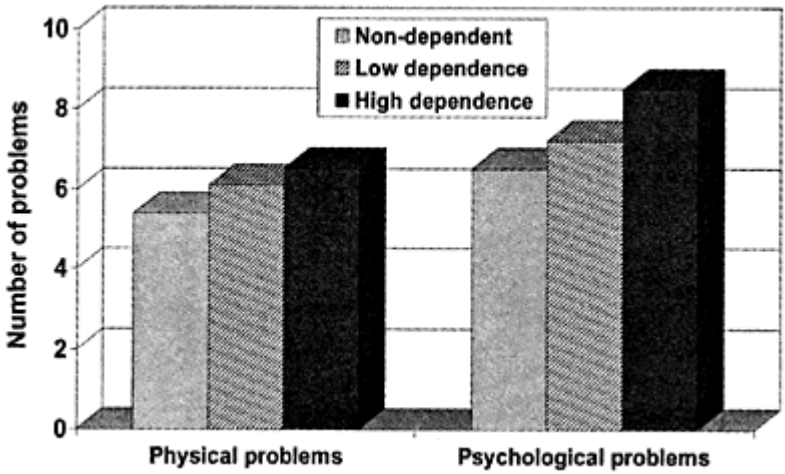

Figure 3 The association between alcohol dependence and physical and psychological health problems among a treatment sample of drug-dependent patients (13).

drinking acts as an independent risk factor for mortality because of its adverse effects upon the physical health of the user. For individuals with chronic viral hepatitis infections, heavy drinking is especially risky, but even low levels of alcohol consumption have been found to be associated with increased risk of viraemia and hepatic fibrosis (68).

Heavy drinking, alcohol dependence, and liver disease are all likely to affect treatment response and treatment outcome among patients in methadone maintenance programs. Alcohol may affect the metabolism of other drugs, either directly or indirectly. Chronic alcohol consumption may produce significant liver damage which impairs the elimination of many drugs, particularly those that undergo phase I metabolism. The presence of chronic liver disease may lead to significant alterations in methadone metabolism which may interfere with methadone treatment (66).

The effects of alcohol can also interfere more directly with the provision and effectiveness of methadone maintenance treatment. Alcohol use, and especially heavy drinking, may lead to an inhibition of methadone metabolism. Conversely, after chronic use of large amounts of alcohol, and during subsequent periods of abstinence from alcohol, methadone metabolism is accelerated (66). As a consequence, the use of large amounts of alcohol after taking methadone can produce an enhancement of the psychoactive effects of methadone, but this comes at a cost of also increasing the likelihood of early-morning opiate abstinence symptoms which are experienced between 18 and 24 hours after the last dose of methadone. As a consequence, the methadone patient may experience some discomfort which manifests itself in the form of craving for drugs and which increases the probability that the misuse of extra drugs or further drinking may occur.

In a study of methadone maintenance patients who were drinking heavily, patients were further categorized according to whether they were dependent upon alcohol or not. The alcohol-dependent drinkers responded better to treatment than the non-dependent drinkers in terms of reduced illicit opiate use, greater reductions in morning drinking and in drinking more than intended, and in terms of improved social relationships and psychological functioning (14). However, the dependent drinkers had poorer outcomes in terms of continued cocaine use, and the authors suggested that these patients may have been dependent upon cocaine as well as upon opiates and alcohol.

Heavy drinking and alcohol dependence by drug misusers may aggravate other drug-related problems, and may adversely affect outcomes after treatment. Dually (drug and alcohol) dependent patients have been found to have worse treatment outcomes than those who are not heavy drinkers (69). Chronic alcohol abuse has been linked to the premature discharge of patients from treatment programs (70,71). Some recovering drug addicts have been found to turn to alcohol as a substitute (15,16), and cocaine misusers who also have drinking problems have been found to be more likely to relapse to cocaine use after treatment, with drinking often being closely linked to their relapse episodes (72).

The problems of continued drug misuse and heavy drinking during and subsequent to treatment pose a number of serious challenges for addiction treatment services. For many years, there has been concern about those patients who do not appear to get better despite treatment. Even in studies that have demonstrated the efficacy of specific treatment

interventions, some patients fail to respond to the effective intervention (73,74). Although methadone maintenance is effective for many patients in leading to reductions in illicit drug use, their use of illicit drugs is often not completely extinguished, and continued polydrug use is frequently found among many patients in such programs.

In a study of methadone maintenance patients, it was found that 22% of the sample continued to use illicit opiates despite having been in treatment for at least 6 months (74). A U.S. Institute of Medicine report (75) suggested that about one in four methadone maintenance patients tended to show a poor response to treatment. In a study of methadone patients in the United Kingdom, several subgroups were identified who showed different clinical response profiles corresponding to the amount of improvement in drug use between admission to treatment and follow-up (76). More than half of the sample showed clear improvements: for example, their illicit opiate use at follow-up had fallen to about one-quarter of its pre-intake level. However, about one-fifth of the sample (18%) failed to show improvement on virtually all outcome measures. In addition to their continued use of opiates, the patients who failed to improve also continued to use considerable amounts of stimulants after treatment, and were using significantly increased amounts of benzodiazepines at follow-up. At 4–5-year follow-up, crack cocaine and alcohol outcomes were not significantly different from those at intake levels (77). The less satisfactory outcomes for heavy drinking and use of crack cocaine suggest the need for treatment services to strengthen interventions to tackle these problems more effectively.

Studies in the United States have found that benzodiazepines are widely abused by opiate addicts in methadone maintenance programs (78). In a survey of patterns of benzodiazepine use by predominantly heroin-dependent drug addicts attending treatment services in seven cities across Britain, the use of benzodiazepines was found to be extremely common (59). The most worrying feature of benzodiazepine misuse involved the injection of benzodiazepines, among which the most likely to be injected was temazepam. A study of patients attending methadone treatment services in the north-west of England reported that 70% were injecting temazepam capsules (79). This is an extremely dangerous practice and puts the health of the user at risk through the possible “blocking” of peripheral veins in the arms and legs, skin abscesses, and the development of deep vein thrombosis. Problems can be exacerbated if large quantities of temazepam are abused.

The use of multiple drugs by different routes of drug administration has implications for both preventive and treatment interventions. Where multiple substance use continues despite treatment, and especially if this involves the intravenous use of opiates in combination with the misuse of benzodiazepines or heavy drinking, treatment services and other programs should clearly and explicitly inform opiate users of the risks of fatal overdoses which are associated with respiratory depression in relation to the concomitant use of sedatives and alcohol. Where multiple drug misusers seek treatment in areas where the prevalence of drug injecting is relatively low, it may be appropriate to design and deliver interventions specifically targeted to prevent transitions from non-injecting to injecting routes of drug administration (80). However, little is known about whether such interventions are effective or what is the most effective way to provide them. Similarly, where injecting is more prevalent, services should ensure that both clinical staff and users

are aware of how overdoses occur and what sorts of response are appropriate to overdoses. One possible option is that antagonist drugs such as naloxone be made available to opiate misusers as a public health measure (81). The antagonist could then be administered in the event of an overdose. However, given the short half-life of naloxone, opiate misusers would have to be informed about the necessity of seeking treatment immediately, should the use of the opiate antagonist be required.

Severity of dependence upon heroin is associated with increased rates of sharing injecting equipment, and consequently with increased risk of infection with blood-borne diseases (82). More severely dependent heroin injectors have been found to be more likely to inject with equipment after it had already been used by another injector. Dependence serves as a barrier to giving up drug misuse, and leads to an increased probability that the user will be exposed to risks for longer periods of time. In a study of the relationship between severity of dependence and health risk factors, the strongest predictor of seropositivity for viral hepatitis infection was the number of years for which the user had been injecting drugs (83). Among chronically dependent intravenous drug misusers, damage to their veins may lead to risky injection practices. The congruence of consumption behaviors, dependence, and problems is well illustrated in the use of dangerous injection practices such as attempts to inject into the femoral vein, or the use of other inappropriate and dangerous injection sites.

Some treatment programs have responded to the misuse of crack, benzodiazepines, or heavy drinking with punitive measures, such as reducing methadone dosage or discharging patients from programs. This is often counterproductive and can lead to an escalation of illicit drug use and associated problems (78). With patients who respond poorly to existing programs, the use of contingency management interventions has been found to be an effective and generally useful approach in this context (84). Even with otherwise unmotivated patients, a substantial number can be helped to give up drugs when the reward value is sufficiently increased. For example, it has been found that combining a high magnitude reinforcer and a low response requirement, such as 2 days of abstinence, yielded cocaine abstinence initiation in approximately 80% of multiple drug misusing patients (85). However, contingency management strategies have been found to be more effective when directed towards changing the use of a single illicit drug than when they were targeted towards reducing multiple drug use (86).

In some circumstances, multiple dependence disorders may require a broader range of treatment interventions and services than would be required for the patient with dependence upon a single substance. For example, the provision of methadone on its own has been found to have an impact upon opiate use, but it has a less reliable effect on other types of substance misuse or other problem behaviors.

In an investigation of whether the addition of counseling, medical care, and psychosocial services improved the efficacy of methadone treatment programs, patients were randomly assigned to one of three levels of treatment. These were: methadone with no other services, methadone plus counseling, or methadone plus counseling and medical/psychiatric and family therapy. The results showed that the provision of additional counseling, medical, and psychosocial services produced marked improvements in the efficacy of treatment compared to methadone alone (87). The enhanced group showed better outcomes than the other treatment groups on a range of

outcome measures, including reduced alcohol use. These treatment gains were most evident among patients with multiple problems.

Drug users with concurrent multiple substance use problems and other mental health problems may require special consideration and treatment planning (88). Drug treatment service personnel should undertake a thorough assessment of substance use behaviors with specific attention to heavy drinking and alcohol dependence, and it has been suggested that the AUDIT may serve as a promising instrument for the identification of hazardous and harmful drinking among patients in treatment for drug dependence (89). A comprehensive assessment of alcohol use among drug misusers should include separate assessments of the three dimensions of drinking patterns, alcohol-related problems, and severity of alcohol dependence.

In other areas, the separation of services by problem area has been found to lead to less efficient provision of treatment services. Treating dually diagnosed patients in separate mental health and addiction treatment services is often unsatisfactory, especially for those with severe psychiatric disorders. Many general psychiatrists and mental health clinicians fail to obtain a thorough history of drug use, and drug problems often go undiagnosed in mental health treatment settings (90). Mental health staff often lack the training, the expertise, and the confidence to respond appropriately to drug misuse among their patients. Conversely, addiction service staff may not respond effectively to mental health problems among their patients. The reliance upon separate services systems can lead to a lack of liaison between mental health and addiction treatment services, and disagreement over treatment practices and treatment goals. Improved outcomes have been found among substance abusers with severe mental illnesses who were treated in integrated programs compared to a similar group who received a traditional service intervention (91).

This same point has been made with regard to the care of pregnant drug addicts. Communication and liaison between addiction services, antenatal clinics, and obstetric hospitals is often unsatisfactory, and better results have been obtained through a multidisciplinary service which incorporated treatment specialists for addiction, mental health, obstetric/gynecological, family planning, and pediatrics, within a single program (92). The common problem of multiple drug and alcohol misuse, as well as the issue of dual dependence upon both drugs and alcohol, raises challenging questions about the wisdom of continuing to maintain the traditional separation of drug addiction and alcoholism treatment services.

It is increasingly clear that the focus upon single substance disorders is both clinically and theoretically inadequate. Treatment practice needs to develop and strengthen diagnostic and assessment procedures to take account of the multiple substance use and multiple dependencies which are so common among patients presenting for treatment. Treatment programs need to develop and implement more comprehensive treatment packages to deliver a broader range of interventions that are appropriate to achieve changes in multiple substance misuse behaviors. This applies not only to the short-term detoxification of patients, but also to treatments designed to achieve longer-term relapse prevention and rehabilitation goals.

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6
Substance Abuse and Mood Disorders

Prevalence, Diagnosis, and Treatment

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INTRODUCTION

Epidemiological studies in the U.S. general population show that mood disorders and substance use disorders are highly prevalent and that they frequently co-occur (1–3). Although the rate of co-occurrence, as reflected in odds ratios, generally exceeds 1.0, indicating that the association exceeds that due to chance, the prevalence rates vary substantially among the different mood disorders. For example, the Epidemiologic Catchment Area Study (ECA) showed that, among individuals with a lifetime diagnosis of bipolar disorder, 41% had a lifetime drug use disorder and 46% had a lifetime alcohol use disorder (1). This translates into an odds ratio of 5.6 for alcohol use disorders and 11.1 for drug use disorders. In contrast, although significantly elevated, the odds ratio for comorbid major depressive disorder (MDD) and alcohol use disorder was only 1.3 and for MDD and drug use disorder it was 3.8.

There is also considerable variation in rates of comorbidity among the different epidemiologic studies. Both the ECA and the National Longitudinal Alcohol Epidemiological Survey (NLAES) (4) showed a significant association between MDD and substance use disorders. However, in the NLAES, the odds ratio for lifetime MDD and alcohol use disorder was 3.8, nearly three times that seen in the ECA (1). Similarly, in the NLAES, individuals with a lifetime diagnosis of drug dependence were nearly seven times as likely as those without drug dependence to have lifetime MDD (3), which is nearly double that in the ECA (1).

Despite differences in the epidemiologic estimates of their co-occurrence, there is general agreement that the co-occurrence of mood disorders and substance use disorders complicates efforts to diagnose and treat these disorders. In this chapter, we review the current literature on the diagnosis and treatment of comorbid mood and substance use disorders, starting with general issues, followed by a summary of findings relevant to diagnosis and treatment for each specific substance of abuse.

GENERAL DIAGNOSTIC AND TREATMENT ISSUES

The Diagnosis of Comorbid Mood and Substance Use Disorders

Early views of the relationship between mood and substance use disorders focused on depression, which was thought to predispose an individual to substance use in an effort to relieve dysphoric mood states (i.e., the self-medication hypothesis) (5). Subsequent work led to the recognition that both neurochemical and psychosocial sequelae of addiction can cause depressive and other mood symptoms.

Currently, clinically significant mood symptoms in patients with substance use disorders are viewed as either the manifestation of an underlying comorbid mood disorder, the product of substance use, or possibly a combination of the two. Dysphoric mood, as well as disturbed sleep, appetite, energy level, and concentration, occur as part of acute withdrawal from a variety of substances (6–10). DSM-IV (11) goes beyond a dichotomous distinction between substance-induced and independent disorders in the interpretation of these symptoms by recognizing that many of these symptoms are expected effects of substance intoxication or withdrawal. For example, stimulant-induced mood disorder with manic features has its onset during intoxication or withdrawal and results from the pharmacological effects of stimulants. These mood symptoms tend to subside spontaneously with the resolution of intoxication or withdrawal, and with continued abstinence. However, despite abstinence, a significant minority of substance abusers exhibit persistent symptom states that may signal the presence of a comorbid mood disorder (8,12). A mood disorder that persists beyond the period of intoxication or withdrawal, but which does not meet criteria for an independent disorder, is called a substance-induced mood disorder.

The primary-secondary distinction (13,14) may be useful in the evaluation of patients with comorbidity. This approach is based on chronology, with the disorder that occurred first in an individual's life considered the primary disorder. The course of illness is thought to more closely parallel this disorder than the disorder that develops subsequently (i.e., the secondary disorder). Abraham and Fava (15) examined the onset of various substance use disorders and MDD in 375 outpatients with these comorbid disorders. Among polydrug-dependent patients, the onset of dependence on all drugs of abuse except LSD followed the onset of MDD, while the onset of LSD dependence coincided with the onset of MDD. On average, cocaine dependence occurred 6.8 years and alcohol dependence 4.5 years after the onset of the first major depressive episode. Given these findings, MDD would be considered the primary disorder and, as such, would likely persist or recur despite recovery from the substance use disorder(s). Conversely, a diagnosis of primary alcohol dependence with a secondary depressive episode would suggest that the depressive symptoms were due to the effects of alcohol and that the course of the illness would more closely resemble that of alcohol dependence. Although the clinical utility of the primary/secondary model is limited by difficulties in obtaining accurate longitudinal information, use of a collateral informant and emphasis on the age of onset of the disorders in question (as distinguished from the first symptoms) strengthens the approach. A growing number of diagnostic assessments have been

developed that serve to determine the primacy of mood disorders or substance use disorders (16).

The degree to which mood symptoms are independent or autonomous of substance use has also been used to evaluate substance-dependent patients with prominent mood symptoms (17). According to this approach, a mood disorder that occurs in the context of heavy substance use is considered autonomous if the onset of the mood disorder precedes the substance use disorder or persists despite abstinence from the substance. Conversely, in a non-autonomous (or substance-induced) mood disorder, the onset of the substance use disorder occurs prior to that of the mood disorder and symptoms subside during periods of abstinence. Although DSM-IV includes an effort to guide the application of this distinction, additional research is needed to determine the clinical utility and predictive validity of subtyping mood disorders in substance abusers on the basis of this approach. As with the primary-secondary distinction, diagnostic interviews developed to assess the onset of substance use disorders and comorbid disorders may be particularly useful in drawing the distinction between autonomous and substance-induced mood disorders (16).

The Treatment of Comorbid Mood and Substance Use Disorders

There are comparatively few studies that have examined effective strategies to treat patients with comorbid mood and substance use disorders. The majority of studies conducted to date have been limited either by the use of an open study design or by small sample size. For example, in a pilot study, Brady et al. (18) found that divalproex sodium was efficacious and well tolerated in nine acutely manic patients with a comorbid substance use disorder. These patients showed a significant decrease in the number of days of substance use during treatment. Divalproex sodium was also found to produce positive results when added as an open-label adjunct to addiction treatment in 20 inpatients with a DSM-IV mood disorder (primarily bipolar type) (19). Specifically, some patients reported decreased craving and, by self-report, all patients remained abstinent. This suggests that divalproex sodium is efficacious and safe, both alone and in combination with other psychiatric medications for the treatment of comorbid substance abuse and mood disorder. The potential utility of anticonvulsants for treatment of comorbid mood and substance use disorders is underscored by studies of carbamazepine (20) and topiramate (21) that show beneficial effects on alcohol consumption among alcoholics. However, randomized controlled trials are needed to confirm these findings and to examine the potential anti-craving properties of a variety of promising anticonvulsant agents (22). While initial studies suggested that bipolar patients with comorbid substance use were unresponsive to lithium (23), more recent findings (24) indicate that comorbid substance use disorders do not directly alter the efficacy of lithium or valproic acid in compliant patients.

Integrated dual-diagnosis programs may enhance treatment compliance and offer strategies to support abstinence. These programs aim to educate patients about the relationship between substance use and psychiatric disorders and to treat both disorders concomitantly. Recent data from a Canadian study suggest that there are beneficial effects of integrated treatment among patients with substance use disorders and comorbid

MDD (25). At intake, 35.8% of 120 substance-using subjects met DSM-IV criteria for current MDD. Despite higher levels of psycho-pathology at intake, these patients did as well in the integrated treatment on both substance use and psychiatric outcomes as non-depressed patients. A growing literature (26–28) supports the utility of combining antidepressants with substance abuse counseling for the treatment of depressed alcoholics (29).

However, the implementation of new findings in clinical practice often lags behind research advances. In a recent U.S. study examining patterns of treatment, depressed patients with comorbid substance use disorders (n=495) received treatment that was similar to that given to depressed patients without substance abuse (30). Among the dually diagnosed patients, only 8.4% received substance abuse counseling and only 2.2% were prescribed a medication such as disulfiram or naltrexone to assist in relapse prevention.

In summary, although recent findings support the beneficial effects of integrated treatment for patients with comorbid substance use and mood disorders, the approach is not widely used. Standard treatments for mood disorders or substance use disorders may be less effective for comorbid patients than for patients with only one diagnosis. Therefore, the incorporation of specific evidence-based treatments in clinical practice is likely to improve outcomes for these patients.

COMORBIDITY OF MOOD DISORDERS WITH DEPENDENCE ON SPECIFIC SUBSTANCES OF ABUSE

Alcohol

Among the substance use disorders, comorbidity involving mood disorders has been studied most extensively in relation to alcohol use disorders. The association between mood and alcohol use disorders has been well documented in both community and clinical samples (1–3,31). Among the mood disorders, bipolar disorder is the one for which substance use disorders are most likely to co-occur (2,32).

In general, female alcoholics are more likely to suffer from comorbid mood disorders (1,2) and to have higher rates of primary depression (33,34) than male alcoholics. Sex differences in the comorbidity of mood disorders and alcohol use disorders may also extend to alcohol-related treatment outcome. In most studies, these comorbidities are associated with poorer alcohol-related outcomes (35–39). However, in two studies (40,41), the presence of comorbid depression in women alcoholics was associated with better alcohol-related outcomes. Analysis of three-year outcomes from one of these study samples (41) showed no advantage for depressed women over those without a lifetime diagnosis of depression, suggesting that the effects may decline over time (42).

Other studies have shown that untreated depression in alcoholics may contribute to a relapse to drinking (35), psychosocial deterioration (36), treatment noncompliance, and re-hospitalization (37). Similarly, patients with comorbid bipolar disorder and alcohol dependence experience more hospitalizations (38), decreased time to drinking relapse (39), earlier onset of the bipolar disorder, and higher levels of dysphoria (43) than bipolar

patients without alcohol dependence.

Comorbid depression (44–47) and bipolar disorder (48,49) also appear to increase suicidal behavior in alcoholics. In a study of 229 Finnish suicide victims, 43% had an alcohol use disorder and 59% had a depressive disorder. Among the 77 suicide victims with alcohol dependence, 22% had MDD and 26% had the depressive disorder NOS (44). Cornelius et al. (45) found that the variable that best differentiated depressed alcoholics from alcoholics without depression or from non-alcoholic depressed patients was greater severity of suicidality in the comorbid group. Similarly, Bulik et al. (48) found that comorbid alcoholism and bipolar II disorder was one of the five variables that served to correctly classify 77% of suicide attempters. More recently, Potash et al. (49) found that subjects with bipolar disorder and alcoholism had a 38.4% lifetime rate of attempted suicide, compared with 21.7% among those without alcoholism. Comorbid alcoholism was also associated with a high rate of attempted suicide among family members with bipolar disorder (49).

The time course of the occurrence of depression among substance-dependent patients may also be an important determinant of the risk for suicidal behavior. Schuckit et al. (46) found that alcoholics with independent major depression were more likely to attempt suicide than those with substance-induced depression. However, it has been argued that the occurrence of major depression before the onset of a substance-related disorder may have different implications for suicidal behavior than major depression that occurs during periods of sustained abstinence. In a recent study of 602 substance-dependent patients, major depression that occurred before the onset of substance dependence was associated with a greater severity of suicidal intent, while major depression that occurred during abstinence predicted the number of suicide attempts (47). These results underscore the importance of assessing the onset of depression relative to the onset of substance dependence.

Overall, comorbid alcohol dependence and mood disorders are associated with chronic symptoms that may result in increased hospitalization, more frequent relapses, greater impairments, and heightened risk of suicide in comparison with either diagnosis alone. These findings, combined with an emerging literature on the beneficial effects of treatment in these populations, underscore the need for careful diagnosis and empirically based treatment of patients with these comorbid disorders.

Diagnostic Issues

The presence of mood symptoms among alcohol-dependent individuals can result from the pharmacological or psychosocial effects of heavy drinking (8,50,51). For example, alcohol-induced depressive symptoms may develop during intoxication, chronic heavy drinking, or alcohol withdrawal (8,50,51). However, recent data from a sample of more than 6000 respondents from the NLAES indicate that, independent of mood effects related to intoxication and withdrawal, abstinent alcoholics have a four-fold risk of developing MDD (52).

Structured interviews can help to differentiate alcohol-induced from independent mood disorders by clarifying the chronology of mood and alcohol-related symptoms. However, patients may have difficulty in providing accurate information about the onset and

duration of symptoms. Then, a clinical judgment is required to determine whether the observed symptoms constitute a disorder that requires specific treatment.

Symptom scales such as the Hamilton Depression Rating Scale (53) and the Beck Depression Inventory (54) may be useful in establishing the severity of current symptoms and in monitoring changes in symptom severity over time. In general, unless mood symptoms are severe, or there is clear-cut evidence of a primary mood disorder, pharmacologic treatment should be reserved for those with symptoms that persist for at least a week without evidence of substantial improvement despite abstinence.

Recent findings from genetic studies may enhance our understanding of the pathophysiology of comorbid alcohol dependence and MDD. One such approach involves study of a functional polymorphism in the gene encoding the serotonin (5-HT) transporter protein. Blunted 5-HT neurotransmission has been implicated in the pathophysiology of both major depression and alcohol dependence (55). Therefore, genes encoding 5-HT system proteins have been studied as candidates in the etiology and pathophysiology of these disorders. A polymorphism identified in the promoter region of the gene encoding the 5-HT transporter protein consists of two common alleles, which are designated “long” (L) or “short” (S) with 16 and 14 repeat units, respectively (56). Compared with the L allele, the S allele is associated with lower basal and induced transcriptional efficiency of the promoter, resulting in lower 5-HT uptake activity (56,57).

Heinz et al. (58) found an association of this polymorphism with an *in vivo* measure of 5-HT transporter binding, with LL subjects having abnormally low binding; they interpreted this as reflecting greater vulnerability to the neurotoxic effects of chronic alcohol consumption. Furthermore, reduced 5-HT transporter binding has been associated with increased severity of depressive symptoms among alcoholics (59), as well as among individuals with MDD (60). Twitchell et al. (61) found that, among children of alcoholics, individuals homozygous for the L allele had higher levels of behavioral disinhibition (i.e., impulsive aggression and type II alcoholism) and negative affect (i.e., depression and anxiety), compared with individuals having one or more S alleles. Nellissery et al. (62) observed an increased frequency of the S allele among individuals with comorbid alcohol dependence and MDD, compared with either non-depressed alcoholics or healthy controls.

From a pharmacogenetic perspective, the promoter polymorphism in the gene encoding the 5-HT transporter has been shown to influence response to the selective serotonin reuptake inhibitors (SSRIs) fluvoxamine (63) and paroxetine (64). In these studies, individuals with the LL and LS genotype had a better antidepressant response than those with the SS genotype. Similarly, Benedetti et al. (65) reported that LL subjects demonstrate a greater antidepressant response to total sleep deprivation than subjects with the LS or SS genotype.

Although these findings have not yet had a substantial effect on the clinical management of comorbid depression and alcohol dependence, they may provide insight into the risk and pathophysiology of this comorbidity. In the not-too-distant future, these developments may make it possible to determine the genotype of a depressed alcoholic or drug abuser at a locus such as that encoding the 5-HT transporter protein, and to apply this information to the diagnosis and treatment of that individual.

Treatment Issues

Early studies of tricyclic antidepressants (TCAs) failed to show a substantial advantage for these medications over placebo in the treatment of comorbid depression and alcoholism (66). However, the negative results appear to have been due to the methodological limitations of the early studies, including the cross-sectional assessment of mood symptoms (rather than the establishment of a mood disorder diagnosis) and an inadequate dosage of the medication, with lack of attention to plasma concentrations (66) (Table 1).

The second generation of antidepressant studies in depressed alcoholics has yielded more promising findings. In an open trial, Nunes et al. (26) treated 60 depressed alcohol-dependent patients with imipramine, 45% of whom showed improvements in mood and drinking measures. In a double blind, placebo-controlled trial of imipramine treatment, in alcoholics with a diagnosis of primary depression, McGrath et al. (67) demonstrated a modest advantage for active medication on depressive symptoms. Reduced depression in these patients was associated with a decreased rate of relapse to heavy drinking. Mason et al. (27) found that desipramine

Table 1 Pharmacotherapy Studies in Depressed Alcoholics

Reference	Total *N*	Medication	Study design	Study duration (weeks)	Comment
Nunes et al., 1993 (26)	60	Imipramine (IMI)	Open trial	12	45% of subjects were responders in terms of both depressive symptoms and drinking behavior.
McGrath et al., 1996 (67)	69	IMI+relapse prevention psychotherapy	Placebo-controlled	12	Improvement in depressive symptoms. Although no overall effect on drinking, patients whose mood improved showed decreased drinking.
Mason et al., 1996 (27)	28	Desipramine (DMI)	Placebo-controlled	24	DMI-treated patients with depression showed a significant decrease in depressive symptoms. Overall, DMI-treated patients were abstinent significantly longer.
Cornelius et al., 1997 (28)	51	Fluoxetine (FLX)	Placebo-controlled	12	FLX reduced both depressive symptoms and drinking, particularly heavy drinking. One-year follow-up of 31 subjects showed continued

					advantage for fluoxetine on both outcomes (Ref. 68).

Reference	Total *N*	Medication	Study design	Study duration (weeks)	Comment
Roy, 1998 (70)	36	Sertraline (SERT)	Placebo-controlled	6	SERT significantly reduced depressive symptoms among inpatient alcoholics. Drinking behavior was not measured.
Pettinati et al., 2001 (74)	100	SERT	Placebo-controlled	14	SERT reduced drinking only among patients without lifetime depression.
Roy-Byrne et al., 2000 (73)	64	Nefazodone (NEF)	Placebo-controlled	12	At endpoint, there was significantly greater mood improvement in the NEF group (48%) than in the placebo group (16%). The groups showed a comparable decrease in drinks per day.
Salloum et al., 1998 (75)	14	Naltrexone+a serotonergic antidepressant	Open trial	12	Naltrexone significantly decreased urges to drink alcohol and drinking. There was a trend toward improvement in depressive symptoms and overall functioning.

was superior to placebo in alcoholics with secondary depression. Its use in this population significantly decreased depressive symptoms and prolonged periods of abstinence from alcohol, irrespective of the presence of comorbid depression.

Some controlled studies also support the utility of SSRIs for the treatment of depressed alcoholics. Cornelius et al. (28) found that fluoxetine was superior to placebo in reducing depressive symptoms and drinking behavior, including heavy drinking, among depressed alcoholics recruited from an inpatient psychiatric unit. Furthermore, in a naturalistic one-year follow-up study of 31 patients who had completed the trial, the fluoxetine group continued to have lower depression scores and to report less drinking than the placebo group (68). Kranzler et al. (69) found that fluoxetine significantly reduced depressive symptoms relative to placebo in a sub-sample of alcoholics with current MDD. However, fluoxetine did not significantly alter alcohol consumption in these patients. Roy (70) compared the effects of sertraline treatment on depressed inpatient alcoholics during a 6-week study. He found a significant advantage for active medication on depressive symptoms, though, given the inpatient setting of the study, effects of the medication on drinking behavior were not evaluated.

In practice, SSRIs have become the first-line treatment of depression, not because they are more efficacious than TCAs, but because they have a more favorable side-effect profile. SSRIs do not have the anticholinergic, hypotensive or sedative effects of the TCAs, nor do they have the adverse cardiovascular effects which, in overdose, can be lethal; they thereby limit the potential for deliberate self-poisoning (71). However, not all SSRIs are well tolerated by alcoholics (72). SSRIs can exacerbate the tremor, anxiety, and insomnia often experienced by recently detoxified alcoholics. A study of nefazodone, a serotonergic antidepressant, demonstrated antidepressant efficacy in depressed alcoholics (73). Although nefazodone may be particularly useful in alcoholics due to its sedative effects, which may help treat the chronic insomnia that is commonly associated with both alcohol dependence and MDD, its association with a limited number of cases of idiosyncratic hepatic failure limits its clinical utility.

Compared with the antidepressant effects of SSRIs in depressed alcoholics, the effects of these medications on alcohol consumption are less consistent. It has been argued that reductions in drinking produced by SSRIs may be contingent on an antidepressant effect (29). However, in a study of the effects of sertraline on alcohol consumption in 100 alcohol-dependent patients, sertraline was superior to placebo in reducing alcohol consumption among half of the patients without a lifetime history of depression (74). In this study, there was no effect of the medication on drinking behavior in patients with a current diagnosis of MDD.

An emerging area of interest in the pharmacologic treatment of comorbid alcohol dependence and MDD is the use of combination therapy. In an open-label, 12-week study, 14 depressed alcoholics who had continued to drink despite receiving antidepressants and chemical dependence counseling were treated with naltrexone at 50mg/day (75). Following the addition of naltrexone, alcohol consumption decreased substantially, with a concomitant reduction in depressive symptoms. Although this approach requires validation in controlled trials, it adds to a growing literature suggesting that there are beneficial effects in combining pharmacotherapy with substance abuse counseling in the treatment of depressed alcoholics.

Despite its clear epidemiological and clinical importance, there are no controlled trials in the literature to guide the pharmacological treatment of bipolar alcoholics. And, except for one promising study that examines the effects of cognitive behavioral therapy in depressed alcoholics (51), psychotherapeutic trials for either depressed alcoholics or bipolar alcoholics are also lacking.

Opioids

An association between MDD and opioid abuse has been well documented, though the prevalence of these comorbid disorders varies considerably (76–82). The lifetime prevalence of MDD in a sample of 716 opioid abusers seeking methadone maintenance treatment was 15.8%, which was second only to a 25% prevalence for antisocial personality disorder (77). Rounsaville et al. (83) found that 54% of 533 opiate addicts in substance abuse treatment had a lifetime history of a depressive disorder. At the time of the evaluation, approximately 24% of patients were experiencing an episode of major depression and 2% were dysthymic. Brienza et al. (78) interviewed 528 opioid users

participating in needle exchange or methadone maintenance programs. Fifty-four percent of those in the needle exchange program and 42% of those enrolled in methadone maintenance met criteria for MDD during the six months prior to the interview.

Family studies also support the association between opioid abuse or dependence and depression. Higher rates of psychopathology, including MDD, antisocial personality disorder, and substance use disorders, have been reported among relatives of opioid-dependent patients compared with the family members of controls (84–86). Nunes et al. (86) found that sons of opioid-dependent patients with MDD are at increased risk for conduct disorder, as well as social and intellectual impairment. Similarly, McAvay et al. (87) reported increased health problems in sons of opiate addicts with MDD compared with sons of opiate addicts without depression.

Rounsaville et al. (82) studied the course of depressive symptoms among 157 opioid-dependent patients in treatment. On admission to treatment, 17% met criteria for MDD and an additional 60% had significant depressive symptoms. Upon evaluation six months later, the rate of MDD dropped to 12%, with another 31% reporting depressive symptoms. Interestingly, only 2% of the sample met criteria for MDD at both time points. Although this study demonstrated that the majority of patients with MDD improved with addiction treatment alone, it also showed that 10% of the sample developed major depression during the course of treatment.

The notion that continued opioid use leads to the development of depressive symptoms is supported by at least two studies (88,89). Mirin et al. (88) found that when opioid-dependent subjects were allowed to self-administer intravenous heroin there was an initial improvement in mood; however, over time this changed to increased dysphoria. Maddux et al. (89) evaluated the relationship between opioid use and depressive symptoms by interviewing 173 opioid users twice over a period of 4.5 years. In this sample, occasional opioid users had the lowest depressive symptom scores and opioid-dependent individuals had the highest scores. Moreover, a change in opioid use status from not dependent at the first interview to dependent at the second interview was associated with an increase in depressive symptoms. These studies suggest a progression in the severity of depression with increased opioid use. This is consistent with observations that opioid-dependent patients generally experience major difficulties managing dysphoric mood states (90). In one study, depression induced through hypnosis produced significant increases in drug craving for opiates (91). Brewer et al. (92) found depression to be one of 10 variables that predicted continued opiate use. Kosten et al. (93) showed that opiate abusers who are depressed at the beginning of drug abuse treatment were less likely to be abstinent over the long term than non-depressed opiate abusers. Depression may also contribute to suicidal behavior in opiate addicts. Chatham et al. (94) found that suicidal methadone-maintained patients had higher levels of social dysfunction, risk-taking behavior, hospitalization, and depression than did non-suicidal methadone-maintained patients.

There are few rigorous studies evaluating the efficacy of antidepressants for the treatment of MDD in opiate-dependent patients. Nunes et al. (95) noted a number of methodologic limitations in the early studies, particularly the cross-sectional assessment of mood, which may reflect transient symptoms rather than an autonomous mood disorder. A subsequent double-blind, placebo-controlled trial examined the effects of

imipramine in a sample of 137 methadone-maintained opiate addicts with primary depression (96). Among patients who completed the 6-week trial (*n*=84), 57% of the imipramine-treated patients and 7% of those on placebo were identified as responders. The authors concluded that imipramine was an effective antidepressant among methadone-maintained patients with a comorbid depressive syndrome (96).

Three studies examined the effects of fluoxetine in depressed methadone-maintained patients (97–99). An open trial of the drug showed that, although fluoxetine appeared to significantly decrease depressive symptoms, its effects on substance use were inconclusive (98). In a subsequent 12-week, double-blind trial in which 44 depressed methadone-maintained patients were randomized to fluoxetine or placebo, depressive symptoms and heroin use improved equally in both groups (99). More recently, 49 methadone-maintained patients were randomly assigned to receive fluoxetine or placebo over 12 weeks (97). In this study, both groups showed significant improvements in depressive symptoms, life functioning, and social impairment, with no advantage for the fluoxetine treatment group (Table 2).

In summary, as with alcohol dependence, the relationship between opioid use disorders and depression appears to be bidirectional, in that chronic opioid use leads to depressive symptoms and persistent depressive symptoms increase the risk of drug use. TCAs appear to be efficacious in depressed opioid addicts. Additional trials are required to determine what role fluoxetine or other SSRIs may play in this population. Since antidepressants have been reported to inhibit the metabolism of methadone and buprenorphine (100–102), the potential for such an interaction should be considered when antidepressants are prescribed for patients receiving opioid agonist maintenance.

Cannabis

The “amotivational syndrome,” which consists of social and intellectual impairments in chronic marijuana users (103), has also been called a “depression equivalent” (104). This conceptualization has sparked interest in the relationship between cannabis use and depression. Andreasson and Allebeck (105) reported an elevated suicide rate among Swedish cannabis users, though these findings were not replicated in the U.S. (106).

In one of the first studies of the comorbidity of cannabis use with depression, Paton et al. (107) followed cannabis-using high school students for one year. These investigators found that depressed mood was related to the initiation of cannabis use in first-time users, but was also associated with

Table 2 Pharmacotherapy Studies in Depressed Opioid Addicts

Reference	Total *N*	Medication	Study design	Study duration (weeks)	Comment
Nunes et al., 1991 (95)	17	Imipramine (IMI)	Open trial	6–44	53% of patients showed reduced depressive symptoms and drug

					use.
Petrakis et al., 1994 (98)	22	Fluoxetine (FLX)	Open trial	12	Although FLX decreased depressive symptoms among subjects with depression, its effect on substance use was inconclusive.
Nunes et al., 1998 (96)	137	IMI	Placebo-controlled	12	Robust effect of IMI on depressive symptoms. IMI was also superior to placebo on self-reported measures of substance use and craving.
Petrakis et al., 1998 (99)	44	FLX	Placebo-controlled	12	No effect of FLX on either depressive symptoms or drug use.
Dean et al., 2002 (97)	49	FLX	Placebo-controlled	12	No effect of FLX on depressive symptoms, life functioning, or social impairment.

the termination of cannabis use among regular users. Weller and Halikas (108) found that 44% of 97 regular marijuana users had a history of major depression, although, interestingly, 50% of the control group also reported a history of major depression. More recently, the Australian National Survey of Mental Health and Well-Being (109) showed a moderate association between cannabis use and the prevalence of anxiety and mood disorders in the past year. Among those with DSM-IV cannabis dependence, 14% met criteria for a mood disorder compared to 6% of non-users, and 17% met criteria for an anxiety disorder compared to 5% of non-users. However, these associations did not remain significant after controlling for potential confounds (e.g., other drug use, demographics, and neuroticism). Green and Ritter (110) found a weak association between early use of marijuana and depression during adulthood, which was mediated by psychosocial variables (e.g., education and marital status) and other drug use. In this study, the frequency of marijuana use during adulthood was not significantly associated with increased depression.

In order to clarify the longitudinal relationship between cannabis use and mood symptoms, Bovasso (111) studied 1920 participants at the Baltimore site of the ECA study. They subdivided the sample on the basis of presence of depressive symptoms and of a cannabis abuse diagnosis at baseline. Among participants who at baseline had no depressive symptoms, a diagnosis of cannabis abuse was associated with a four-fold increased risk of developing depressive symptoms during a two-year follow-up period. The converse was not true: among participants with no diagnosis of cannabis abuse, the presence of depressive symptoms at baseline failed to predict cannabis abuse at the follow-up assessment. In a study of 133 draftees to the Italian army, Troisi et al. (112) assessed depressive and anxiety symptoms after 2–5 days of abstinence from cannabis. In this cross-sectional study, the severity of depressive and anxiety symptoms increased progressively with the degree of involvement with marijuana.

While a number of studies suggest that heavy cannabis users are likely to develop depressive symptoms, none of them directly implicates the pharmacologic actions of cannabis. However, two small studies examined the effects of cannabis on the mood of depressed individuals (113,114). In a one-week study, Kotin et al. (113) administered 5mg of tetra-hydrocannabinol (THC) daily to eight patients hospitalized for moderate-to-severe depression. Among these individuals, four experienced drowsiness with no mood changes, while the other four experienced anxiety, depersonalization, and/or increased dysphoria. Ablon and Goodwin (114) compared the effects of THC (5–40 mg/day) with placebo in 13 depressed inpatients. Seven of the participants had dysphoric reactions. Together, these studies suggest that cannabis may act as a "mood intensifier" and as such may worsen already existing depressive symptoms.

To date, there are only two reports of controlled studies of antidepressant treatment in cannabis-dependent patients (115,116). In the first study (115), 10 daily marijuana smokers (who smoked 6–7 cigarettes/ day) were given bupropion, with little effect. However, during cannabis withdrawal, use of the medication was associated with a worsening of depressed mood, restlessness, irritability, and insomnia. The authors concluded that bupropion does not show promise as a potential treatment for marijuana dependence (115). In a recent placebo-controlled study, Haney et al. (116) examined the effects of nefazodone treatment of marijuana withdrawal in seven heavy smokers. Nefazodone significantly improved marijuana withdrawal symptoms such as anxiety and muscle pain, but participants still reported substantial discomfort. These results highlight the need for research directed toward the identification of efficacious pharmacological treatments for cannabis dependence (116).

In summary, although marijuana is the most commonly used illicit substance in the U.S., its association with mood symptoms remains unclear. Because depressive symptoms do not appear to be pharmacologically induced by cannabis, the DSM-IV (11) has no diagnostic category for cannabis-induced mood disorder. Nevertheless, heavy cannabis users often present with depressive symptoms, which may be clinically significant and may require treatment interventions. Additional research is needed to evaluate the efficacy of antidepressant therapy in these patients.

Amphetamines

Over the past 40 years, there have been a number of published reports about the effects of stimulant use on mood among depressed patients (117,118). Masand et al. (118) reported three cases of medically ill patients who developed elated mood, pressured speech, flight of ideas, and decreased need for sleep following stimulant therapy. Discontinuation of the stimulant led to a rapid resolution of symptoms. El-Mallakh (117) found, in an open-label study, that methylphenidate, when added to a mood stabilizer, was effective in treating depressed bipolar patients. Treatment produced adverse effects that required three patients (21%) to discontinue the treatment because of anxiety, agitation, or hypomania.

Recent studies have examined the relationship between methamphetamine abuse and depressive symptoms (119,120). Kalechstein et al. (119) found that methamphetamine-dependent arrestees (n=1580) were more likely to report depressive symptoms and suicidal ideation in the 12 months preceding the assessment than arrestees without

methamphetamine dependence. Rawson et al. (120) found high levels of depressive symptoms in methamphetamine users, which, despite improvements in drug use, persisted for 2.5 years after they had entered outpatient treatment for methamphetamine abuse. Depressive symptoms have also been associated with amphetamine withdrawal. Watson et al. (121) described four cases of amphetamine withdrawal characterized by fatigue, psychomotor depression, anhedonia, and sleep disturbances. For three of the four individuals, depressive symptoms peaked 48–72 hours after the last dose of amphetamine, and declined substantially by the fourth day. The depressive symptoms correlated with a decrease in the excretion of 3-methoxy-4-hydroxyphenethyleneglycol, a metabolite of norepinephrine, and changes in sleep EEG patterns.

Amphetamines have also been used as pharmacologic probes in depression (122,123). Because of their ability to release dopamine within the mesocorticolimbic area and other components of the brain reward system, these agents elicit positive mood and physiological (e.g., increased heart rate) responses that may be altered in depressed individuals (123). Tremblay et al. (123) compared the behavioral and physiological effects of a single (30 mg) dose of oral dextroamphetamine in 40 unmedicated individuals with MDD and 36 control subjects. In the depressed group, baseline severity of depression was highly correlated with the intensity of the rewarding effects of the drug.

In summary, there is clear evidence that amphetamines and mood are linked. Human and animal studies show that significant mood abnormalities may occur during intoxication or chronic use of amphetamines, as well as during withdrawal from these drugs. In addition, the use of amphetamines has been advocated to treat a variety of depressive disorders, including bipolar depression (117), refractory depression (124), depression in the medically ill (124,125), and AIDS-related depression (126). Amphetamines have also been studied as pharmacologic probes of depression, and current evidence from such studies (122,123) suggests that there may be a hyper-sensitive brain reward system in depressed patients. Since amphetamines directly affect this brain system, elucidation of the mechanism of this effect has important implications for understanding the comorbidity of mood disorders and stimulant abuse.

Cocaine

Several studies have shown high rates of mood disorders in cocaine abusers. In an early study, Weiss et al. (127) found that 52% of cocaine abusers met DSM-III criteria for a mood disorder (30% unipolar depression and 23% bipolar spectrum disorder). Kleinman et al. (128), using DSM-III-R criteria, found a rate of 28% for current major depression in a sample of 76 cocaine abusers seeking substance abuse treatment. Rounsaville et al. (85) found that, among 298 cocaine abusers seeking treatment, 29% of men and 35% of women met current criteria for major depression. In the same study, 20% of subjects met criteria for bipolar disorder.

While cocaine abusers with mood disorders may represent a clinically and neurobiologically heterogeneous group, most studies have focused on comorbid depression, thereby leaving the important subgroup with comorbid bipolar disorder largely unexplored (129–131). Schmitz et al. (129), in a comparison of depressed with

nondepressed cocaine-dependent patients, found that the comorbid group had higher levels of psychiatric symptoms, higher craving for cocaine, lower perceived social support, and lower self-efficacy to refrain from using drugs. A study by Roy (130) suggests that major depression, among other factors (e.g., sex, family history of suicidal behavior, other psychiatric comorbidity), can predispose cocaine-dependent patients to suicidal behavior.

Although there may be neurochemical differences among subgroups of cocaine users, neurobiological studies have focused on identifying markers that are common to both cocaine dependence and MDD. Elman et al. (131) assessed the correlation between baseline depressive symptoms and the degree of hypothalamic-pituitary-adrenal (HPA) axis activation induced by acute cocaine challenge in 12 cocaine-dependent patients. Cocaine challenge increased plasma levels of ACTH and cortisol, which were correlated with the total score on the Hamilton Depression Rating Scale. This suggests that the HPA axis may be involved in cocaine-induced mood disturbances. Pathiraja et al. (132) found that cocaine withdrawal was associated with transient decreases in platelet imipramine binding, which is thought to reflect altered serotonergic activity in patients with depressive disorders. Further studies on the neurobiologic correlates of cocaine withdrawal may clarify its relation to primary depressive disorders.

Other studies have examined the relationship between depressive symptoms in cocaine users and their response to cocaine administration. Sullener et al. (133) assessed the relationship between the severity of depressive symptoms during early abstinence and subjective effects of intravenous cocaine (40 mg) administered after 5 days of abstinence in 17 cocaine-dependent inpatients. Cocaine users with higher levels of depressive symptoms experienced greater cocaine-induced highs than those with low levels of depression. Sofuoglu et al. (134) examined the relationship between depressive symptoms as measured by the Beck Depression Inventory (BDI) and subjective and physiological responses to smoked cocaine. Lower BDI scores were associated with a smaller subjective and physiological response to cocaine, while higher BDI scores were associated with an enhanced cocaine response. If, as suggested by these studies, the severity of depression experienced by cocaine users is associated with the intensity of cocaine-induced euphoria, then the presence of depressive symptoms may predispose an individual to cocaine use and should be aggressively treated.

Cocaine users experiencing cocaine withdrawal often experience depressive symptoms similar to those of a major depressive episode (135). Animals also exhibit a transient syndrome characterized by anhedonia and depressive symptoms following periods of cocaine self-administration (136). Pharmacological studies targeting depressed cocaine users are largely based on hypothesized neurochemical alterations thought to be produced by chronic cocaine use.

The hypothesis that a hypodopaminergic state underlies cocaine-induced depressive symptoms led to the study of dopamine agonists such as amantidine and bromocriptine in the treatment of depressive symptoms occurring during cocaine withdrawal. However, these studies failed to show a consistent advantage of these medications in reducing cocaine withdrawal symptoms (137,138).

The study of antidepressant therapy of cocaine dependence was fueled by theories implicating monoaminergic dysregulation as a correlate of cocaine-induced depressive

symptoms (139). To date, controlled trials do not consistently support the use of antidepressants for either cocaine dependence (139) or cocaine dependence with comorbid depression. Gawin and Kleber (140) were the first to report on the benefits of desipramine in reducing depressive symptoms associated with cocaine withdrawal. Several subsequent trials, however, failed to replicate these results (136,141–143). TCAs have also been examined for treating cocaine users with comorbid depressive disorders. In a 12-week, placebo-controlled, randomized study, Carroll et al. (144) evaluated the effects of desipramine combined with cognitive behavioral therapy (CBT) or case management in cocaine abusers with or without depression. These investigators found an advantage for desipramine in decreasing depressive symptoms, but no effects on cocaine use. In contrast, CBT enhanced treatment retention and improved cocaine use measures, but had no effect on depressive symptoms. One of the largest placebo-controlled trials in cocaine users (n=113) found that imipramine reduced depressive symptoms, particularly among intranasal users (143). Although imipramine was also superior to placebo in improving cocaine craving, its effects on cocaine use were less clear. In practice, however, the use of TCAs in cocaine users is limited by potential cardiotoxic interactions. Two double-blind, controlled studies evaluating the effects of fluoxetine for depressed cocaine users (145,146) failed to support the role of fluoxetine for the treatment of comorbid cocaine dependence and MDD. However, findings from a small (n=13), 12-week pilot study of venlafaxine for comorbid cocaine dependence and major depressive disorder are promising (147). The 11 patients who completed this study showed significant mood improvements on a median daily dosage of 150mg of venlafaxine. The medication was well tolerated and there was a 75% reduction in self-reported cocaine use from baseline (Table 3).

Although no controlled studies have been conducted for the treatment of cocaine abuse and comorbid bipolar disorder, the use of lithium in this impulsive population may be problematic due to the potential for neurological and renal toxicity in lithium overdose. In addition, this subgroup of bipolar patients may be more likely to have mixed manic episodes, which are more responsive to anticonvulsants than to lithium (24,148). Further studies are needed to demonstrate the relative advantages and risks of various antidepressants and mood stabilizers, as well as psychosocial strategies to treat cocaine abusers with comorbid mood disorders.

Benzodiazepines

The literature examining the association between benzodiazepines and mood symptoms focuses on the adjunctive use of benzodiazepines in depressive disorders (149,150) or their potential to induce depression (151). Although there are case series that report anxious (149) and elderly (152) patients becoming depressed on benzodiazepines, no additional evidence is available to support these findings.

A recent meta-analysis of eight controlled trials of antidepressant treatment of major depression (150) showed that patients receiving antidepressants alone were more likely to have a therapeutic response than were patients on a combination of an antidepressant and a benzodiazepine. Patients on an antidepressant-benzodiazepine combination, however, were 37% less likely to drop out of treatment due to adverse effects compared to those

receiving antidepressants alone. This suggests that adding benzodiazepines to antidepressants in the treatment of depressed patients may enhance treatment retention but could contribute to a reduced therapeutic response. An alternative interpretation of these findings is that patients who need adjunctive benzodiazepine treatment may be those who do not respond well to antidepressants.

The identification of a subgroup of depressed patients who are more likely to benefit from the adjunctive use of benzodiazepines would be clinically useful. In a cross-sectional study, Bruijn et al. (149) evaluated the response of 101 unipolar depressed inpatients to a single high dose of

Table 3 Effects of Different Treatments of Cocaine Use and Associated Mood

Reference	Total *N*	Medication	Study design	Study duration (weeks)	Comment
Gawin and Kleber, 1984 (140)	16	Desipramine (DMI) +psychotherapy	Open trial	12	DMI reduced depressive symptoms associated with cocaine withdrawal.
Arndt et al., 1992 (141)	59	DMI	Placebo-controlled	12	At 12 weeks, the DMI group showed significantly better psychiatric status than the placebo group, but the groups did not differ on any other outcome measure, including cocaine use.
Kosten et al., 1992 (136)	61	DMI or Amantadine	Placebo-controlled	12	Although at week 4 self-reported cocaine use was significantly reduced in the active medication groups compared with the placebo group, this difference became non-significant at week 8.
Carroll et al., 1995 (144)	109	Desipramine+ cognitive-behavioral therapy (CBT)	Placebo-controlled	12	DMI was effective in decreasing depressive symptoms. However, DMI treatment was not associated with greater reductions in cocaine use in either the depressed or the euthymic subgroup.
Nunes et al., 1995 (143)	113	Imipramine (IMI) +counseling	Placebo-controlled	12	Compared to the placebo group, the IMI group showed greater reductions

					in cocaine craving, cocaine euphoria, and depression, but the effect of IMI on cocaine use was less clear.
Cornelius et al., 1998 (145)	17	Fluoxetine (FLX)	Placebo-controlled	12	No significant difference in cocaine use or depressive symptoms between the FLX and placebo groups.
Schmitz et al., 2001 (146)	68	FLX+CBT	Placebo-controlled	12	FLX showed no significant effects on mood or cocaine use.
McDowell et al., 2000 (147)	13	Venlafaxine+relapse prevention therapy	Open trial	12	The 11 patients who completed this study showed significant mood improvements with venlafaxine 150mg/day. Overall, subjects reported >75% reduction in cocaine use compared to pretreatement.

diazepam. Response to the diazepam challenge among these patients was dependent upon their level of trait anxiety. Those with high trait anxiety showed a reduction of depressive symptoms and no sedation. In contrast, the subgroup of depressed patients with low trait anxiety showed sedation with no diminution of depressive symptoms.

In summary, the role of benzodiazepines in producing or exacerbating depressive symptoms remains to be determined. However, benzodiazepines may have a role in the treatment of depressed patients with high levels of anxiety. They may also enhance treatment retention among patients who tolerate antidepressants poorly. The use of benzodiazepines in patients with comorbid MDD and substance dependence must, however, be tempered by the recognition that benzodiazepines can be dangerous when combined with other brain depressants and that they have the potential to produce dependence in this susceptible population.

Hallucinogens

Although most hallucinogens may induce transient disturbances of mood (153), reports have focused mostly on the depressant effects of LSD and MDMA. In one of the earliest studies of these effects, Frosch et al. (154) interviewed 34 LSD users, following ingestion of the drug. Thirteen subjects in the group reported enjoying the experience, fourteen had no subjective effects, and seven felt dysphoric with a sense of hopelessness. Among the dysphoric participants, two attempted suicide. Suicidality and intense dysphoria may also be associated with psychosis and intense anxiety (“bad trips”) following LSD ingestion, though these effects typically remit within 24 hours (155).

Two recent studies examined the relationship between MDMA use and depression (156,157). The first study assessed mood over five days among 12 individuals who reported having taken MDMA, comparing it with the effects of 1–3 alcoholic drinks in non-MDMA users (156). The MDMA users reported euphoria on day one and a significantly lower mood on day 5, with some participants scoring within the range for

clinical depression. In contrast, the group that consumed alcohol showed subtle mood changes that followed a U-shaped curve, with the lowest point on day 2. MDMA-induced mood abnormalities may be related to changes in serotonergic functioning. In contrast to other hallucinogens, MDMA appears to cause serotonergic neurotoxicity, which is associated with persistent depression. MacInnes et al. (157) reported that former chronic MDMA users had significantly higher levels of depression than matched controls. Further studies are needed to determine whether MDMA users are at higher risk of experiencing persistent depressive symptoms than are users of other hallucinogens. In view of reports of seizures and exacerbation of flashbacks in former hallucinogen users treated with fluoxetine (158,159), the treatment of clinically significant depression in hallucinogen users also requires systematic study.

CONCLUSIONS

Epidemiological studies, in both community and clinical samples, show high rates of comorbidity between mood and substance use disorders. The association between depression and substance use disorders appears to be bidirectional, in that depressive symptoms may lead to substance use and some substances of abuse may cause or exacerbate depressive symptoms. In general, mood disorder comorbidity has negative prognostic implications, being associated with frequent hospitalizations, relapses, psychosocial impairments, and substantial morbidity relative to substance abusers without mood disorders. Women with substance use disorders show higher levels of comorbid mood disorders and may show a better response to addiction treatment than their male counterparts. While recent data demonstrate the positive effects of integrated treatment for patients with comorbid mood and substance use disorders, these findings have not been consistently implemented in clinical practice. Codification of existing knowledge through practice guidelines may improve the clinical management of these patients. Well designed and carefully implemented research is needed in areas such as the treatment of comorbid bipolar disorder and substance use disorders, and the optimal combinations of pharmacologic and psychosocial treatments for different subtypes of comorbid patients. Findings from such studies could be used to inform clinical care, thereby enhancing both substance use and psychiatric outcomes in this patient population.

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7
Substance Dependence and Anxiety Disorders

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INTRODUCTION

The relationship between anxiety, anxiety disorders, and substance use disorders is complex. A number of studies suggest that anxiety disorders, symptoms of anxiety, and substance use disorders commonly co-occur. In the Epidemiologic Catchment Area Study (ECA) (1), approximately 24% of individuals with anxiety disorders had substance abuse or dependence at some time in their lives. In the National Comorbidity Study (NCS) (2) it was reported that individuals with anxiety disorders were 2.5 times more likely to have a lifetime substance use disorder when compared to the general population. The interaction between these disorders and symptom clusters, however, is not likely to be unidirectional, but rather multifaceted and variable. Anxiety disorders may be a risk factor for the development of substance abuse and dependence. They can modify the presentation and outcome of treatment for substance use disorders, just as substance abuse and dependence can modify the presentation and outcome of treatment for anxiety disorders. Anxiety symptoms are also likely to emerge during the course of chronic intoxication and withdrawal. The interplay of these variables differs in individual clinical cases and between different anxiety disorders.

ETIOLOGY

A number of recent studies have focused on exploration of the etiologic relationships between anxiety and substance use disorders. In the basic science area, the relationship of neuroadaptation and stress in relapse to substance use has been an area of intense investigation. Corticotrophin releasing factor (CRF), one of the key hormones involved in the stress response, has been implicated in the pathophysiology of anxiety and affective disorders as well as addictive disorders (3). Other investigators have explored the role of endogenous opiates in both addictive and anxiety disorders (4). Noradrenergic and other neurotransmitter systems may also provide a neurobiologic link between anxiety and substance use disorders.

On a clinical level, a recent volume of the journal *Addictive Behaviors* (5) focused on the area of anxiety sensitivity and addictive behaviors. Anxiety sensitivity (AS) was defined as a specific tendency to experience fear in response to arousal-related body sensations, and has been linked to increased risk for the development of both anxiety

disorders and substance use disorders. The relationships between AS and cigarette smoking (6), and between AS and alcohol, marijuana, and cigarette use in adolescents (7), were supported by papers in this volume. The editors conclude that there is more evidence supporting a positive relationship between AS and the use/abuse of sedative drugs and alcohol than between AS and stimulant drugs (5).

Another approach to the investigation of the etiologic relationship between disorders is to study the order of onset. In the NCS (2), anxiety disorders were reported as more likely to occur before the onset of substance use disorders, whereas mood disorders were more likely to present after the onset of substance use. In a recent clinical study (8), adults with substance use disorders were evaluated to determine the order of onset of substance use and psychiatric disorders. Attention deficit hyperactivity disorder (ADHD) and multiple anxiety disorders typically preceded the onset of substance abuse, whereas mood disorders generally developed after the onset of substance abuse. Clinical studies of anxiety in substance-dependent individuals have also focused on the relationship of substance use and withdrawal to anxiety symptoms. In a study of treatment-seeking alcohol-dependent individuals, 40% of individuals endorsed significantly elevated levels of state anxiety upon admission, but there was a rapid decrease in symptoms of anxiety over the first week of treatment, and symptoms continued to decrease during each week of continued abstinence (9). In another study (10), anxiety rating scales were administered to a group of alcohol-dependent individuals who were subsequently subdivided by structured clinical interview into a group who had an anxiety disorder and a group who did not. Those individuals who had a comorbid anxiety disorder had higher anxiety levels during and after acute withdrawal. The authors concluded that it may be possible to identify individuals with anxiety disorder early in treatment so that both the substance use and psychiatric problems could be addressed. In a treatment-outcome study (11), the Spielberger State-Trait Anxiety Inventory was administered to a group of cocaine-dependent individuals during treatment. Anxiety scores significantly declined during treatment and elevated anxiety at pretreatment was associated with negative consequences of use. The authors concluded that most anxiety in substance-dependent individuals is related to negative consequences of use and will resolve with abstinence.

Family studies of alcoholism and anxiety disorders have shown mixed results. One recent study found elevated rates of anxiety disorder in the relatives of patients with alcoholism and vice versa, suggesting that these disorders share common susceptibility factors (12). It is clear that there is a great deal of investigation in this area, sometimes producing conflicting results. With this in mind, it is important to individually consider the relationship between anxiety and substance use for each patient.

DIAGNOSTIC CONSIDERATIONS

An overarching concern in the area of comorbid anxiety and substance use disorders is the accurate diagnosis and differentiation between substance-induced states and primary anxiety diagnoses. It is clear that the use of some substances (e.g., marijuana, stimulants) is associated with anxiety symptoms and withdrawal of other substances (e.g., alcohol, opiate, benzodiazepines) is marked by anxiety states. It is also likely that chronic use of

substances of abuse, which have powerful effects on neurotransmitter systems involved in the production of anxiety disorders, may unmask vulnerability or lead to organic changes that manifest as anxiety disorder.

The best way to differentiate substance-induced transient symptoms from anxiety symptoms that warrant independent treatment is through observation during a period of abstinence. A key issue is the duration of abstinence necessary for accurate diagnosis. As mentioned earlier, anxiety disorder symptoms have substantial overlap with symptoms induced by substance use and withdrawal states. The necessary abstinent time for diagnostic purposes is likely to vary by diagnosis and by the substance being used. For long half-life drugs (e.g., some benzodiazepines, methadone), withdrawal symptoms may be quite protracted and several weeks of abstinence may be essential for accurate diagnoses. For shorter-acting substances (e.g., alcohol, cocaine, short half-life benzodiazepines), duration of both the acute intoxication and withdrawal is likely to be briefer and it may be possible to make valid diagnoses with shorter periods of abstinence. A family history of anxiety disorder, the onset of anxiety symptoms before the onset of substance abuse and dependence, and/or sustained symptoms of anxiety disorder during lengthy periods of abstinence in the past all weigh in favor of making a diagnosis of an anxiety disorder in cases where the diagnosis remains unclear.

Another key issue is the best method for diagnosing comorbid anxiety disorders in individuals with substance use disorders. Because anxiety is so commonly seen in association with substance use disorders, any patient presenting for treatment of anxiety should be screened specifically for alcohol and other substance use. It is important to bear in mind that caffeine and some over-the-counter medications (e.g., ephedrine, pseudoephedrine, dextromethorphan) can cause substantial anxiety and, while the use of these substances in an individual case might not constitute substance abuse, decreasing their use may be of enormous benefit in decreasing symptoms of anxiety.

Because of the high rate of co-occurrence of psychiatric and substance use disorders, screening patients presenting at either substance use or psychiatric treatment settings is critical. However, there is increasing pressure within both psychiatric and substance use treatment settings to assess patients quickly and efficiently. There are several brief screening tools that have been demonstrated in psychiatric settings to be useful in screening for substance use disorders. These include the Alcohol Use Identification Test (AUDIT) (13), the Michigan Alcohol Screening Test (MAST) (14), and the Drug Abuse Screening Test (DAST) (15,16). The AUDIT is also useful in the identification of hazardous drinking in substance-dependent patients (17). Screening for psychiatric disorders in substance abusers is an under-investigated area and may be particularly problematic because of symptom overlap. In a recent study (18), the SCL-90 was found to have moderate specificity and high sensitivity in screening for anxiety and mood disorders in substance use patients. In terms of making a more definitive diagnosis of an anxiety disorder in individuals with substance use disorder, the Structured Clinical Interview for DSM-IV (SCID) is widely considered to be one of the best diagnostic instruments for psychiatric disorders. In one study, however, the concurrent, discriminant, and predictive validity of the SCID for making anxiety disorder diagnoses in substance abusers was found to be poor (19). This is probably because of the overlap of symptoms described above. Recently, modified versions of the SCID have been

developed which are designed to overcome some of the drawbacks of the SCID. Specifically, the Psychiatric Research Interview for Substance and Mental Disorder (PRISM) is designed to develop the chronological relationships between the psychiatric symptom and substance use for the purpose of diagnostic clarity (20).

This chapter is divided into sections that address individual anxiety disorder diagnoses. For each diagnosis, the prevalence of comorbidity, as well as diagnostic and treatment considerations, will be discussed. This topic has become a focus of clinicians and researchers relatively recently, so for many of the disorders to be discussed few data exist. There are relatively more studies exploring the relationship between anxiety disorders and alcoholism than for substance abuse. In areas where data are lacking, relevant studies concerning alcoholism and anxiety disorders will be cited and general principles guiding appropriate clinical management of comorbid patients will be reviewed.

PANIC DISORDER

The ECA study revealed a 1.5% lifetime prevalence of panic disorder among adults. Of those patients with panic disorder 36% had a co-occurring substance use disorder (1). In this study, the risk of alcohol or other substance abuse in patients with panic disorder was 2.4 times higher than that in the general population (21). Most of the literature examining panic disorder and substance use disorders has focused on alcoholism rather than drug abuse. The estimated prevalence of panic disorder and agoraphobia in alcoholic samples ranges from 5 to 42% (22). In one study of a methadone-maintained population, 6.9% met criteria for panic disorder and 11.8% met criteria for agoraphobia (23). Rosen and Kosten (24) reported that 13% of 141 methadone-maintained patients had panic disorder. Cox and colleagues (25) studied 144 subjects admitted for the treatment of a variety of substance use disorders and found that 33.8% of individuals with panic attacks reported using non-prescribed substances for reducing these attacks. Panic disorder in cocaine-dependent individuals is relatively less common, with one large study estimating the prevalence of panic disorder to be 1.7% in a group of cocaine-dependent subjects (26).

While the idea of self-medication with alcohol and substances of abuse to decrease anxiety associated with panic has been posited by some to explain the high comorbidity of panic and substance use disorders, many substances of abuse (cocaine, marijuana, other stimulants) may actually induce panic attacks and/or panic disorder during periods of acute intoxication (27,28) or withdrawal. Cocaine, amphetamine, and phencyclidine act on the noradrenergic system, which may explain their ability to induce symptoms of panic. Several reports have noted that cocaine can precipitate panic attacks in patients without previous panic disorder (28,29). Panic attacks have also been noted to occur after the use of intranasal phencyclidine and in the context of both sedative-hypnotic and alcohol withdrawal (30). Moran (27) described a series of six cases of patients presenting for treatment of panic disorder and agoraphobia who associated the onset of symptoms with marijuana use.

Several medications have demonstrated efficacy in the treatment of panic disorder, including selective serotonin-reuptake inhibitors (SSRIs), tricyclic antidepressants

(TCAs), monoamine oxidase inhibitors (MAOIs), and benzodiazepines (31). One must proceed with caution when using antidepressants for the treatment of panic disorder. It is well known that antidepressants like TCAs and SSRIs may cause an initial activation leading to a worsening of panic symptoms, which may cause relapse to substance use. Starting with low-dose TCAs and SSRIs is recommended to avoid activation. Another consideration is the latency of onset of TCAs and SSRIs in the treatment of panic disorder. Maximal effectiveness has been known to take as long as 2 to 6 weeks, which may also place a substance user at risk for relapse during the medication initiation period.

Monoamine oxidase inhibitors (MAOIs) are also effective in the treatment of panic disorder; however, these medications are not recommended in substance-using populations. Dietary restrictions, which may be difficult for patients with substance use disorders to adhere to, are necessary because MAOIs can interact with tyramine in the diet, resulting in a hypertensive crisis. Moreover, MAOIs in combination with stimulant substances may precipitate a hypertensive crisis.

Evidence from clinical trials has demonstrated the efficacy of TCAs and the SSRIs in the treatment of panic disorder in non-substance-using patients (32). None of these agents, however, have been systematically examined in substance-using populations with panic disorder. The SSRIs have been shown by some investigators to have modest effects in decreasing alcohol consumption (33), particularly in subgroups of alcoholics (34). While much work needs to be done in further investigating the subgroup of alcohol-dependent individuals most likely to respond to SSRIs, these agents may be a logical choice for the patient with comorbid panic disorder and alcoholism.

Despite their effectiveness in the immediate relief of panic and other anxiety symptoms, benzodiazepines are generally contraindicated in substance-using populations due to their abuse potential. One review of the literature, however, calls into question the evidence supporting the idea that benzodiazepines should not be used in patients with a history of substance abuse or dependence (35). On the other hand, in a recent study comparing the effects of carbamazepine (an anticonvulsant) to lorazepam (a benzodiazepine) in the treatment of alcohol withdrawal, it was found that both agents were equally effective in decreasing symptoms of withdrawal. In the post-treatment period, however, subjects treated with carbamazepine drank significantly less than those treated with lorazepam (36). Benzodiazepines may be considered as adjunctive medication during the early treatment phase when activation or latency of onset of the antidepressants is an issue. If a benzodiazepine is prescribed to a patient with a co-occurring substance use disorder, close monitoring for relapse and limited amounts of medication should be given. As a rule, benzodiazepines should be avoided in patients with a current substance use disorder and used with caution in those with a history of a substance use disorder.

In one small case series, patients with cocaine-induced panic disorder showed substantial symptom improvement after treatment with carbamazepine or clonazepam (29). Since repeated cocaine administration is associated with neuronal sensitization leading to increased limbic excitability (37), it has been hypothesized that this is the mechanism of cocaine-induced panic. Panic disorder in patients with comorbid psychostimulant use may be linked to a sensitization mechanism and may respond particularly well to anticonvulsant medications such as carbamazepine. This hypothesis

warrants further investigation.

As with most anxiety disorders, panic disorder is quite responsive to nonpharmacologic treatment. Behavioral techniques, such as exposure and systematic desensitization, have been shown to be effective (38–41). Relaxation therapy and supportive therapy may also be helpful in some cases (38). It is particularly important to maximize these nonpharmacologic treatments in patients with substance use disorders. First, the ability to self-regulate subjective states and the confidence that can result from successful mastery through behavioral therapy can be helpful to individuals in recovery. Second, many of the cognitive behavioral (CB) techniques used in anxiety disorders have overlap with CB therapies known to be successful in the treatment of substance use disorders. Finally, by learning therapeutic anxiety-reducing strategies, patients may be able to break out of the mindset of using external agents to combat intolerable subjective states and acquire alternative coping strategies.

GENERALIZED ANXIETY DISORDER

Symptoms of generalized anxiety disorder (GAD) have substantial overlap with those of acute intoxication with stimulants and withdrawal from alcohol, sedative/hypnotics, and opiates. While many substance-abusing individuals report anxiety symptoms consistent with GAD, they may not meet diagnostic criteria for GAD because of difficulty in determining the etiology of these symptoms. Chambless and colleagues (42) reported that, among alcoholics, symptoms of GAD were indistinguishable from the effects of alcohol withdrawal. Withdrawal from other substances such as benzodiazepines, sedative/hypnotics, and opiates present similar problems for diagnosis.

The majority of studies estimate that GAD affects between 8.3 and 52.6% of alcohol-dependent individuals (22). In one of the few studies examining GAD and substance abuse specifically, Massion et al. (43) studied 357 subjects with panic disorder (with or without agoraphobia) or generalized anxiety disorder. Sixty-three, or 18%, of those examined had GAD only. Of those with only GAD, 11 % had a history of substance abuse or dependence, excluding alcohol abuse or dependence. Milby and colleagues (44) found that 21% of a methadone-maintained population met criteria for GAD. In one study of cocaine-dependent subjects, approximately 8% had GAD.

The treatment of GAD complicated by substance abuse is challenging. Benzodiazepines are effective in the treatment of GAD; however, as previously discussed, their use in current substance users is controversial. Buspirone is a non-benzodiazepine anxiolytic with no abuse potential. In a 12-week, double-blind, placebo-controlled trial of 61 anxious alcoholics, the buspirone-treated group had greater retention in treatment, reduced anxiety, slower return to heavy alcohol consumption, and fewer drinking days during the follow-up period (45). However, other studies of buspirone in alcoholic populations have yielded mixed results (46). In a placebocontrolled trial, McRae et al. (47) explored the use of buspirone in 28 methadone-maintained patients with high anxiety ratings and found decreased anxiety in the medication-treated group. The data remain somewhat contradictory; however, because of the low abuse potential and reports of success in well-controlled studies, buspirone remains a good choice in

individuals with comorbid GAD and substance use disorders.

Liebowitz and el-Mallakh (48) have reported a case series in which trazodone was of benefit in the treatment of substance abusers with a variety of anxiety disorders. As with buspirone, this agent appears to have no abuse potential and warrants further controlled investigation in the substance abuse population.

While there are no systematic trials of TCAs or SSRIs in the treatment of GAD in individuals with substance use disorders, these agents are useful in non-substance-abusing populations (49). Venlafaxine, a dual serotonin/ norepinephrine reuptake inhibitor also, has demonstrated efficacy in GAD, but has not been investigated in substance-dependent individuals. In conclusion, the best data currently support the use of buspirone in individuals with comorbid substance use disorder and GAD. Trazodone may be useful, but a well-controlled trial has not been done. TCAs, SSRIs, and venlafaxine may also be useful, but there are no trials of these agents specifically conducted in substance-abusing patients.

As with panic disorder, nonpharmacologic treatments for GAD can be very useful. GAD can be effectively managed using relaxation, coping skills, and cognitive-behavioral therapy techniques (50,51). Pharmacotherapy and psychotherapy are likely to complement one another in optimizing patient outcomes. Nonpharmacologic treatment strategies in conjunction with judicious pharmacotherapeutic management should be encouraged.

SOCIAL ANXIETY DISORDER AND SUBSTANCE ABUSE

Social anxiety disorder is defined as a marked and persistent fear of situations in which an individual is exposed to unfamiliar people or to the scrutiny of others. Typically, this fear leads to avoidance of feared situations and results in impairment of academic, occupational, and social functioning. The NCS (52) demonstrated a 13.3% lifetime and 7.9% 12-month prevalence of social anxiety disorder in the general population. There are high rates of comorbidity with other psychiatric disorders in individuals with social anxiety disorder and, in particular, high comorbidity with substance use disorders. Studies examining the relationship between social anxiety disorder and substance abuse have been primarily limited to alcohol use disorders and have found rates of comorbidity ranging from 8% to 56% (22). Consistent with the self-medication hypothesis, individuals with social anxiety disorder reported that alcohol intake reduced social anxiety and that the onset of social phobia occurred prior to the onset of alcohol abuse or dependence (53). In one study exploring the relationship between social phobia and cocaine dependence, Myrick and Brady (54) found lifetime prevalence of social anxiety disorder in a cocaine-dependent population to be 13.9%. In nearly all cases, the social anxiety disorder preceded the onset of cocaine dependence. Milby and colleagues (23) found a 5.9% prevalence of social anxiety disorder in a methadone-maintained population.

Because social anxiety disorder may interfere with an individual's ability to engage effectively in treatment, early recognition is paramount to an improved chance of recovery. Frequently, the diagnosis is overlooked unless specific symptomatology is

thoroughly assessed. A lengthy period of abstinence may not be needed, as the fear of interaction in social situations, which is the core of social anxiety disorder, is not a specific feature of substance use or withdrawal. However, the social fears that occur only during periods of intoxication with marijuana or stimulants should not be considered sufficient to meet diagnostic criteria for social anxiety disorder.

Once the diagnosis of comorbid social anxiety disorder and a substance use disorder has been made, treatment should address both conditions. It may be difficult for these patients to participate in group therapy or 12-step programs such as Narcotics Anonymous and Alcoholics Anonymous. As might be expected, individuals with social anxiety disorder have poor 12-step group attendance (54). A treatment plan that includes individual cognitive behavioral therapy may prove to be more effective. Although there are no studies that examine behavioral treatments in patients with comorbid social anxiety disorder and substance abuse, several types of nonpharmacological treatment such as systematic desensitization, imaginal flooding, graduated exposure, social skills training, and cognitive approaches have proven effective for patients with social phobia (55,56).

Although there are few studies that specifically examine the efficacy of medication treatment of individuals with comorbid social anxiety disorder and substance abuse, many agents have been investigated in the treatment of social anxiety disorder (57). Of these agents, the MAOIs; the reversible inhibitors of monoamine oxidase (RIMAs); the SSRIs, gabapentin and venlafaxine; and the benzodiazepines have documented efficacy. Specifically, paroxetine has received U.S. Food and Drug Administration approval in the treatment of social anxiety disorder. In one placebo-controlled trial, gabapentin was also efficacious in the treatment of uncomplicated social anxiety disorder (58). Several other agents such as bupropion, ondansetron and buspirone may also have efficacy, but have not been well studied. In one small placebo-controlled trial of alcoholic patients with social anxiety disorder, Randall and colleagues (59) found that paroxetine improved alcohol outcomes and decreased symptoms of social anxiety. In choosing a medication for the treatment of comorbid social anxiety disorder and substance abuse, the SSRIs, gabapentin or venlafaxine, would be a reasonable first choice. As previously mentioned, SSRIs may have the additional benefit of producing modest decreases in alcohol consumption. Benzodiazepines, if used, should be monitored carefully and, as previously mentioned, may have a role in providing symptom relief to patients during initiation of SSRI treatment.

OBSESSIVE-COMPULSIVE DISORDER

The ECA revealed a 1–2% lifetime prevalence of obsessive-compulsive disorder (OCD) in the general population (1). Although OCD has been reported to coexist with many other psychiatric disorders (60), little has been reported about the coexistence of OCD and substance use disorders. Diagnosing OCD in substance abusers is somewhat less problematic than other anxiety disorders because substance use and withdrawal and OCD have fewer overlapping features and the characteristic symptoms of OCD are distinctive.

OCD has been reported in approximately 2.7–12% of alcohol-dependent individuals

(22). Using data from ECA, Crum and Anthony (61) explored the association between substance abuse and OCD. The risk of developing OCD was estimated to be 5.6 times higher for individuals using both cocaine and marijuana as compared to individuals using no illicit substances. The odds ratio for OCD among those with marijuana use alone was 2.1, and was 3.2 for cocaine, marijuana, and at least one other substance. Milby and colleagues (23) found that 2.9% of the methadone-maintained individuals they studied met criteria for OCD.

Compulsive foraging for misplaced cocaine has been noted in cocaine addicts (62), though it has not been reported in individuals addicted to other substances. The description of foraging behavior is much like that seen in patients with OCD. Several other investigators have reported transient, obsessive-compulsive symptoms in individuals during intoxication with opiates (63) and hallucinogens (64). The mechanism by which substances of abuse may produce these symptoms remains unclear.

There are no controlled trials or case reports of the treatment of comorbid OCD and substance abuse. Clomipramine and SSRIs are both efficacious in the treatment of OCD (31). However, clomipramine, like other TCAs, may lower the seizure threshold. Toxic interactions with alcohol, stimulants, and CNS depressants are also more likely to occur with clomipramine. Consequently, SSRIs are recommended as the first line of treatment in individuals with OCD and a substance use disorder since there are fewer side effects or potential toxic interactions.

The use of psychotherapeutic techniques in combination with pharmacotherapy is particularly important in the treatment of OCD (65). Cognitive-behavioral therapies including thought-stopping, exposure, and response prevention have convincingly and reliably been shown to be extremely effective in the treatment of OCD (66,67). Again, a synergistic effect of the pharmacotherapy and psychotherapy might be expected.

POST-TRAUMATIC STRESS DISORDER

Post-traumatic stress disorder (PTSD) is one of the most common anxiety disorders in individuals with substance use disorders. In the NCS study, the odds ratio for substance use disorders was 2–3 for men and 2.5–4.5 for women with PTSD (68). Using data from the ECA study, Cottler and colleagues (69) compared assault histories and PTSD in individuals with a substance use disorder to those without a substance use disorder. Of all subgroups studied, cocaine/opiate users were most likely to report a PTSD-qualifying traumatic event (43%), and the overall rate of PTSD was 10 times higher among these individuals than among individuals without a substance use disorder. Reports from treatment-seeking samples of substance abusers also indicate a high prevalence of PTSD. In a number of studies of either drug or alcohol use disorders, lifetime prevalence of PTSD was found to be between 36% and 50%, and the current prevalence of PTSD between 25% and 42% (70–72).

It is likely that substance use (in particular, cocaine use) and repeated withdrawal (in particular, alcohol, sedative hypnotic, and opiate withdrawal) will exacerbate symptoms of PTSD. Cocaine use is associated with paranoia, hypervigilance, sleep disturbance, and autonomic arousal, all of which are features of PTSD. Alcohol, sedative-hypnotic, and

opiate withdrawal are marked by feelings of anxiety and autonomic nervous system hyperactivity, which are believed to have as their origins excessive firing of neurons in the locus ceruleus (73). It is possible that common pathophysiologic mechanisms are responsible for the symptom overlap and exacerbation of symptoms in individuals with comorbid PTSD and substance dependence.

Little is known about the effective treatment of patients with comorbid PTSD and substance abuse or dependence. While the treatment of PTSD is generally multimodal, pharmacotherapy is playing an increasingly important role. One important goal of pharmacotherapy is to reduce key symptoms of PTSD such that individuals can put greater distance between themselves and the traumatic event(s) without the use of alcohol or non-prescribed substances.

TCAs and MAOIs were shown in double-blind, placebo-controlled trials to improve intrusive and depressive symptoms of PTSD (74). There are also uncontrolled reports of the positive effects of carbamazepine, beta blockers, clonidine, benzodiazepines, and lithium. More recently, a number of placebo-controlled trials with relatively large numbers of subjects have demonstrated that SSRIs, specifically sertraline, fluoxetine, and paroxetine, are useful in the treatment of PTSD (75–78). A pilot study of sertraline treatment of PTSD in individuals with comorbid alcohol dependence demonstrated a positive effect of sertraline in improving symptoms of PTSD and decreasing alcohol consumption (79).

The psychotherapeutic treatment of comorbid PTSD and substance abuse has been an area that has received much recent attention. Previously, the conventional approach was to treat the substance use and defer treatment of PTSD. This approach can be problematic because the symptoms of PTSD (e.g., sleep disturbance, intrusive thoughts) may drive relapse to substance use. Several studies investigating manual guided psychotherapeutic strategies specifically targeting co-occurring PTSD and substance dependence have shown preliminary success (80,81). Further investigation of this important area is clearly warranted.

CONCLUSIONS

The interest in co-occurring psychiatric and substance use disorders has grown tremendously in the past ten years. It is clear that co-occurrence of these disorders is common and has an impact on prognosis and treatment. The co-occurrence of anxiety and alcohol use disorders has been more systematically explored than the co-occurrence of anxiety and drug use disorders. The diagnostic issues at the interface of substance or alcohol use disorders and anxiety disorders are particularly difficult because of the substantial symptom overlap between substance intoxication and withdrawal and symptoms of anxiety disorders.

Advances have been made in the treatment of co-occurring substance use and anxiety disorders. In terms of psychotherapeutic treatments, several manuals specifically targeting treatment of patients with PTSD and substance use disorders have been developed. Further investigation of specifically tailored treatments for patients with co-occurring substance use and other anxiety disorders is underway. Many advances have

been made in pharmacotherapy of anxiety disorders in the past ten years. This progress impacts the population with co-occurring disorders because the newer agents have less toxicity, with fewer side effects and interactions with substances of abuse. While there are not many studies specifically targeting pharmacotherapy for co-occurring disorders, those that have been conducted indicate that similar pharmacotherapeutic agents work for anxiety disorders with or without substance use disorders. Furthermore, treatment of anxiety may be associated with decreased substance use. Clearly, specific considerations in choosing a pharmacologic agent for use in patients with substance use disorders include safety, toxicity, and abuse liability. In conclusion, although the co-occurrence of substance abuse and anxiety disorders is an important area in which recent developments provide cause for considerable optimism, much work remains to be done.

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8
Comorbidity of Nicotine Dependence with Affective, Psychotic, and Substance Use Disorders

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INTRODUCTION

The association of nicotine dependence with psychiatric and substance use disorders has been well documented. Consistent with previous studies (1–3), Lasser and colleagues (4), in an analysis of population-based data from the National Comorbidity Survey, found that mental illness was associated with a doubling of the risk of smoking. Individuals with mental illness had elevated rates of smoking, represented a disproportionately high percentage of current smokers in the United States, and were estimated to smoke nearly half the cigarettes consumed in this country. Persons with a history of mental illness were also shown to have an increased prevalence and a higher rate of smoking. Various psychiatric and substance use disorders have been associated with current smoking status. The heaviest rates of smoking have been found among smokers with multiple lifetime psychiatric diagnoses.

Despite this strong association between mental illness and nicotine dependence, historically there has been reluctance among mental health providers to encourage and counsel psychiatric and substance abuse patients to stop smoking. This reluctance stems from several unconfirmed clinical assumptions: 1) psychiatric patients are not motivated for stopping smoking; 2) psychiatric patients cannot tolerate acute nicotine withdrawal; 3) nicotine withdrawal and smoking cessation may lead to an increase in psychiatric

symptoms and undermine psychiatric treatment; 4) smoking cessation may rob severely ill psychiatric patients of one of their few pleasurable activities; and 5) cigarettes serve as a social reinforcer in the traditional psychiatric treatment milieu, where smoking may be seen as the social norm (5–7). Traditional substance abuse treatment programs have advocated against smoking cessation within the first year of sobriety in the belief that: 1) smoking cessation efforts may reduce the patient's focus on sobriety; 2) acute nicotine withdrawal may increase the urge to drink; and 3) substance users may need cigarettes to cope with cravings for alcohol and drugs. Furthermore, nicotine dependence, having few immediate social, vocational, or legal consequences, has been considered relatively benign compared with dependence on other drugs of abuse.

A recent survey (8) revealed that while physicians are likely to assess smoking status among psychiatric outpatients, they are far less likely to counsel them to quit. Patients with diagnoses of affective disorders were the least likely to be offered smoking cessation counseling. Furthermore, psychiatrists were significantly less likely to counsel psychiatric patients to quit smoking than were primary care physicians. Nonetheless, there are compelling reasons for mental health providers to address tobacco issues in their practices and to counsel psychiatric and substance abuse patients to stop smoking. These include: 1) tobacco and nicotine administration and withdrawal may impact on psychiatric symptomatology and cognition; 2) tobacco and nicotine administration and withdrawal may influence neurotransmitter systems; 3) smoking impacts medication side effects and interferes with pharmacological treatment and dose requirements (1); 4) smoking may be related to the development of certain psychiatric disorders (9,10); and 5) high smoking rates are associated with significantly elevated mortality rates in psychiatric and substance abuse patients (11,12). Furthermore: 6) many psychiatric and substance abuse patients are motivated to attempt smoking cessation (13,14); 7) smoking bans have been generally well accepted rather than associated with deleterious ward behavior, as feared (7); and 8) for many patients smoking cessation has not harmed and may help treatment outcomes (15–17).

This chapter reviews issues in the comorbidity of nicotine dependence with psychiatric and substance use disorders. The focus is on the comorbidity of nicotine dependence with selected disorders in which the most research is available, specifically depression, schizophrenia, and alcohol abuse. Areas covered include the prevalence of smoking in specific psychiatric and substance use disorders, key behavioral and biological mechanisms underlying these associations, clinical treatment studies of smoking within psychiatric and substance abuse populations, and implications/directions.

SMOKING AND DEPRESSION

The association between depression and smoking is well established. Research investigating the association of smoking with the clinical diagnosis of major depressive disorder (MDD), depressive symptoms, and negative affect is summarized below.

Prevalence

Smoking and Major Depressive Disorder

Population studies have shown that individuals with a current or former diagnosis of MDD are more likely to smoke than individuals from non-psychiatric samples. In the National Comorbidity Study, Lasser and colleagues (4) found that, among individuals with a diagnosis of MDD during the past month, the rate of current smoking was 45% compared with 22% among individuals with no psychiatric disorder in the past month. Evidence of moderate to strong comorbidity between MDD and nicotine dependence has been observed among individuals as young as 16 years of age (18). The magnitude of the relationship between MDD and smoking has been shown to be large, and independent of the effects of sociodemographic characteristics, current depression, and other psychiatric disorders (19). Furthermore, substantial proportions of cigarette smokers in the general population report a lifetime history of MDD. Among smokers seeking treatment for nicotine dependence, about one-third report a past history of MDD (range 18–61%) (20–25). These rates are much higher than the estimate of lifetime MDD of 17% in the general population (26). Prior to nicotine dependence treatment, smokers with a past history of MDD report greater severity of symptoms of depression (27–29) and anxiety (30) compared to those without a history of MDD.

Smoking and Depressive Symptoms

Smokers report higher levels of depressive symptoms and negative mood than nonsmokers (31–34). Results of clinical trials of nicotine dependence treatment indicate that 34–48% of enrolled smokers were depressed, as classified by a Center for Epidemiological Studies on Depression (CES-D) score of 16 or more (25,35,36). Scores of 16 or more on the CES-D indicate the likelihood of clinical depression, representing the 80th percentile in a representative population. The rates of depressive symptoms observed among smokers are substantially higher than those observed in the general population (15–19%) (37). In addition to the CES-D, higher levels of depression and negative affect have been found in smoking cessation studies using the self-administered Beck Depression Inventory (BDI) (28), the Positive and Negative Affect Scale (PANAS) (38), the Profile of Mood States (POMS) (39), and the observer-rated Hamilton Rating Scale for Depression (HRSD) (40). Higher levels of depressive symptoms are associated with greater severity of nicotine dependence (41). Depressive symptoms are also associated with the use of tobacco in forms other than cigarettes (e.g., spit tobacco, cigars) (42).

Development of Depression During Smoking Cessation

Given the association between depression and nicotine dependence, research has examined whether smokers develop depressive symptoms when they stop smoking. The nicotine withdrawal syndrome as defined by DSM-IV criteria (43) includes symptoms that may overlap with those of a depressive episode. These symptoms include irritability, dysphoria, difficulty in concentrating, and appetite and sleep disturbances. In a study by Covey and colleagues (27), smokers with a past history of MDD were more likely than

smokers without a history of MDD to experience greater severity of nicotine withdrawal symptoms and particularly depressed mood in their first week after quitting. This study, however, was limited by lack of a baseline assessment of withdrawal symptoms; thus the differences between those with and without prior MDD could have reflected pre-existing differences. In contrast, Hayford et al. (28) found no difference by MDD history in change from baseline in BDI scores during treatment with bupropion.

Furthermore, results of a recent study by Burgess and colleagues (44) indicated substantial heterogeneity in patterns of depressive symptoms during quitting among smokers with past MDD. Cluster analysis of BDI scores in the 163 participants from baseline to two weeks post-quit revealed that although 40% of participants belonged to clusters characterized by increasing depressive symptoms during quitting, 47% were in clusters indicated by decreasing symptoms. In this study, participants with a history of several recurrent episodes of major depression and with a younger age at the onset of the first major depressive episode were found to have a higher risk of developing rapid and sustained elevations in depressive symptoms during quitting. Consistent with other research (27,45), depressive symptoms following smoking cessation were associated with lower smoking abstinence rates.

Research studies have also investigated the development of major depressive disorder during smoking cessation. The rates of developing a major depressive episode during smoking cessation attempts have been found to range from 1 to 14% across clinical trials (46–49). Tsoh and colleagues (49) found that a history of MDD was the best predictor of developing MDD following nicotine dependence treatment, regardless of whether individuals achieved smoking abstinence or not. The 12-month incidence of a major depressive episode following smoking cessation treatment among the 304 participants was higher for those with prior MDD (24%) than for those without this history (10%). In this study, baseline depressive symptoms were found to have a significant linear association with risk of manifesting major depression after treatment. Other research has also found that a history of MDD is a risk factor for developing major depression following smoking cessation treatment, especially among individuals who achieved smoking abstinence. In a placebo-controlled trial of sertraline for smoking cessation in smokers with a history of MDD, Glassman and colleagues (47) found that 31% of subjects abstinent from smoking had developed a major depressive episode compared to 6% of those who continued to smoke at 6-month follow-up.

Taken together, it appears that smokers with a history of MDD may be at increased risk for developing depressive symptomatology and major depression during smoking cessation. Furthermore, it appears that certain subsets of smokers with a history of MDD, notably those with early-onset and recurrent MDD, and higher levels of baseline depressive symptoms, may be particularly vulnerable to developing depression during smoking cessation (44,49). Although some research has detected depressive symptoms soon after stopping smoking in individuals with a history of MDD (27), it is possible that the development of depression following smoking cessation may be delayed for some smokers. In a study investigating the impact of smoking cessation on mood levels over 12 months post-quit in individuals with or without MDD histories, the excess incidence of major depression was greatest during the first three months after cessation. In contrast, the excess incidence of depressed affect was most evident during the nine-month post-

quit period (27). Thus, it is possible that differences across studies may be in part due to variances in subsets of subjects with a history of MDD, and in length of time of follow-up.

Most studies of depression during smoking cessation have included individuals with a past history of MDD rather than individuals with current MDD. However, in a study of adult smokers with current MDD enrolled in a smoking cessation program, Thorsteinsson et al. (39) found that those who were successful in quitting showed significant improvement in mood, whereas mood ratings deteriorated in those who resumed smoking. The authors attributed this finding to the considerable professional attention that subjects received during the study period (e.g., support groups, telephone follow-up) as well as the sense of pride and achievement that depressed patients may experience as a result of stopping smoking. Alternatively, it is possible that the 3-week follow-up period used in the study may not have been long enough to detect mood changes. Furthermore, similar to research in smokers with a past history of MDD, it is possible that a subset of smokers with current MDD may be most vulnerable to the depressant effects of smoking cessation.

Depression and Smoking Cessation Outcomes

Research has examined the impact of depression on quitting and on nicotine dependence treatment outcomes. There is inconsistency across studies as to whether a history of MDD is associated with a reduced likelihood of quitting (21,23,29,50–53). An open-label nicotine patch study found that 71% of smokers with a history of MDD, compared to 45% of smokers without a history of MDD, had relapsed to smoking by 4-month follow-up (30). In contrast, other researchers found that the antidepressant bupropion SR was effective for smoking cessation (28), independent of a past history of MDD.

Because smokers with a history of MDD tend to report higher levels of depressive symptoms prior to treatment, baseline depressive symptoms may mediate the relationship between MDD history and smoking treatment response (19,22,53). Indeed, the evidence indicates that baseline depressive symptoms and other negative affect-type symptoms are consistently associated with poorer smoking treatment outcomes (35) and reduced likelihood of quitting (30,40,54). Over a decade ago, Anda and colleagues (55) found in a population-based sample that smokers classified as depressed on the CES-D were 40% less likely to quit smoking at 9-year follow-up than nondepressed smokers. Subsequent research indicates that even low levels of depressive symptoms prior to treatment are associated with relapse to smoking. Among those receiving placebo medication in a trial of fluoxetine for smoking cessation, smokers with baseline scores of 2 or more on the HRSD were more likely to relapse to smoking compared with participants with scores of 0 or 1 (40).

Moreover, increases in depressive symptoms following smoking cessation, particularly during the first weeks of abstinence, have been associated with poorer smoking cessation outcomes and subsequent relapse across several studies (27,28,44,56,57). Similar to other addictive behaviors, negative mood states are the most frequently reported precipitant of smoking relapse episodes (34).

Depression and Adherence to Nicotine Dependence Treatment

Some research has examined whether a history of MDD or baseline depressive symptoms impact on adherence to smoking cessation treatment regimens. It might be expected that depressive symptoms and history may reduce a smoker's motivation to comply with a medication regimen or to engage in the behavioral changes encouraged in a structured treatment program. However, in a study of bupropion SR for relapse prevention, no differences were found by MDD history on self-reported medication compliance throughout the 45-week double blind phase (21). Similarly, Hitsman et al. (57) observed that baseline depressive symptoms were not associated with degree of medication compliance in a trial of fluoxetine. With respect to session attendance, some studies indicated that a history of MDD (58) or baseline depressive symptoms (59) was associated with fewer treatment sessions attended, although these findings were not confirmed in other reports (60). Overall, findings suggest that smokers with a history of MDD and baseline depressive symptoms can engage in smoking cessation treatment and comply with treatment regimens.

Gender Differences

Significant gender differences exist in the prevalence rates of MDD (61), with women twice as likely as men to report a lifetime history of the disorder (21.3% vs. 12.7%) (26). Depressed women may be particularly vulnerable to smoking cessation treatment failure and relapse following a period of abstinence (46). Among low-income women bringing their children to pediatric clinics, greater levels of depressive symptoms and perceived stress were associated with higher levels of nicotine dependence (62). These relationships were stronger for African American than for Caucasian women. The authors postulate that the observed ethnic differences may reflect social-environmental influences rather than biological-metabolic differences. Recent studies indicate that, among smokers attending clinic-based cessation programs, women are less likely than men to be successful in maintaining smoking abstinence (63,64). Given the greater likelihood that females will respond with depressive symptoms post-quit (27,65), researchers have noted the importance of tailoring smoking cessation interventions to women, and focusing on depression and negative mood in treatment (46).

Mechanisms Underlying the Smoking/Depression Association

Several mechanisms have been hypothesized to explain the observed relationships between depression and nicotine dependence. They include: 1) depression predicting smoking onset; 2) smoking predicting development of depression; and 3) shared familial, genetic, and psychosocial etiologies.

Longitudinal, epidemiological studies indicate that *depression is associated with initiation of cigarette smoking* (66,67). These observations are consistent with the self-medication model of substance use. According to this model, depressed individuals may use cigarettes as a strategy to cope with negative affect by deriving stimulant, mood-elevating properties from nicotine (68). Mood enhancement may result from nicotine's

ability to effect changes in neurotransmitters and acute physiological processes. It has been hypothesized that nicotine administration may impact on the dopaminergic system through increased activity in the nucleus accumbens (69). Other research suggests that nicotine use is associated with increased release of norepinephrine at the locus ceruleus (70). Nicotine may affect the dopaminergic and adrenergic systems through its impact on catecholamine release—a process similar to that found in antidepressant medications (71). Further mood-enhancement properties of nicotine may be linked to cortical arousal associated with activation of nicotinic receptors in the midbrain reticular formation and limbic systems (72).

There is some evidence that nicotine may act as an antidepressant. Nicotine administered through smoking has rapid action and produces almost immediate drug effects including pleasure, arousal, and attenuation of negative mood (68). Although relatively little is known about the effect of nicotine on mood independent of smoking behavior or nicotine withdrawal, some data suggest that nicotine administered transdermally is associated with acute reductions in depressive symptoms in nonmedicated *nonsmokers* with current MDD (73,74). The mood-enhancing, reinforcing effects of nicotine may be especially motivating for currently depressed smokers. Persistent mood disturbance has been found after 30 days of cigarette abstinence, reflecting a loss of inherent self-medication effects of smoking and/or the unmasking of psychopathology (75,76). Research suggests that the psychological function of regulating negative affect is a motive for cigarette use (77). Positive smoking outcome expectancies, such as social facilitation, mood enhancement, and relaxation, may augment the relationship between negative affect and smoking over time (78).

On the other hand, some epidemiological investigations of adolescents indicate that *smoking leads to the development of depression* (79,80). In a study of 6863 U.S. adolescents aged 12–18, cigarette smoking at baseline was the strongest predictor of notable depressive symptoms four years later (32). Moreover, teens that remained or became current established smokers during the follow-up period had the highest rate of development of depressive symptoms (19% for both groups) compared with those who quit smoking (12%) or were nonestablished smokers at both time periods (10%). A subsequent study also observed that, among adolescents initially depressed at baseline, initiation of cigarette smoking during the follow-up period was associated with persistence of depression (81). It is possible that depressed adolescents who take up smoking may be less likely to develop alternative coping skills to manage stressful situations, resulting in a continuation of depressed mood.

The observed influences from depression to smoking and smoking to depression also support the plausibility of *shared etiologies*, including environmental, genetic, and psychosocial variables. Because familial factors are etiologically important in both depression and smoking, the observed association could result from familial, environmental, and/or genetic factors that predispose to both conditions (50). For example, maternal depression could be an important factor in the development of both depression and smoking (82). Furthermore, genetic similarity among family members may manifest in specific personality attributes (e.g., neuroticism) that underlie both smoking and depression (75). In a large investigation of female twin pairs, higher concordance rates for comorbid smoking and MDD were found in the monozygotic

probands than in the dizygotic probands, suggesting that the relationship between smoking and major depression may result from genetic factors that predispose individuals to both conditions (83). However, in a recent case-control study (84) researchers interviewed relatives of probands selected from the community and found that major depression in the probands was not associated with an increased risk of smoking in the relatives.

It is also possible that genetic variation in certain neurotransmitter systems may increase liability to both depression and substance use. For an overview of the common neurobiological mechanisms implicated in depression and nicotine use, the reader is referred to an article by Laje and colleagues (76). Lerman and colleagues (36) hypothesized that, of the five known types of dopamine receptors, the D4 receptor may be especially relevant to self-medication smoking among depressed smokers because it is highly expressed in areas of the brain involved in emotion and reward-seeking behaviors. Smoking to increase arousal and to reduce negative affect was significantly heightened in depressed smokers homozygous for the short alleles of DRD4, the gene encoding the D4 receptor, but not in those heterozygous or homozygous for the long alleles of DRD4. These preliminary results suggest that the rewarding effects of smoking may depend, in part, on genetic factors involved in dopamine transmission.

Psychosocial and cognitive coping factors have also been found to mediate or moderate the relationship between smoking and depression in adolescents, including rebelliousness (85), high receptivity to tobacco advertising (42), and deficits in coping resources and emotional self-regulation (86). Depressed smokers report less self-efficacy or confidence in their ability to quit smoking prior to nicotine dependence treatment (33), and exhibit significantly fewer active coping responses (35). Richmond and colleagues (87) found that a ruminative response style, which involves self- and symptom-focused attention, accounted for more variance in current and past depressed mood and lifetime depressive symptoms in smokers than in nonsmokers. These findings suggest that, by responding to their depressed moods with thoughts and behaviors that direct attention toward self and symptoms, depressed smokers may exacerbate their depressed moods.

Depression and Nicotine Dependence Treatment

Pharmacotherapy

Researchers have attempted to improve smoking cessation outcomes for depressed smokers with treatments that target negative affects. The efficacy of several antidepressant therapies has been investigated in relation to increasing smoking abstinence rates. For example, bupropion SR (28) and nortriptyline (52) are effective for smoking cessation for smokers with or without a history of MDD. Moreover, baseline depressive symptoms were not predictive of response to 7 weeks of bupropion therapy (300 mg/d) prescribed for smoking cessation (28). In a relapse prevention trial, smokers abstinent at the end of 7 weeks of open-label bupropion SR were randomly assigned in a double-blind fashion to bupropion or placebo for 45 weeks. No differences were found in the point prevalence abstinence rates or smoking relapse rates by history of MDD (21).

Research has examined whether the positive smoking outcomes of these

antidepressants are mediated by reductions in depressive symptoms when quitting. Some studies examining bupropion (88) or nortriptyline (52) did not find treatment effects to be associated with decreased depression after quitting. However, Hall et al. (52) found that, compared to placebo, nortriptyline appears to alleviate post-cessation negative affect as measured with the POMS. Moreover, a recent study that enrolled 600 African American smokers found that, compared to placebo, bupropion SR was associated with a significantly greater mean reduction from baseline in CES-D depressive symptoms at 6 weeks (89). In addition to ethnic differences, the participants in that study had, on average, lower income and education levels, and were less likely to be living with a partner, than participants in other studies. Thus, there may be related differences in stress and distress levels that could account for the discrepant results.

Interesting findings have emerged with the antidepressant fluoxetine, in that it appears to selectively benefit smokers with depressive symptoms. Participants reporting depressive symptoms at baseline show significantly higher smoking abstinence rates with fluoxetine (20mg/d) than placebo (88). Hitsman and colleagues (57) also found that higher HRSD scores were associated with increased likelihood of quitting at 3-month follow-up among those receiving fluoxetine. In contrast, among those receiving placebo, higher HRSD scores were associated with a decreased likelihood of abstinence. Another study (90) randomly assigned smokers to active or placebo fluoxetine. All participants also received the nicotine inhaler and five group sessions of behavior therapy. As in other studies showing no main effect for fluoxetine in the overall sample, this study found that fluoxetine added to nicotine inhaler did not improve the abstinence rates at post-treatment or any follow-up period. However, in a sub-group analysis, active treatment was more beneficial than placebo at 1-year follow-up in the depressed (BDI score of ≥10) (19% vs. 7%) versus the nondepressed (31% vs. 23%) sub-samples.

Nicotine replacement therapy may also benefit smokers with depression (39). Kinnumen and colleagues (35) found that only 12% of depressed smokers quit successfully with placebo gum, whereas 29% were abstinent with nicotine gum at 3-month follow-up. Also, depressed smokers using nicotine gum reported fewer depressive symptoms 1 week after quitting compared with baseline, while depressed smokers using placebo gum and nondepressed smokers reported no change in depressive symptoms. Further controlled studies using nicotine replacement therapies with depressed populations warrant attention.

Behavioral Treatment

Studies indicate that smokers with depressive symptoms respond favorably to behavioral interventions designed to assist them in managing negative mood. Some reports indicate an interaction between vulnerability to negative affect and the type of treatment on smoking abstinence. Zelman and colleagues (91) found that smokers reporting high levels of negative affect on the PANAS prior to treatment were more likely to be abstinent from smoking at one year with supportive counseling than with standard cognitive behavioral coping skills training (45% vs. 19%). In contrast, among those with low negative affect scores, abstinence rates were lower for the supportive counseling condition (38%) than for coping skills training (58%). Another investigation compared standard behavioral

smoking treatment and the nicotine patch with a condition that was supplemented with the provision of portable audiotape players containing therapist messages that were personalized and supportive (38). Again, compared to smokers low in negative affect prior to treatment, those with high negative affectivity benefited more from the addition of the therapeutic messages. Researchers have theorized that while the addition of depression-specific therapy content is helpful for those who need it, affect regulation treatments may hinder cessation attempts for those without depressive symptoms by diluting the smoking content (38).

Cognitive behavioral mood management interventions have also been studied as a smoking treatment adjunct for smokers with a past history of MDD. These interventions are similar to the type used in the treatment of depression (e.g., Ref. 92). Treatment components include emphasizing the connection between mood and smoking, enhancing awareness of and modifying negative thoughts, increasing pleasant activities, and social skills training. Hall and colleagues (24,52) demonstrated in two studies that a mood management intervention was more effective than a standard behavioral treatment for smokers with a past history of MDD. In contrast, the abstinence rates among those without a history of MDD were lower in the mood management intervention than in the standard treatment condition. However, the two treatment conditions differed with respect to the number of sessions (eight vs. five, respectively). Another study that controlled for therapist contact time found no effect of mood management intervention on smokers with a history of MDD (93). Brown and colleagues (93) recruited 179 smokers with a past history of MDD and compared a standard behavioral treatment to a mood management intervention. Neither condition included pharmacotherapy, but the two treatments had an equal number of sessions. Overall, there was no effect of the mood management intervention on outcome. However, on further analysis, mood management intervention led to better outcomes for heavier smokers and for participants with a history of recurrent, but not of single episode MDD. Another investigation (94) also found that smokers with recurrent MDD benefited more from mood management than from standard behavioral treatment. Overall, these data suggest that behavioral mood management treatment may have particular benefit for smokers with a history of recurrent MDD; however, further research on the role of interventions targeting negative affect is warranted.

Treatment Issues

The potential mechanisms for the effect of mood management intervention are not well understood. Unexpectedly, mood management has not been found to attenuate post-cessation increases in depressive symptoms among smokers with a past history of MDD (93,94). Rabois and Haaga (95) examined whether depression-history smokers are actually deficient in the skills taught in mood management interventions. Smokers with a history of depression were more often rated as responding to negative automatic thoughts with cognitions considered negative and dysfunctional (e.g., catastrophizing, overgeneralizations). Furthermore, smokers scored lower than nonsmokers in overall quality of coping response to negative automatic thoughts, and there was a nonsignificant trend for those with a history of depression to score lower. Thus, future studies should

assess changes in both cognitive and coping skills as potential mediators of treatment effects.

Nicotine dependence intervention trials have not specifically recruited currently depressed smokers. These smokers are often selected out of clinical trials as a result of the stringent inclusion criteria for pharmacotherapy, for example, antidepressant medications. One study (39) enrolled smokers with current MDD into a nicotine patch study but only randomized 38 due to difficulties in recruiting this population. Although difficult to directly recruit for research studies, these smokers are likely to be seen in general clinical practice. Thorndike et al. (96) found that while physicians were as likely to identify smoking in those with or without an affective disorder (76% vs. 77%), they were much less likely to counsel patients with affective disorders to quit smoking (18% vs. 32%). Clearly, more information is needed to inform smoking cessation treatments for smokers with current depression.

Summary

The prevalence of smoking is higher in individuals with MDD, and smokers are more likely than nonsmokers to present with a history of MDD and current depressive symptoms. Depressive symptoms following smoking cessation are more likely in individuals with a history of MDD. Furthermore, those smokers with a history of recurrent and early-onset MDD and higher baseline depressive symptoms may be particularly vulnerable to developing depressive symptoms post-quit. Depression following smoking cessation is predictive of relapse and poorer smoking outcomes. Some smoking cessation treatment studies in smokers with a past history of depression have shown promising results with antidepressants, particularly fluoxetine, and with nicotine replacement. Supportive counseling and CBT mood management have been helpful, particularly for smokers high in negative affect and for the subsample of depressive smokers with a history of recurrent MDD; however, these treatments may not help, or may even hinder, smoking outcomes in smokers with low levels of negative affect or without a history of MDD.

Future Directions and Implications

1. Further work is needed to identify depressed smokers who are most vulnerable to depressive sequelae following smoking cessation, and who are most likely to profit from specialized treatment programs. Further research is needed to develop pharmacological and behavioral treatments for this population, to maximize smoking abstinence outcomes and to reduce the likelihood of depression after quitting.
2. Several antidepressant medications and cognitive-behavioral interventions appear to be effective for depressed smokers. It may be useful to study the effects of less intensive behavioral treatments (e.g., home-based exercise) for this population.
3. Research should be extended to evaluate nicotine dependence interventions for under-served populations and depressed smokers of various ethnic minority groups.
4. Smokers with current depressive disorders may readily seek treatment; however, relatively little research has been conducted with this population. More information is

needed on pharmacological and behavioral treatments for this group, as well as on the impact of smoking cessation and nicotine withdrawal on mood.
5. Further study is needed to understand the link between depression and nicotine dependence. For example, current research on depression and smoking might be extended to account for genetic differences relevant to dopaminergic neurotransmission as well as other neurotransmitter systems (36).
6. Additional work is needed to determine the cognitive factors that mediate mood responses and outcome efficacy during smoking cessation among individuals with either a past history of or current MDD. This work may help in the development of more efficacious cognitive-behavioral treatments.

SMOKING AND SCHIZOPHRENIA

Prevalence of Smoking in Schizophrenia

Compared with the prevalence of smoking in the U.S. population (~25%), the prevalence of smoking in clinical samples of patients with schizophrenia in Western countries ranges from 58 to 88% (97). There are higher rates of smoking in schizophrenics living in non-Western societies as well. A study of Chinese schizophrenics in Singapore reported that the rate of smoking in schizophrenics was 31.8%, as compared to a rate of 15% in the general population. These relatively low rates both in the general population and among schizophrenics, may have been a function of societal prohibitions on smoking in Singapore (98). Research using the National Comorbidity Study (NCS) database (4) may give a more accurate estimate of smoking prevalence in individuals with schizophrenia as compared to other psychiatric disorders. In general, current (past 30 days) smoking rates were lower (45.3%) in the schizophrenic disorders (defined loosely in this study as the "nonaffective psychoses") than the composite rate derived from published clinical studies (72.5% (99)). Lasser and colleagues (4) found that smoking prevalence among individuals with no mental illness was 22.5%, comparable to recent U.S. government estimates (100). This is clearly lower than the prevalence of smoking in patients with other psychiatric disorders such as bipolar disorder (60.6%), major depression (44.7%), post-traumatic stress disorder (44.6%), and drug abuse or dependence (67.9%). These figures were comparable to smoking rates found in clinical samples with these psychiatric disorders (97). In addition, the Lasser et al. populationbased study suggested lower quit rates in individuals with schizophrenia than those in people without mental illness.

Smoking rates in schizophrenics may vary as a function of illness severity and setting, with greater smoking prevalence shown among individuals with greater severity of schizophrenia and receiving inpatient as opposed to outpatient treatment (101–103). The highest smoking rate (93%) has been observed in institutionalized male schizophrenics (104). In a cross-sectional study that examined smoking and nonsmoking schizophrenic outpatients, smokers were more likely to have higher ratings of psychopathology as measured by the Brief Psychiatric Rating Scale (BPRS). In this study, smokers also had higher subscale scores for both positive and negative symptoms, more hospitalizations, and earlier ages of schizophrenia onset, and were receiving significantly higher doses of

neuroleptic medications (105). Ziedonis et al. (106) found greater positive symptoms and less negative symptoms in schizophrenic smokers as compared to nonsmokers. Heavy smokers had the highest positive and lowest negative symptom scores. Although their sample was confounded by diagnostic heterogeneity, Hall and colleagues (107) found that chronically mentally ill patients (87% with schizophrenia or schizoaffective disorder) who were former smokers had fewer negative symptoms (on BPRS) than current schizophrenic smokers.

However, the effects of smoking on clinical symptoms of schizo phrenia that have been observed in cross-sectional studies have not been supported by controlled prospective studies. Recent laboratory studies of tobacco abstinence (108,109) and data from smoking cessation trials have shown no evidence for significant changes in psychotic symptoms with smoking abstinence (102,110,111) or with smoking reduction (112) in schizophrenic patients.

Health Impact of Smoking in Schizophrenics

Compared with the general population of smokers, cigarette-smoking schizophrenic patients are more vulnerable to smoking-related morbidity and mortality, including an increased risk of cardiovascular disease and some forms of cancer (113,114). Previous epidemiological studies had suggested that schizophrenic smokers were protected against the development of malignancy (114), and this was thought to relate to neuroleptic drug exposure (115). In addition, there is evidence that urinary levels of the peptide bombesin, a possible marker of pre-cancerous cigarette smoking-induced lung damage, are lower in schizophrenic patients than in controls (116). This reduction in urinary bombesin levels is independent of smoking status in schizophrenic patients, which supports the notion that schizophrenic patients may be protected against the development of malignancy. However, several subsequent epidemiological studies have provided no evidence for a greater (or lower) risk of malignancy in schizophrenic patients or other patients with serious mental disorders (117,118). Previous studies may have been confounded by a selection bias. Rates of malignancy in older schizophrenics were lower because most of this cohort had died from other causes related to their psychiatric illness (e.g., suicide) before they reached the age at which cancer risk is substantially increased (e.g., 50 years or higher) (119). Since schizophrenic smokers are vulnerable to smoking-related malignancies, disease prevention through smoking cessation/reduction in this population is an important public health issue, especially because schizophrenic patients constitute about 1% of the population in the United States (120).

Smoking and Neuroleptic Medications

Cigarette smoking has been shown to increase dose requirements for neuroleptic medications in schizophrenics. Several survey studies have shown that schizophrenics who smoke receive higher doses of neuroleptics than nonsmoking schizophrenics (105,106,121). In two studies, schizophrenic smokers were found to receive nearly twice the dosage of neuroleptic medications of schizophrenic nonsmokers (105,106). In an investigation of neuroleptic dosages in three groups of schizophrenics, schizophrenic

nonsmokers were prescribed only 71% of the neuroleptic dosage prescribed to schizophrenic smokers, even under double-blind treatment (121). One explanation for these findings is that smoking (through the various carcinogens found in tobacco smoke) may directly reduce neuroleptic levels by inducing the activity of liver enzymes (e.g., cytochrome P450 1A2) that are involved in the metabolism of several antipsychotic drugs. Lower plasma concentrations of chlorpromazine, haloperidol, fluphenazine, and thiothixene have been observed in smokers (105,122,123). Smoking has been found to reduce neuroleptic side effects, including chlorpromazine-induced drowsiness (124,125), orthostatic hypotension (125), and parkinsonian symptoms (105,106,126). This latter finding is independent of the use of anticholinergic medications, age, and gender. One recent study showed that nicotine could reduce the bradykinesia associated with haloperidol administration in schizophrenic patients (127).

Higher levels of akathisia have been observed in schizophrenics who smoke, although it is unclear whether this finding is due to a direct effect of smoking or mediated by higher neuroleptic dosages (105). Data are mixed on the impact of smoking on tardive dyskinesia. While one study showed a trend for lowered tardive dyskinesia scores for schizophrenic smokers (105), other studies have shown an increase in tardive dyskinesia symptoms in this group (128,129), particularly following acute nicotine administration (130).

Mechanisms Underlying Smoking and Schizophrenia Association

Various hypotheses have been proposed to explain the high rates of smoking in schizophrenia (99,103). These theories include 1) self-medication, and 2) social and behavioral reinforcement.

The *self-medication hypothesis* suggests that schizophrenics may use nicotine to relieve certain clinical symptoms, medication side effects, and cognitive deficits associated with schizophrenia. Theoretically, nicotine may be used to 1) improve cognition and attention (131), 2) decrease anxiety (132), 3) reduce medication side effects (124,125) and parkinsonism (105,126), and 4) prevent the onset of negative withdrawal symptoms such as agitation, impaired concentration, etc. (1).

The majority of experimental support for self-medication effects of nicotine in schizophrenics comes from studies of nicotine's improvement of several cognitive measures. Important effects of nicotine include changes in sensory gating deficits in P50 event-related potentials (133), various deficits in neuropsychological performance such as reaction time (134,135), hit rate and attentional index (135) on the Continuous Performance Test, spatial working memory (99), and spatial organization and selective attention (136).

The mediating effects of smoking on schizophrenia may be related to nicotine's enhancement of dopamine release in the subcortical and cortical areas linked to extrapyramidal motor function and cognition, and also to enhancement of glutamatergic and GABAergic function (103,137). There is a preliminary report in first-episode schizophrenic patients naïve to antipsychotic medications that found extremely high smoking rates (92%), which suggests that smoking may be more related to pathophysiological features of the illness than to antipsychotic medication (138). The

sequence of smoking behavior preceding the onset of psychotic symptoms does not suggest a causal connection between smoking and the onset of schizophrenia, since a significant proportion of schizophrenic patients are not current smokers and smoking cessation in schizophrenics does not appear to lead to significant changes in psychotic symptoms (41,108,111,112). In fact, some evidence suggests that never smoking and former smoking schizophrenic patients may have a more chronic form of the illness, characterized by higher levels of negative symptoms and lower levels of depressive symptoms (108).

Another theory suggests that smoking may have potent *behavioral and social rewards*. Schizophrenics frequently have impairments in social skills, and this often leads to social isolation. Smoking has been shown to increase levels of extroversion (139), may serve as a basis for interpersonal communication (140), and may lessen levels of aggression and improve relaxation (141). Smoking may be a self-stimulatory activity that can relieve boredom as well as improve concentration (1,142). Smoking can also serve both as common ground and as a buffer among schizophrenics, allowing for parallel social participation while maintaining interpersonal and emotional distance.

Nicotine Dependence Treatment in Schizophrenia

The available evidence suggests that smoking cessation efforts are safe in schizophrenic patients in that acute smoking cessation is not associated with exacerbations of clinical symptoms (41,102,111). Published controlled studies on smoking cessation in schizophrenics are reviewed below, along with information from our clinical experience derived from work with these patients in cessation settings.

Motivation for Quitting Smoking

While the interest of schizophrenic patients in quitting smoking is generally thought to be low, approximately 20–40% have a substantial desire to quit (143–145), based on ratings of motivational level on the Stages of Change scale (e.g., preparation or action stages) (146). In cases where smoking cessation is not possible, a reduction in smoking consumption (e.g., a “harm reduction” approach) may produce some health benefits for schizophrenic smokers (147). However, no studies have been published to suggest that reducing smoking reduces the risk of developing smoking-related illness in either nonpsychiatric or schizophrenic smokers (148). Thus, an understanding of the biological and psychosocial factors that render schizophrenic patients at high risk for developing nicotine addiction and contribute to their low intrinsic motivation to change smoking behaviors is critical to improving smoking cessation treatment in this population.

Pharmacological Treatment

Role of Atypical Antipsychotic Treatment

Several studies have suggested that switching schizophrenic smokers from typical antipsychotic agents to clozapine leads to reductions in cigarette smoking (149–151),

especially in heavier smokers (149), and that such an effect may be dependent on clozapine plasma levels (150,151). A related study found that administration of the typical antipsychotic drug haloperidol leads to increased smoking in schizophrenics compared to a baseline medication-free condition (152). These studies suggest a role for atypical antipsychotic drugs in reducing smoking behavior.

Compared to typical antipsychotic drugs, atypicals, in particular risperidone and olanzapine in combination with the nicotine transdermal patch (NTP), may enhance smoking cessation rates in treatment-seeking schizophrenic smokers with high pre-trial levels of motivation to quit (111). Recent data from a preliminary placebo-controlled trial that compared bupropion to placebo in schizophrenic smokers suggest that atypical antipsychotic treatment significantly enhances smoking cessation responses to bupropion (102).

We would speculate that atypical antipsychotic drugs may be more helpful than typical neuroleptic agents for treatment of nicotine addiction in schizophrenics for the following reasons: 1) atypical agents have fewer extrapyramidal side effects and improve negative symptoms, both of which may be improved by cigarette smoking; 2) treatment with atypical agents is associated with improvement in the deficits in certain aspects of neuropsychological function that also appear to be alleviated by smoking; 3) sensory gating deficits (e.g., P50 responses, prepulse inhibition) that are temporarily normalized by nicotine administration or cigarette smoking are also normalized by atypical antipsychotic drugs (153,154); and 4) atypical agents are associated with augmentation of dopamine (DA) and acetylcholine release in the prefrontal cortex in rodent studies (155,156); this may normalize presumed deficits in cortical DA function in schizophrenia that may also be remediated by nicotine or cigarette smoking (102,111).

Standard Nicotine Dependence Pharmacotherapies

Standard FDA-approved smoking cessation pharmacotherapies such as nicotine transdermal patch (NTP) (41,111) and sustained-release bupropion (Zyban®) (102,112,157) appear to be safe and efficacious for smoking cessation in schizophrenic patients during the course of controlled studies. Use of the NTP is known to facilitate smoking reduction (158) and cessation (41,111) in schizophrenic smokers, albeit at lower rates (approximately 36–42% at trial endpoint) than in healthy control smokers (50–70%) (159). Nonetheless, NTP (at the dose of 21 mg/day) appears to effectively reduce cigarette smoking and nicotine withdrawal symptoms in schizophrenic smokers (41,111,158). Similarly, smoking cessation rates at the end of drug treatment with bupropion (11–50%) (102,112,157) are modest compared to those achieved in nonschizophrenic control smokers (50–75%) (159), but may be improved when patients are prescribed atypical antipsychotic agents (102,111). Differences in study design, patient selection (e.g., level of motivation to quit smoking), medication dosage (in the studies with bupropion: 150–300 mg/day), and criteria used to determine smoking abstinence may explain the variability in quit rates found in these studies.

In studies that use the NTP, patients are expected to stop all smoking when they begin the NTP on the "quit date." When using the NTP, patients should be cautioned not to smoke while they are wearing the patch, because of concerns about nicotine toxicity,

symptoms of which can include tremor, nausea, vomiting, dizziness, and in rare cases seizures, arrhythmias, and death. In the research clinic of one of the authors (TPG), nicotine toxicity has not been a significant problem, but we tell patients that if they do smoke they should remove the patch and wait 1–2 hours before smoking. Cigarette craving and continuing withdrawal symptoms typically indicate incomplete nicotine replacement, and, if needed, another patch of 7–21 mg/day can be added to therapy with the 21 mg/day NTP. For Zyban, controlled studies have started at dosages of 150mg daily, and increased to 150mg twice daily by the fourth day of treatment. The "quit date" is typically set once drug levels reach steady state, usually 3–4 days after beginning the full 300 mg/day dose. A history of seizures of any etiology is a contraindication to the use of Zyban, as is indicated by the product labeling, and we recommend not to exceed the 300 mg/day dosage, since some antipsychotic drugs may reduce seizure threshold. At the same time, Zyban at 150–300 mg/day does not appear to worsen positive symptoms of schizophrenia, and may reduce negative symptoms (102,111). The typical duration of therapy studied in schizo phrenic patients with these agents is 8–12 weeks. To date, studies with a longer duration of treatment in this population have not yet been conducted.

Combined Pharmacological and Psychosocial Nicotine Dependence Treatments in Schizophrenia

Our research and clinical experience in treatment studies for smoking cessation in schizophrenia has underscored the utility of optimizing both pharmacological and psychosocial interventions (102,111). While atypical antipsychotic drugs may be one factor that predicts improved smoking cessation or reduction outcomes, schizophrenic patients need persistent encouragement to quit smoking. Motivational enhancement therapies and education about the danger that smoking poses may be useful. We have found that schizophrenic smokers often know surprisingly little about the adverse effects of tobacco. Once they achieve smoking abstinence, they will also require ongoing teaching in methods to prevent smoking relapse (41,102,111,112,160).

Additional strategies to combat certain nicotine withdrawal symptoms, such as restlessness and concentration impairment, are often helpful for schizophrenics trying to stop smoking. Drug refusal techniques are also important, as peer pressure to resume smoking after successful abstinence is typically very high on these individuals, and in our experience teaching assertiveness skills (in the context of social skills training) has been effective for those who have high motivation to remain tobacco-free. Furthermore, a period of several weeks to months of ongoing support for continued smoking cessation may also be helpful in this population to maintain coping skills and self-efficacy for cigarette abstinence.

Summary

Schizophrenia is associated with a very high prevalence of smoking and low quit rates, which result in increased morbidity and mortality. It is unclear whether smoking influences the clinical symptoms of patients with schizophrenia (e.g., positive and

negative symptoms), leading to higher neuroleptic dosage requirements. The high rates of comorbid smoking in schizophrenic patients may relate to abnormal biology of nicotinic receptor systems and central dopamine pathways associated with schizophrenia. Evidence from controlled studies suggests that smoking cessation does not worsen schizophrenic symptomatology. Recent clinical research findings suggest that the atypical antipsychotic medications along with nicotine replacement or bupropion, plus behavioral counseling and support, are promising treatments for schizophrenics trying to stop smoking; however, outcomes to date are modest.

Future Direction and Implications

1. Schizophrenics may self-medicate clinical and cognitive deficits that are nicotine responsive. These findings may have important implications for understanding the neurobiology of schizophrenic disorders and for the development of better treatments for these disorders. It is important to improve the treatment of nicotine dependence in schizophrenia, since these patients frequently smoke and appear to be at increased risk of developing smoking-related medical illness (118).
2. Motivation to quit smoking is often low in schizophrenic patients. Efforts are needed to increase the awareness of both patients and their clinicians of the dangers of tobacco smoking. Motivational-enhancement and relapse-prevention methods are the mainstays of behavioral treatment for nicotine dependence in these patients, and further work is needed to develop behavioral treatment protocols specific to the needs of this population.
3. There is increasing evidence from controlled studies that certain pharmacological agents (e.g., atypical antipsychotic drugs, nicotine replacement, bupropion) safely promote smoking reduction and cessation in clinically stable patients with schizophrenic disorders.
4. Taken together, these findings suggest that clinicians should actively assess smoking in their patients and encourage them to stop smoking. While there is little evidence from controlled clinical studies that smoking cessation produces a deterioration of clinical function in stabilized patients, clinicians should not attempt to engage patients to quit smoking when they are clinically unstable, since the likelihood of success is low.

SMOKING AND SUBSTANCE USE DISORDERS

Prevalence

There is a well-known association between alcohol and drug use disorders and cigarette smoking. One perspective on this association comes from an examination of the prevalence of cigarette smoking among drug and alcohol abusers. A survey of patients in substance abuse treatment found that 74% of alcoholics, 77% of cocaine addicts, and 85% of heroin addicts were current smokers (161). Hughes (162) reviewed 11 studies that investigated the prevalence of smoking in alcoholics and found that a median of 83% of

alcoholics were current smokers, compared to 30% in the general population. In contrast to the general population, the samples of alcoholics were more likely to have ever smoked, be heavy current smokers, and less likely to be former smokers.

Most published studies surveyed alcoholics seeking alcohol treatment, and the rate of smoking is thought to be somewhat lower among alcoholics who are not in treatment. In studies of smoking among alcoholics in the general population, smoking rates were moderated by levels of alcohol dependence, with the highest prevalence of smoking observed in individuals with the most severe alcohol dependence (163,164). Epidemiological data have shown that alcoholic smokers tend to smoke heavily, at approximately twice the daily rate of cigarette consumption of nonalcoholic smokers (165). Although several studies have shown a historical trend for a marked decline in the prevalence of smoking in the general population, little decline in smoking rates has been seen among alcoholics (166,167). Hughes (168) has suggested that if this trend continues, the future population of smokers may consist largely of alcoholics. Thus, the association between smoking and alcoholism may become stronger over time.

Another perspective on the association between smoking and substance use is to examine the prevalence of alcohol and drug abuse among cigarette smokers. DiFranza and Guerrera (169) found that alcoholism was 10–14 times more prevalent among smokers than among nonsmokers. A high prevalence of alcoholism has been shown particularly among women smokers (170). Hughes (168) showed that both lifetime and current prevalence of alcoholism were significantly higher in heavy smokers than in individuals who never smoked. On the basis of the association between heavy smoking and alcoholism, Hughes suggested that heavy smoking could be used as a marker for alcohol abuse.

Breslau and colleagues (171) examined the prevalence of lifetime substance use disorders among smokers. This research showed that the level of nicotine dependence moderates the strength of the association between smoking and substance dependence, and that alcohol dependence is the substance disorder that most commonly co-occurs with nicotine dependence. These investigators also found that individuals with moderate nicotine dependence were three to nine times more likely than individuals with no nicotine dependence to have a lifetime diagnosis of alcohol or drug dependence (odds ratio=3.20 for alcohol dependence, odds ratio=9.72 for cocaine dependence). In this study, the prevalence of cocaine dependence was most greatly moderated by the level of nicotine dependence. However, the research on specific cocaine/tobacco interactions is limited (172). Since, in contrast, there is an extensive literature on alcohol/tobacco interactions, the remainder of this section will focus on the association between alcohol dependence and nicotine dependence.

Health Impact of Alcohol/Tobacco Abuse

The negative health consequences of smoking among alcohol and drug abusers are substantial. Many drug and alcohol abusers die of smoking-related causes (11,17,168,173,174). One study that examined mortality across a 12-year period in a sample of 845 patients from an inpatient addiction treatment program showed that smoking killed more alcoholics than did alcohol (11). On admission, 80% of patients in

the study were current tobacco users. A review of death certificates from 214 of the patients revealed an alcohol-related underlying cause of death in 34%. However, 51% of the deaths were tobacco-related.

While high rates of smoking account for much of the increased mortality in smoking alcoholics, some data indicate that alcohol and tobacco abuse may act synergistically on mortality risk in specific serious illnesses such as cancers of the larynx, pharynx, and mouth (175–177). Compared with the risk of nonsmoking nondrinkers, the relative risk of developing mouth and throat cancer is six times greater for those who use alcohol, seven times greater for those who use tobacco, and 38 times greater for those who use both alcohol and tobacco (178).

Alcohol/Tobacco Association in Commencement of Drug Use

Alcohol and tobacco use are associated in the early stages of substance use. Alcohol and tobacco are commonly the first-used psychoactive drugs, and have been considered a "gateway" to the use of drugs such as marijuana and cocaine (179). Teenage drinking strongly increases the probability of smoking. In a 1994 Surgeon General's review, 40% of teenagers who drank alcohol were found to smoke cigarettes, while only 10% of nondrinkers smoked. Although teenage smoking increases the probability of drinking, this is a weaker relationship. Eighty-eight percent of teenage smokers drank alcohol, while 55% of nonsmokers drank (180).

Alcohol/Tobacco Association in Relapse

Research indicates that alcohol use increases the likelihood of relapse to smoking. Callers to a smoking relapse hotline identified alcohol use as being frequently associated with relapse to smoking (181). In a more recent study, in which real-time data were collected on relapse experiences using hand-held computers, alcohol use was significantly more likely to occur prior to smoking relapse than it was in smoking temptation situations or at randomly sampled time points (182). Research that specifically examines the effect of smoking on alcohol relapse is limited. A longitudinal investigation of natural recoveries from alcohol and tobacco dependence found that, among individuals who quit smoking and drinking, risk of relapse to alcohol use was significantly greater among those who relapsed to smoking than among subjects who remained smoke-free (183).

Alcohol/Tobacco Association in Cessation

Epidemiological data have suggested that alcohol abusers are less likely than nonabusers to succeed in quitting smoking. In a population-based sample, individuals with a history of alcohol dependence were 30% less likely to stop smoking than individuals with no history of alcohol dependence (170). A review of retrospective studies showed that a median of 17% of current alcoholics who ever smoked were able to successfully quit smoking, which is less than half the quit rate observed in the general population (162). Other studies have shown that alcoholics in recovery have better smoking quit rates than alcoholics who are currently drinking (183,184). Two prospective studies found that

individuals with current alcohol dependence or a past history of the disorder were less successful in quitting smoking than was a nonalcoholic sample (20,168).

Other studies have examined the effect of smoking status on the ability to abstain from alcohol. Sobell and others (183) examined alcohol/tobacco recoveries longitudinally in subjects who never smoked or who quit smoking before the initial interview. These subjects were found to have superior rates of abstinence from alcohol relative to those who continued smoking. Other researchers have also documented that the rate of positive alcohol outcomes is higher in individuals who quit smoking than in those who continue to smoke (167,185,186).

Mechanisms Underlying Alcohol/Tobacco Interactions

Numerous hypotheses have been developed to explain the association between smoking and alcohol abuse. Three of these hypotheses are summarized here: 1) synergistic or antagonistic pharmacological effects; 2) shared predisposition due to genetic, environmental, personality, and/or demographic characteristics; and 3) behavioral theories, including cross-substance coping responses and cue reactivity. The reader is referred elsewhere for a discussion of hypotheses based upon state-dependent learning (187) and reduced restraint after alcohol intoxication (182).

Nicotine and alcohol administration may combine to produce *synergistic or antagonistic pharmacological effects* (187). Intake of one substance may potentiate cravings for the other through a variety of neurobiological pathways. Smoking and alcohol both increase release of endogenous opiates and dopamine in the ventral tegmental area and nucleus accumbens, which may result in one drug enhancing the reinforcing effect of the other (188,189). Alcohol increases microsomal enzymatic activity, serving to increase the rate of nicotine metabolism, thereby facilitating tolerance to nicotine. This tolerance may then be matched by a cross-tolerance to alcohol (190,191).

Furthermore, use of one of these drugs may also counteract potential aversive effects of the other. Nicotine may lessen the degree of alcohol intoxication by stimulating peptides such as arginine vasopressin (AVP) (192) and by slowing absorption of alcohol (193). Acute effects of nicotine may reduce levels of sedation and motor impairment, which may be a consequence of acute alcohol administration (194,195).

Several theories suggest that alcoholics and smokers may have *common genetic, environmental, personality, and/or demographic characteristics* that predispose them to abuse of both substances. Shared genetic factors have been found to exert a moderate influence on the initiation of alcohol and tobacco use, and on subsequent abuse and dependence liability in women (194,196). In a study by Prescott and Kendler (196), common environmental factors showed a modest liability for alcohol and tobacco initiation. In contrast, other research has shown a significant percentage of the variance of alcohol and tobacco abuse to be attributable to environmental factors (e.g., Refs. 197–199). Personality characteristics such as extroversion (139) and rebelliousness (180) have been linked to both alcohol and tobacco abuse, particularly among adolescents. Individuals of lower socioeconomic status and lower education levels are also more likely to be smokers and drinkers (200).

B*ehavioral theories* have been developed to explain the relations between alcohol and tobacco relapse. These include the idea that smoking behavior may be used as a *cross-substance coping response* among recovering alcohol and drug abusers, and the idea of *cross-cue reactivity* whereby smoking cues elicit urges to drink, or drinking cues elicit urges to smoke. The *cross-substance coping response* hypothesis postulates that smoking may be used to cope with cravings for alcohol or drinking may be used to cope with cravings for cigarettes. This theory may be particularly relevant to phases of relapse and abstinence as it suggests, for example, that an abstinent alcoholic may use smoking as a substitute for drinking when confronted with urges to drink, as opposed to returning to drinking. This process would suggest that cigarette abstinence along with alcohol abstinence might make relapse to drinking more likely. Carroll and Meisch (201) showed that when animals were deprived of one drug, they were less likely to resist the second drug.

Research on the cross-substance coping hypothesis has yielded mixed results. This theory was not supported by a recent study conducted by our research group (202). In this laboratory study alcohol-dependent smokers in an intensive substance abuse outpatient program were deprived of cigarettes for 34 hours. Cigarette deprivation and acute nicotine withdrawal produced high levels of cigarette craving but had no effect on urges to drink or physiological reactivity to alcohol cues (202). However, a study conducted with a hazardous drinking, non-treatment-seeking sample showed that 6 hours of cigarette deprivation was associated with an increase in urges to drink, expectations of enhanced availability of alcohol, and greater alcohol consumption on an alcohol taste test (203).

Another recent study by our research group, briefly described in an article by Cooney and colleagues (204), used ecological momentary assessment methodology (205) to examine alcohol-tobacco interactions in treated alcoholic smokers. Participants in a substance abuse intensive outpatient program collected computerized self-monitoring data for 14 days after leaving treatment. They were instructed to monitor moods, self-efficacy, urges to drink or smoke, and drinking and smoking behavior, using a handheld computer that signaled them for assessment at quasi-random intervals. They also completed assessments on the hand-held computer before and after smoking episodes. These assessments revealed that alcohol urges were less frequent before smoking episodes than at random time points. Alcohol urges did not significantly increase or decrease after smoking episodes. These data suggest that among alcoholic smokers in early alcohol abstinence smoking is not used to cope with alcohol urges and that smoking neither elicited nor reduced the level of alcohol urges. Taken together, Palfai's data (203) and data from our laboratory suggest that an active, heavy drinker who is not engaged in alcohol treatment may be more likely than a recovering alcoholic in alcohol treatment to use alcohol as a means of coping with smoking urges.

Another behavioral alcohol-tobacco interaction hypothesis suggests that smoking and drinking become conditioned stimuli for each other (187,206), producing *cross-substance cue reactivity*. Alcohol and tobacco are very often consumed together in individuals with both alcohol and tobacco dependence. Repeated pairings of smoking cues with drinking behavior and vice versa may result in these cues acquiring conditioned stimulus properties through a classical conditioning process. Smoking may come to elicit urges to

drink and drinking may stimulate urges to smoke. The process of conditioned cue reactivity has been described in various forms (207–209). Conditioned learning theory suggests that simultaneous treatment of smoking and drinking would lead to better outcomes than alcohol treatment alone, because individuals abstinent from one substance would have fewer urges for the other substance. For example, ex-smokers would have fewer cravings for alcohol than continued smokers.

Laboratory studies have demonstrated cross-cue reactivity. Cooney and colleagues (202) found that alcohol cue presentations in the absence of cigarette deprivation were associated with significant increases in urges to drink and urges to smoke in a sample of alcohol-abstinent, alcohol-dependent smokers. This is consistent with findings in other laboratories (e.g., Refs. 210,211). Taylor et al. (212) reported that tobacco cues presented with guided imagery elicited craving for both tobacco and other drugs in a sample of individuals with a history of nicotine dependence and drug abuse. Drobes et al. (213) found that alcohol-dependent smokers reported increased cravings for cigarettes in response to alcohol cues, as well as increased cravings to drink in response to smoking cues. Taken together, these studies provide substantial evidence for cross-substance cue reactivity.

The cross-substance coping response and cross-cue reactivity hypotheses have different implications for treatment of individuals with both alcohol and nicotine dependence. The coping response hypothesis implies that simultaneous alcohol/tobacco treatment may have a deleterious impact on alcohol treatment outcome because an important means of coping with alcohol craving may be taken away. The cross-substance cue reactivity hypothesis implies that simultaneous alcohol-tobacco treatment would improve alcohol treatment outcome because a significant trigger for alcohol craving would be eliminated. The treatment outcome literature may help to resolve these conflicting predictions.

Simultaneous Treatment of Alcohol and Tobacco

Acceptability of Simultaneous Alcohol/Tobacco Treatment

There has been concern that the stress of smoking cessation would put a recovering substance abuser at increased risk of relapse (214). Conventional wisdom has been that alcoholics in alcohol treatment are not interested in smoking cessation. Existing scientific evidence contradicts this notion. One survey of people seeking outpatient alcohol and drug treatment found that 57% were moderately or very resolved to give up smoking, and that 46% were moderately or very interested in participating in a quit smoking program as part of their treatment (215). Sees and Clark (161) surveyed 223 daily smokers from a substance abuse inpatient unit and reported that 50% of the alcoholic patients, 37% of the cocaine-dependent patients, and 30% of the heroin-dependent patients were interested in stopping smoking at the time they started treatment for their other addictions. A third survey of homeless veterans in residential treatment found that 68% wanted to quit smoking and 66% reported that the best time to quit smoking was during inpatient substance abuse treatment (216). A study by Burling et al. (217) offered an intensive smoking cessation program to substance-dependent inpatients (51% alcoholics) and

found that 75% of them enrolled in the program.

Smoking programs are most acceptable to individuals in alcohol treatment if they are viewed as being voluntary. In a survey of inpatient alcoholics, 60% indicated that they might or they would try a voluntary smoking cessation program, but only 41% responded similarly if the program was made mandatory (218). In summary, survey studies show that a substantial number of alcoholic smokers are interested in participating in simultaneous alcohol and tobacco treatment, particularly if these treatments are voluntary.

Effects of Simultaneous Alcohol/Tobacco Treatment

Five controlled long-term outcome studies have tested the efficacy of concurrent treatment. Joseph et al. (219) conducted a study in a VA hospitalbased residential substance abuse treatment program. Subjects (N=314; 69% reported that alcohol was their drug of choice) in two treatment cohorts were examined. The intervention cohort was subjected to a mandatory smoking ban, both on and off the treatment site, plus three hours of didactic lectures. The control cohort received no specific smoking intervention and was permitted to use designated smoking rooms. There was a nonsignificant trend toward worse substance abuse outcomes in the mandatory smoking intervention group. There was no significant difference between the smoking intervention and control groups in smoking quit rates at follow-up, with both groups showing low smoking quit rates.

Bobo et al. (220) conducted a community intervention study in 12 residential alcohol treatment centers that were randomly assigned to smoking intervention or control conditions (N=575). The intervention consisted of four 15-minute individual smoking-cessation counseling sessions based on a readiness-to-change model. Alcohol outcome at 6 and 12 months showed significantly lower moderate and heavy drinking rates in the smoking intervention group than in the usual care group. Tobacco outcomes showed nonsignificant differences between groups with 12-month point prevalence (7-day) abstinence rates of 9% in the intervention group vs. 7% in the control group.

Burling et al. (221) conducted a study in a homeless veterans' residential substance abuse program. Subjects (N=39 with 44% who identified alcohol as their preferred drug) were randomized to a smoking intervention or wait-list control. The smoking intervention consisted of daily 15-minute individualized sessions across 3 to 4 weeks. Smoking treatment subjects were more likely to continue inpatient drug treatment than controls (p<0.001), but differences in drug and alcohol abstinence at 3 and 6 months were not statistically significant. There were no nonsmokers at 3- or 6-month follow-up.

Hurt et al. (17) conducted a study in an inpatient substance abuse treatment program. Alcohol-dependent subjects (N=101) were assigned in cohorts to usual care (no smoking cessation treatment) or to an intervention group consisting of 10 hours of group behavioral smoking cessation counseling. Nicotine gum was available to the intervention group, but only 12% chose to use it. At 1-year follow-up, there was a nonsignificant difference in alcohol and drug use; seven-day point prevalence smoking cessation rates were 12% in the intervention group and 0% in the control group (p<0.05).

Burling et al. (217) conducted a second study of homeless veterans in a residential substance abuse program with an average length of stay of 3.5 months. Subjects (N=150

treatment acceptors, 52% with alcohol problems) who completed 30 days of residential substance abuse treatment were randomized to a multi-component smoking treatment (MST) consisting of 4 weeks of nicotine patch therapy (14 to 7mg) plus seven weeks of daily one-to-one counseling (30–45 min/day) followed by 2 weeks of bi-weekly counseling. Another condition consisted of the multi-component smoking treatment plus "generalization training" (MST+G) that emphasized the similarities between smoking cessation and quitting alcohol and drug use. Thirty-day alcohol abstinence at 12 months was 61% for MST but only 39% for MST+G ($p<0.05$). Seven-day smoking abstinence at 12 months was 19% for MST and 13% for MST+G, a nonsignificant difference.

Other tobacco intervention studies have been conducted with substance-abusing smokers, but they did not include long-term (6 months or more) follow-up (222,223), did not include randomized controls (224), or did not examine concurrent substance abuse and tobacco treatment (28,168,225–228).

Several conclusions can be drawn from the available substance abuse-tobacco treatment studies. First, the impact of concurrent treatment on alcohol and drug outcomes is dependent on several factors. Voluntary smoking cessation treatment either does not harm alcohol and drug outcomes (16,17) or improves alcohol and drug outcomes (220). However, a mandatory smoking ban (219) and an intervention that strongly emphasized the similarity of tobacco cessation and alcohol/drug cessation (217) were associated with worse alcohol/drug outcomes. Second, long-term smoking abstinence rates are low for brief smoking interventions, but better quit rates are seen for more intensive behavioral smoking treatments such as that provided by Hurt et al. (17). In that study, ten one-hour sessions led to a one-year cigarette abstinence rate of 12%. Similarly, the study by Burling et al. (217), which provided over 50 smoking treatment sessions, led to a one-year abstinence rate of 19%. Third, most studies have used only behavioral counseling interventions, and those that have used pharmacotherapy have not employed optimal treatment. For instance, Hurt et al. (17) offered nicotine gum but had poor compliance (only 12% of the sample chose to use the gum), while Burling et al. (217) used a lower dose and shorter duration of nicotine patch therapy than is recommended. Fourth, all studies of concurrent alcohol-tobacco treatment have been conducted in inpatient or residential treatment settings. Research is needed in outpatient settings that are often the preferred and currently used setting for alcohol treatment, due to economic considerations.

Treatment Issues

Motivation

Individuals entering alcohol treatment may be motivated for changes in a range of health-related behavior and may be at an action stage of change for both drinking and smoking. There may be an advantage in "striking while the motivational iron is hot." This idea is supported by a report from Burling et al. (16). They randomly assigned patients in residential substance abuse treatment to a smoking cessation intervention or a waiting list control group. Although waiting list subjects were eligible for the smoking cessation intervention upon discharge from the residential treatment program, none of them

enrolled in the intervention. Over time subjects apparently lost interest in smoking cessation or were no longer able to engage in such treatment following inpatient discharge. Other research investigating contemplation for quitting smoking during alcohol treatment has yielded different results. Monti et al. (218) observed a significant increase in the number of individuals contemplating smoking cessation just one month into sobriety (52%), compared to when they were in detoxification (28%).

N*icotine replacement therapy* may be especially beneficial for alcoholic smokers. Evidence suggests that smokers with a history of alcoholism smoke more cigarettes per day and smoke each cigarette more intensely (206,229), are more dependent on nicotine (228), and have higher serum nicotine and cotinine levels (225) than smokers who have no history of alcoholism. A recent study examined preference for active nicotine gum vs. placebo gum in abstinent smokers with or without a history of alcoholism (230). Compared with smokers who have no history of alcoholism, smokers with a history of alcoholism reported a greater preference for active nicotine gum and self-administered more milligrams of nicotine, suggesting that nicotine may be more reinforcing among smokers with a history of alcoholism. A secondary analysis of a placebo-controlled trial of nicotine gum, reported by Hughes (122), showed that smokers with a history of alcohol problems appeared to benefit more from nicotine gum therapy than subjects without this history. However, another study showed that the nicotine patch had a similar degree of benefit in smokers with or without a history of alcoholism (225). Prospective studies examining this issue may help to resolve these discrepant findings.

Generalization of Coping Skills and Self-Efficacy

Behavioral interventions for smoking and drinking have much in common. Both include identification of high-risk relapse situations, instruction in interpersonal and mood management skills, and instruction in skills for coping with craving. It is likely that skills taught for smoking cessation generalize to alcohol cessation and vice versa. Skills transfer could explain the improvement in drug abstinence rates in smokers randomized to concurrent nicotine dependence treatment. In the study by Burling et al. (16), subjects able to stop smoking for 10 days were more likely to be abstinent from their drug of choice at three and six months after treatment (80% vs. 30%). Skill transfer may help smoking cessation efforts as well. Reliance on AA principles was the second most common technique employed by recovering alcoholics successfully able to quit smoking (231). Additionally, self-efficacy or confidence acquired from initial success with one habit may enhance self-efficacy for coping with the other habit. Our enthusiasm for transfer of abstinence skills across tobacco and other substances is tempered by the results of the previously mentioned study by Burling et al. (217), which showed that explicit efforts to train patients to generalize skills resulted in worse substance use outcomes. Further research in this area would be helpful in explaining these different findings.

Summary

There is a high prevalence of concurrent alcohol and tobacco dependence. Excessive drinkers are likely to be heavy smokers and smokers are also likely to be excessive drinkers. As smoking decreases in the general population, there is a trend toward a greater association between smoking and alcohol dependence. Although smoking rates have declined in the general population, there has not been a decline in the rate of smoking among alcoholics. The association between heavy smoking and alcoholism is strong enough that heavy smoking could be used as a screening indicator of likely alcohol problems (232). Furthermore, there is evidence that heavy alcohol and tobacco use work synergistically to increase mortality risk. Alcohol and tobacco are factors in the initiation of drug use among adolescents. The association between alcohol and nicotine has important implications for cessation and relapse rates as well.

Contrary to conventional wisdom, simultaneous alcohol/tobacco treatment has been found acceptable to patients undergoing alcohol rehabilitation. Voluntary smoking treatment for alcohol patients has been found to have no negative impact on alcohol outcomes; in fact, some research suggests that smoking cessation may improve alcohol outcomes. Acute nicotine deprivation and smoking cessation treatment have not been found to harm alcohol treatment outcomes.

Future Directions and Implications

1. Epidemiological data can demonstrate associations between alcohol and tobacco use, but cannot elucidate the processes underlying the interaction. Studies using sophisticated behavioral technologies such as ecological momentary assessment (205) may be needed to advance our understanding of these processes.
2. The strong epidemiological relationship between heavy drinking and heavy smoking suggests that heavy smoking can be used as a screening indicator for alcohol problems.
3. To date, smoking cessation treatments for alcoholics have yielded modest benefits on outcomes. Further research is needed to identify optimal levels of nicotine replacement and effective behavioral treatments. More information is also needed on the relative benefits of generalizing alcohol and tobacco treatments.
4. Additional research on pharmacotherapy is needed to evaluate the effectiveness of potential anti-craving agents for both alcohol and tobacco abuse. Would the use of combination or high-dose nicotine replacement, naltrexone, and other medications be beneficial within the context of simultaneous alcohol/tobacco treatments? A better understanding of the neurobiological mechanisms of craving would help to guide this research.
5. Most research to date has focused on alcohol/tobacco treatments, with little research on interactions of tobacco with cocaine and other drugs. Research is needed on the interactions of tobacco with drugs other than alcohol. The process of relapse and the efficacy of simultaneous tobacco/drug treatment are topics that require additional study.

CONCLUSION

This chapter summarizes epidemiological, bio-behavioral, and clinical advances in the area of comorbidity of nicotine dependence with affective and psychotic disorders and substance abuse. The field has grown at a remarkable rate since our first review was published in 1998 (233). Developments in biological and genetic mechanisms and improvements in clinical treatments are most notable. However, insofar as individuals with psychiatric and substance use disorders remain the largest consumers of cigarettes, have the greatest difficulty in quitting, and suffer enormous health consequences, further research is needed to address this area of comorbidity.

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9
Comorbidity of Personality Disorders and Substance Use Disorders

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INTRODUCTION

Clinical Context

Since the introduction of DSM-III in 1980, there has been a growing interest in the study of dual-diagnosis patients, including substance abusers with a comorbid personality disorder. The driving force behind this movement has been and still is the difficult clinical management of these patients. The reason why the empirical interest started in the 1980s is probably strongly related to the introduction of explicit diagnostic criteria for personality disorders in DSM-III, as well as the availability of semistructured interview schedules for the assessment of these conditions. A similar interest in Axis II comorbidity took place simultaneously in the fields of affective, anxiety, and eating disorders.

Clinical problems with these patients are partly related to their particular characteristics. For example, the problematic and disruptive nature of their symptoms can complicate standard treatments, interfere with relapse prevention, and slow recovery and rehabilitation. The mechanisms underlying the interference with treatment and the unfavorable prognosis among substance abuse patients with personality disorders may be different from those among substance abuse patients with psychiatric disorders such as affective, anxiety, or eating disorders. Comorbid Axis I disorders, at least when not properly addressed as a part of the therapeutic regimen, have the potential to increase the risk for relapses due to, for example, self-medication as a means to cope with painful affects. Therefore, Axis I comorbidity in substance abuse treatment generally indicates the need for more intensive treatment and specific interventions to reduce symptomatology (1). On the other hand, Axis II pathology is more often associated with problems in the therapeutic relationship or working alliance, noncompliance, resistance to change, and/or dropout (2–5).

Since clinical problems are often considered to result from the patient's personality problems, many clinicians have adopted an attitude of therapeutic nihilism toward individuals assigned an Axis II diagnosis, in particular those with comorbid antisocial personality disorder (ASPD) (6). However, there is a growing body of evidence suggesting that this attitude is not an adequate response to patients with comorbid Axis II pathology. It could even be argued that the clinical problems are attributable to poor therapist functioning. It is likely that some therapists have difficulty dealing with these patients due to a lack of skill in diagnosing and treating such patients, inappropriate reactions to the patients, or countertransference problems (1,7,8).

In addition to problems related to individual patient and therapist functioning, several factors inherent to the mental health system can contribute to poor treatment response and outcome in these patients. For example, it has been suggested that traditional psychiatric and substance abuse treatment strategies are of limited use for many dual-diagnosis patients because they fail to address this population's unique needs (9). In addition, substance abusers with borderline personality disorder (BPD) tend to be treated differently from their non-borderline counterparts (10). This differential treatment occurs both in research and in clinical practice. First, substance abusers are often excluded from studies examining the efficacy of treatments designed to target borderline symptoms. For example, several randomized, controlled trials of psychosocial treatments for BPD have excluded borderline patients with substance use disorders (SUD) (11–13). Second, it has often been reported that borderline patients with SUD have trouble when applying for treatment. Anecdotal data indicate that this group may be caught in a therapeutic "catch-22" situation, in which they cannot enter the mental health system until they stop using substances and cannot enter substance abuse treatment facilities until suicidal and other self-destructive behaviors are under control (9). Strikingly, the differential exclusion of borderline patients with SUD from both treatment programs and treatment efficacy studies is poorly explained. The exclusion from research is often justified as a strategy to preserve the homogeneity in cohorts. Similarly, it has become common practice among many substance abuse treatment programs to deny psychotherapeutic treatment to opiate abusers, in large part because of an assumption that opiate addicts are likely to have ASPD and will therefore not benefit from psychotherapeutic treatment (2). These examples illustrate the limitations specific to a mental health system oriented towards the treatment of single rather than multiple disorders (14).

Historical Context

Throughout the last centuries, thinking about the role of personality and personality pathology in the pathogenesis of addictive problems has been influenced by a diversity of both theoretical schools and public domains, including politicians, legislators, and industry (15). The models in Table 1 represent the global evolution of the conception of addiction (16). In the table, the respective models are specified by their relative emphasis on agent (pharmacological factors), host (biological factors; personality and other psychological factors), or environment (social and cultural factors) in the etiology of addictive problems.

According to the *moral model*, addiction is a form of sinful or criminal behavior, and

substance abusers are sinners or immoral individuals with a weak, or even bad, character (16). This model has dominated thinking about additive behaviors for centuries and is still widely held among the public with regard to abuse of illicit drugs. Although personality—i.e., "character weakness"—is considered the main etiological factor, it should be realized that within the moral model the concept of character is not understood in contemporary scientific terms but is reduced to a dichotomous construct with strong moral connotations. With the introduction of the *pharmacological model* of addiction, the central role of personality pathology in the causation of addiction was replaced by the addictive potential of the substance itself (17). Although this model is considered obsolete with respect to alcohol addiction, much of our thinking regarding the cause of drug addiction is still dominated by the pharmacological model. According to the *classic disease model*, substance abuse, roughly speaking, is considered a permanent and irreversible physical condition beyond the individual's conscious control (i.e., body-system reactivity/sensitivity to substances and physically determined loss of control). Within this model, personality is not clearly referred to as an etiological factor. In the *symptomatic model*, which dominated the psychiatric literature during the first half of the twentieth

Table 1 Conceptions of the Nature of Addiction and the Role of Pharmacological, Biological, Psychological, Social, and Cultural Factors in the Pathogenesis of Addictive Problems

	Causal factor			
		Host		
Conceptual model	Agent: pharmacological factor	Biological factor	Personality and other psychological factors	Environment: social and cultural factors
Moral model	−	−	++++	−
Pharmacological model	++++	−	−	−
Classic disease model	−	+++	+	−
Symptomatic model	+	−	+++	−
Learning model	+	−	+	+++
Cognitive model	+	−	+++	+
Sociocultural model	−	−	−	++++
Biopsychological	+	++	++	++

model

− Factor is assumed not to play a significant etiological role; + Factor is of some etiological importance but not necessarily in all cases; ++ Factor is etiologically important but not necessarily in all cases; +++ Main etiological factor in all cases; ++++ Exclusive etiological factor in all cases.

century, addiction was considered a symptom of another primary mental disorder rather than a distinct syndrome. For example, addiction was thought to be a "symptom of an underlying personality disorder evidenced by maladjustment, neurotic character traits, emotional immaturity or infantilism" (18). This influential perspective, derived mainly from psychoanalytical thinking, was adopted by the DSM-I (19), in which addiction was included as a variant of the sociopathic personality disturbance. As a consequence, treatment models of that time implied sidestepping the drinking as "merely" a symptom and treating the assumed underlying conflicts instead of the substance abuse. In the DSM-II (20), addiction was still categorized under "personality disorders and certain other nonpsychotic mental disorders."

More recent approaches, except for the sociocultural model, differ from previous approaches by a greater emphasis on empirically based, multi-factorial models. These models provide the theoretical base for so-called "hybrid" treatments and intervention methods that have been developed to address psychiatric comorbidity among addicted individuals (9). According to the *learning model*, in particular as proposed by classic behaviorists, addictive behaviors result from learning processes that are largely accounted for by environmental influences and reinforcement through the pharmacological properties of substances. In later formulations of the learning model, such as Bandura's social-learning model, strict environmentalism was replaced by the recognition that direct environmental effects are modified by psychological factors such as cognition, coping, and self-regulation. Psychological factors are the focus of the *cognitive model* (4). According to this model, progression from recreational use to addiction is due to both psychological and social factors. Although pharmacological factors are not considered as important, beliefs about the affect-regulation properties of substances are crucial in this model. Personality and personality pathology are thought to account for pathological core beliefs that may initiate and maintain substance use and abuse. The *cognitive-behavioral model* is a conjunction of the social-learning and cognitive models. In reaction to the traditional models that sought explanations within either the host or the agent, the *sociocultural model* emphasizes the etiological significance of social factors (e.g., peer pressure, family factors) and sociocultural setting (e.g., social acceptance, substance availability). Contemporary scientific views of the causes of addiction can best be described as *biopsychosocial* (16,21,22). Within the biopsychosocial model of addiction, the onset and course of the addiction are thought to result from continuous reciprocal interaction between the individual's (inherited) biological and psychological vulnerabilities and his or her psychosocial circumstances. Examples of biopsychosocial models include Cloninger's neurobiological learning model (23) and Tarter's developmental behavior genetic perspective (24,25).

In conclusion, personality factors play an important role in current thinking about the

nature of addiction. However, this role is neither exclusive nor essential to all cases. The interest in concomitant personality disorders fits in with the idea of SUD as etiologically and clinically heterogeneous entities. Considerable evidence indicates that this heterogeneity is not random, suggesting distinct subtypes of individuals with SUD (23,26). Within this framework, it is reasonable to hypothesize that temperamental or personality factors are etiologically and/or clinically linked to substance abuse within some subtypes of addiction, but not other subtypes. Therefore, the interest in the co-occurrence of personality disorders among substance abusers is fueled by the idea that studying comorbidity will lead to a better understanding of the etiology of both substance use and personality disorders. Furthermore, understanding comorbidity is paramount for treatment planning and for the development of more effective strategies to treat both substance abuse and personality disorders (3,9). For example, assessment of personality pathology may be useful to match clients to different treatment modalities in order to increase treatment effectiveness (16). Addressing comorbid personality disorders may also be important for enhancing the therapeutic working alliance and prevent patients from dropping out of treatment (4,7).

This chapter aims to provide both a critical review of the empirical literature on the topic and—based on the evidence—practical guidelines for clinical practice. The review of empirical findings includes discussion of epidemiology (i.e., prevalence of comorbidity), causality (i.e., causal directions between conditions and pathways from personality to addiction), and treatment outcome (i.e., response to standard substance abuse treatment and response to treatment focusing on Axis II). The chapter concludes with our perspective on the assessment and treatment of these dual-diagnosis patients.

REVIEW OF EMPIRICAL FINDINGS

Epidemiology

Many authors have emphasized the strong association between personality disorders and SUD (27–30). In a review by Verheul et al. (31), 52 prevalence studies were identified, covering the time period 1982–1994. These studies provide empirical data regarding the prevalence of one or more DSM-III-R personality disorders, particularly ASPD and BPD, among substance abusers. Based on median rates (see Table 2), the best estimate of Axis II prevalence ranges from 44% among alcoholic patients to 79% among opiate

Table 2 Median Rates of Overall, ASPD, and BPD Prevalences Among Substance Abusers Specified by Substance, Method, and Setting

		Overall prevalence (%)	ASPD prevalence (%)	BPD prevalence (%)
Substance[a]	Alcohol	44	18	21
	Cocaine	70	24	18

	Opiates	79	24	7
	Miscellaneous[b]	62	30	22
Method[c]	Structured interviews	NA	40	NA
	Self-report questionnaires	58	21	17
	Semistructured interviews	90	34	11
	Clinical assessments	46	10	19
	Other nonstandardized assessments[d]	46	34	44
Setting[e]	VA in- and outpatients[f]	90	25	5
	Inpatients	74	18	22
	Outpatients	48	21	13
	Nonpatients	48	15	7
	In-/out-/nonpatients[g]	50	32	36

[a]The substance to which all subjects in a sample are addicted, irrespective of other substances used; [b]Mixed samples (e.g., alcohol and/or amphetamines and/or heroin), polydrug use (e.g., both cocaine and opiates), and other combinations (e.g., both alcohol and cocaine); [c]Assessment method for the DSM-III-R personality disorder(s). Instruments are listed according to the level of structure, with fully structured interviews on top and fully unstructured clinical assessments below; [d]Includes assessments that are not fully specified; these methods may or may not be structured; [e]A distinction is made between inpatients (residential treatment), outpatients (ambulatory treatment), and nonpatients (samples of addicts in the community); [f]Patients in specific American hospitals for war veterans; [g]Mixed samples that are not differentiated by setting in the reports.
Source: Ref. 31.

abusers. These individuals have one or more Axis II disorders. For example, DeJong et al. (32) found that, among individuals with at least one disorder, alcoholics had an average of 2.3 personality disorders and drug abusers had an average of 4.4 disorders. The best estimate of ASPD prevalence ranges from 18 to 30%, and the best estimate of BPD prevalence ranges from 7 to 22%. Although most studies that cover Axis II disorders indicate that cluster B disorders are most prevalent (in particular antisocial, borderline, and histrionic), both cluster C disorders (passive-aggressive, avoidant, dependent, and obsessive-compulsive) and cluster A disorders (paranoid and schizotypal) also seem to be highly prevalent among substance abusers (32–36). Narcissistic and schizoid personality disorders may be more prevalent among substance abusers than among normal individuals, but they are clearly less prevalent than other personality disorders among substance abusers.

An important finding is that studies yield a wide range of prevalence rates for all personality disorders. For example, prevalence estimates of comorbid ASPD range from

1 to 62%, and prevalence estimates of comorbid BPD range from 2 to 66% (31). The median rates in Table 2 summarize the available prevalence studies subdivided by substance, method, and setting, showing that the wide range of prevalence rates can be accounted for partly by differences in these factors. Several other factors may explain variation (37). The most important findings are discussed below.

Sampling

Sampling factors include setting, primary substance of abuse, gender, and age:

- Inpatient samples generally yield higher prevalence rates than either outpatient or nonpatient samples (see Table 2). As the differences are small, the high Axis II prevalence in patient samples can be accounted for only partly by a treatment-seeking or referral effect.
- The primary substance of abuse has a clear effect on the overall prevalence estimate (see Table 2). Alcoholic patients show lower Axis II comorbidity than do drug abusers, although this effect is rather small for ASPD and is not evident for BPD. No clear difference is evident between cocaine and opiate abusers, except for BPD, which is more prevalent among cocaine abusers.
- Gender does not seem to have a clear effect on the observed Axis II prevalence, except for ASPD. Of the prevalence rates reported, the median male ASPD prevalence is 39%, whereas the median female ASPD prevalence is 19%.
- Finally, an effect of age on the observed comorbid Axis II prevalence has been reported in only one recent, cross-sectional study (38). Age appeared to show a strong inverse relationship with Axis II prevalence rates among alcoholic patients. This effect occurred for all specific Axis II disorders and was established using two assessment methods. An inverse relationship with age is consistent with studies reporting that substance abusers with personality disorders are significantly younger than those without personality disorders (36). A partial explanation for this phenomenon is provided by follow-up studies indicating that many individuals outgrow their personality pathology (39). It should be noted, however, that age-related differences in prevalences cannot be directly interpreted as maturational in nature; maturational effects are confounded with generational effects and other selection biases in cross-sectional analyses (40). For example, selective mortality among individuals with either BPD (41) or ASPD (42) may also contribute to age-related differences in the observed prevalence. Furthermore, early treatment-seeking behavior due to the early onset of addictive problems and increased problem severity in comorbid individuals may account for an age effect.

Diagnostic Criteria

Sampling factors cannot fully account for different prevalence rates. Within the same sample, significant differences may result from different sets of diagnostic criteria, the different use of timeframe requirements, and the application of exclusion criteria for substance-related pathology:

- Sets of diagnostic criteria differ across classification systems. For example, DSM-III-R ASPD and ICD-10 dyssocial personality disorder show little conceptual concordance, and therefore a lack of empirical agreement (43). However, different versions within one classification system may also lack agreement (44). For example, in a mixed sample of substance abusers, poor rates of diagnostic agreement between DSM-III and DSM-III-R were obtained for the histrionic and dependent diagnostic categories (45). Similarly, in a sample of cocaine abusers, using either DSM-III or DSM-III-R criteria for ASPD resulted in dramatically different prevalence rates (46).
- The chosen timeframe—i.e., the required period in a person's life (in terms of onset, duration, and recency) in which pathological traits must be present to be relevant for diagnosis—seems to affect the prevalence to a great extent (37). In the empirical literature, the recency requirement is addressed by the distinction between current and lifetime ASPD diagnoses (47,48). These studies point to a dramatic drop from lifetime to current ASPD prevalence rates, raising questions about the stability of personality disorder diagnoses. The effect of excluding substance-related pathology depends on the exclusion strategy chosen (31). For example, the strategy that is prescribed by the Schedule for Affective Disorders and Schizophrenia, Lifetime Version (SADS-L) (49), using the Research Diagnostic Criteria (RDC) (50), is the most stringent: any trait or behavior that has ever been linked to substance abuse is not taken into account for diagnosis. This rigid exclusion strategy results in a clear drop in the observed prevalence. In contrast, the exclusion strategy applied to studies using the NIMH Diagnostic Interview Schedule (DIS) (51) requires only traits or behaviors that have been exclusively linked to substance abuse to be excluded from diagnosis; consequently, the effect is minimal. The strategies undertaken by Weiss et al. (34) using the Structured Clinical Interview for DSM-III-R Axis II (SCID-II) (52) and by Verheul et al. (37) using the International Personality Disorder Examination (IPDE) (43) are similar to this DIS strategy, also resulting in negligible effects. Nace et al. (53) and Dulit et al. (54) employed an exclusion strategy that removed questions related to substance abuse from the Diagnostic Interview for Borderline patients (DIB) (55,56), resulting in a clear drop in prevalence rates. Finally, Rounsaville et al. (57) determined, on an item-by-item basis, whether symptoms were attributable to the subjects' SUD or independent of these disorders. They found that inclusion of substance-related symptoms led to a substantial number of newly diagnosed cases, especially for ASPD (19.4%) and BPD (11.4%).

Assessment Procedures

Even if the same diagnostic criteria are employed in two identical samples, the observed prevalence rates may differ due to the choice of method and time of measurement:

- The assessment method seems to have a large effect on the observed prevalence (see Table 2). In general, self-report questionnaires and fully structured interviews yield the highest rates, whereas semistructured interviews produce intermediate rates and unstructured clinical assessments produce a wide range of rates and the lowest median prevalence. Two explanations may account for this effect: 1) structured instruments rely heavily on self-report and do not distinguish between accentuated (or

subthreshold) traits and behaviors and their pathological equivalents (58); and 2) the timeframe criteria applied by structured methods are less stringent than those of semistructured or nonstructured methods, thereby leading to higher rates. It is important to realize that both explanations account for overrating by fully structured instruments, but not for underrating. Other factors, such as sensitivity to state effects or idiosyncratic interpretation of certain questions or specific wording by the patient, may further explain disagreement between instruments (58,59).

- In addition, the time of measurement may affect the observed prevalence because state effects (e.g., withdrawal symptoms) are stronger at admission and during detoxification than when substance abusers have been sober and free of drugs for several weeks. A study among alcoholic patients showed a decreased prevalence rate of BPD and avoidant personality disorder over a 6-week treatment interval, but no effect of time of measurement for the other personality disorders (37). Whereas changes over time are generally considered to result from the confounding of trait by state, no such explanation is available for the results of studies that compared prevalence between treatment episode and 1- or 2.5-year follow-up, showing dramatic drops at follow-up (60–62). These findings and their implications are not yet well understood.

CAUSAL PATHWAYS

Reported prevalence rates of overall, ASPD, and BPD prevalence in nonpatient samples of substance abusers (see Table 2) are at least three times higher than in normal individuals (i.e., those without psychiatric and/or SUD). Specifically, the median rates are 48%, 15%, and 7%, respectively, among nonpatient substance abusers, compared with 10–15%, 3%, and 2%, respectively, among normal subjects (59,63,64). These findings strongly suggest that the co-occurrence between SUD and personality disorders is not due solely to random or coincidental factors. One factor that may contribute to the strong relationship is the overlap between the diagnostic criteria of Axis II disorders and SUD. However, clearly overlapping criteria seem to be restricted to ASPD (65) and BPD (54). Therefore, it seems reasonable to explore the assertion that addiction and personality disorders are in some way causally linked. Further evidence for causal relationships between SUD and personality disorders can be derived from long-term longitudinal studies, familial aggregation studies, and retrospective studies that account for the order of onset of each disorder. This section provides an overview of the evidence regarding the nature of the causal connection(s) between substance use and personality disorders. Different causal models have different implications for the treatment of comorbid patients. We distinguish three superordinate meta-models of comorbidity:

the primary substance use disorder model;
the primary personality disorder model;
the common factor model.

Primary Substance Use Disorder Model

The primary substance use disorder model postulates that substance abuse contributes to the development of personality pathology. An important ongoing controversy is whether and to what extent Axis II diagnoses in alcoholics and drug addicts are substance-related artifacts, reflecting transient conditions secondary to the addictive problems rather than "true" personality disorders with early onset and an enduring course independent of Axis I symptoms (66). However, several recent findings have supported the construct validity of Axis II diagnoses in substance abusers. First, Skodol et al. (67) reported similar prevalence rates of personality disorders among those with a current SUD and those with a lifetime SUD. Furthermore, Axis II diagnoses in adult alcoholics have been found to be associated with maladjustment in childhood, even after partialling out the current and cumulative effects of substance use (68,69). Finally, in a sample of 273 mixed substance abusers it was found that remission of SUD was not significantly associated with remission of the personality pathology, which suggests that the two conditions follow an independent course (60). Altogether, these findings do not confirm the notion (28) that chronic and severe substance use leads to transient manifestations of personality pathology that are independent of antecedent psychopathology and diminish with abstinence. On the other hand, it would be premature to preclude the possibility that some symptoms in some individual substance abusers are shaped and maintained by the reinforcing and conditioning properties of psychoactive substances.

Bernstein and Handelsman (70) proposed three mechanisms underlying the causal pathways between substance-related effects and a broad range of behavioral problems resembling personality disorders. As they point out, it is unclear to what extent these effects can "overwrite" pre-existing personality patterns or interact with pre-existing patterns to form new personality configurations. Considering the secondary personality disorder model, it is important to distinguish "new" enduring personality patterns from temporary behavior patterns that disappear with reductions of substance use. The latter should not be taken into account for an Axis II diagnosis. According to DSM-IV, it is only when the consequences of substance abuse persist beyond the period of alcohol and/or drug consumption that these features constitute personality pathology.

The first mechanism described by Bernstein and Handelsman (70) suggests that substance abuse often occurs within the context of a deviant peer group and that antisocial behaviors are shaped and reinforced by social group norms (social learning hypothesis). This model mainly applies to ASPD secondary to substance abuse, and is consistent with Gerstley and colleagues' (65) concept of "symptomatic psychopathy," i.e., a behaviorally based diagnosis of ASPD with concomitant neurotic symptoms (e.g., depression) and an underlying character structure that is different from that of so-called "true psychopaths."

The second mechanism refers to the potential of substances to alter behavior through their effects as reinforcers or conditioning agents, linking environmental and internal cues to substance use (behavioristic learning hypothesis). Some cluster A traits (e.g., paranoid ideation, suspicion, eccentric behaviors, ideas of references, magical thinking), cluster B traits (e.g., interpersonal exploitativeness, egocentrism, manipulativeness), and cluster C traits (e.g., passivity, social avoidance) may be shaped and maintained by the reinforcing and conditioning properties of psychoactive substances. For example, addicts may suspect other addicts in order to avoid being exploited, or substance abusers may

manipulate friends and family members in order to get financial support. Furthermore, intoxication may produce distorted perceptions of one's social environment that may shape the thinking and behavioral style into one of frequent ideas of reference, eccentric behaviors, and social avoidance.

According to the third mechanism, chronic substance abuse or withdrawal may alter personality through a direct effect on brain chemistry (neuropharmacological hypothesis). Neuroadaptive changes in response to chronic substance abuse may underlie prolonged disturbances in affect, cognition, or social interaction. Animal studies show decreased motivation and activity levels subsequent to both opioid and cocaine use (70). Furthermore, some evidence indicates that alcohol may act as both an anxiolytic and a psychomotor stimulant, and may reduce inhibitory control and increase pain sensitivity (71). These properties of alcohol may set the conditions for behaviors such as aggression, but it is unknown whether the neuropharmacological effects are enduring. Protracted withdrawal from many psychoactive substances may also produce features that resemble pathological personality traits.

Primary Personality Disorder Model

The primary personality disorder model describes comorbid relationships in which (pathological) personality traits contribute to the development of a substance use disorder. One line of investigation, fitting into a symptomatic conception of addiction, has sought to identify a unique (pre) addictive personality. This approach was largely discarded in the 1970s, because a multitude of retrospective and prospective studies had consistently failed to identify a unique type of preaddictive personality (72–74). Keller's often cited law—"the investigation of any trait in alcoholics will show that they have either more or less of it" (75)—reflected the state of the art. Consequently, the primary personality disorder model was generally rejected at that time.

In the late 1980s, several criticisms of the early studies were raised, e.g., ignorance of heterogeneity regarding such factors as age of onset, sample specificity, use of instruments focusing on abnormal or clinical dimensions rather than on personality, including the Minnesota Multiphasic Personality Inventory (MMPI) (15,76,77). Two developments resulted from these criticisms. First, the investigations were focused specifically on antisocial personality. Many prospective studies consistently demonstrated that, at least for a subgroup of men and possibly women, a history of traits such as aggression, conduct problems, hyperactivity, impulsivity, and unconventionality predate the later development of alcohol problems and other substance abuse (78–80). Second, a "nonlinear approach" was taken. For example, Cloninger et al. (77) found that absolute deviations from the mean of each of three temperament dimensions (novelty seeking, harm avoidance, and reward dependence) at age 11 were associated with an *exponential* increase in the risk of later alcohol abuse. Furthermore, Shedler and Block (81) found *curvilinear* (U-shaped) relations between maladaptive personality traits and the level of drug use; i.e., moderate users were found to be psychologically healthier than either abstainers or problem users. Personality differences between these three categories could be traced to the earliest years of childhood. These studies overcome two important shortcomings of earlier research. First, the effects of absolute (i.e., bidirectional, ignoring

sign) deviations from the population mean have been detected, whereas earlier studies were insensitive to these effects because they simply compared the arithmetic means of high- and low-risk groups on several personality traits. Second, nonlinear (i.e., curvilinear, exponential) relationships between personality traits and addictive behaviors have been detected, whereas earlier attempts assumed but did not test for linearity.

The studies focusing on antisocial traits and those taking a nonlinear approach reanimated the primary personality disorder model. From the 1990s until now, many studies have been published supporting the model. Recently, it was proposed that the available evidence suggests at least two or three different causal or developmental pathways to addiction, in which personality factors are likely to be an important etiological factor (66,82,83). These pathways were defined as follows:

the behavioral disinhibition pathway;
the stress reduction pathway;
the reward sensitivity pathway.

The *behavioral disinhibition pathway* to addiction predicts that individuals scoring high on traits such as antisociality and impulsivity, and low on constraint or harm avoidance, have lower thresholds for deviant behaviors such as alcohol and drug abuse. Of the three proposed pathways, this one is the best documented. First, high relative comorbidity is observed between SUD and Axis I and Axis II disorders from the impulse control spectrum. For example, in a large sample recruited from the general population, individuals with SUD were 17.2 times more likely to have ASPD than those without SUD (35). Second, several longitudinal studies have shown that teachers' ratings of low constraint, low harm avoidance, lack of social conformity, unconventionality, antisociality, and aggression in children, particularly boys, predicted alcohol and drug abuse in adolescence and young adulthood (77,78,84–86). The same pattern was reported in university students (87). Third, a recent study found that the onset of ASPD characteristics precedes that of alcohol dependence by some 4 years (88). The relationship between behavioral disinhibition and early-onset addictive behaviors is probably mediated through deficient socialization, school failure, and affiliation with deviant peers (25,78,89). Finally, this pathway has been supported in a study among homosexual men (90). It was shown that baseline cluster B disorders predicted the subsequent onset of SUD. Moreover, subjects with 11 or more personality disorder symptoms were more likely than those with 10 or fewer symptoms to be diagnosed with subsequent SUD. The behavioral disinhibition pathway is differentially associated with the natural course of addictive behaviors. For example, Hesselbrock et al. (91) found that subjects with ASPD had an earlier onset of drinking and a more rapid development of alcohol dependence once drinking began than non-antisocial subjects. This finding is consistent with studies showing antisocial alcoholic patients to be significantly younger (92) and to have more severe symptoms than nonantisocial alcoholic patients (93–95). It is also consistent with Cloninger's male-limited, antisocial, type 2 alcoholism, which is characterized by early-onset drinking problems (before age 25) and an inability to abstain from alcohol (23).

The *stress reduction pathway* to addiction predicts that individuals scoring high on

traits such as stress reactivity, anxiety sensitivity, and neuroticism are vulnerable to stressful life events. These individuals typically respond to stress with anxiety and mood instability, which, in turn, can become a motive for substance use as self-medication. Several studies have provided strong evidence for the stress reduction pathway. Longitudinal studies have shown that teachers' ratings of negative emotionality, stress reactivity, and high harm avoidance in children predicted substance abuse in adolescence and young adulthood (77,85,89). Retrospective accounts of the order of onset have shown that anxiety disorders precede SUD in a large proportion of comorbid individuals (96–99). In general, phobic disorders (which are closely related to avoidant personality disorder) seem to precede SUD in most cases, whereas panic disorder and generalized anxiety disorder may be more likely to follow from excessive and chronic substance use. The self-medication pathway, which has most frequently been investigated for alcoholism, typically accounts for late-onset alcohol use disorders and is more prevalent among women than among men. Consistent with the stress reduction pathway, a recent study (100) showed that coping motives for drinking as well as the fear-dampening properties of alcohol were far more pronounced among men scoring high on anxiety-sensitivity than among their low-scoring counterparts.

The *reward sensitivity pathway* predicts that individuals scoring high on traits such as novelty seeking, reward seeking, extraversion, and gregariousness will be motivated to substance use for its positive reinforcing properties. Consistent with this hypothesis, some longitudinal studies (77,84,89) have shown that novelty seeking as a temperamental trait in childhood predicts later substance use and related problems. Furthermore, some evidence suggests that students' scores of extraversion, at least among those without a family history of alcoholism, predict alcohol dependence at age 30 (80). As observed in animal studies, hyper-responsiveness to the positive reinforcing or rewarding effects of substances is partly accounted for by the sensitization processes initiated by the repetitive use of the substances themselves (101), and to that extent is not precipitated by premorbid personality factors. However, this hyper-responsiveness or hypersensitivity might develop most strongly among individuals characterized by a more general sensitivity to positive reinforcements, as is suggested by several authors (23,102,103). A recent study showed that men with multigenerational family histories of alcoholism demonstrated elevated resting heart rates (index of psychostimulation) in response to alcohol intake, suggesting that this pathway partly mediates the role of genetic vulnerability in the etiology of alcoholism (100).

Some evidence indicates that the proposed pathways are related to dysregulation of distinct neural circuitries or neurotransmitter systems (103). Behavioral disinhibition or impulsivity is likely to be primarily related to serotonergic deficiencies; stress reactivity or anxiety sensitivity is probably primarily related to increased neuronal excitability as a result of reduced inhibition via the GABA-glutamatergic receptor system; and reward sensitivity or extraversion might be related to dopaminergic or opioidergic hyperreactivity (23,103–106). The evidence for such associations between clinical characteristics and underlying neurochemical dysregulation is still preliminary, but holds promise for specific patient-treatment matching in the future.

It should be noted that the three pathways described above are likely to differ with respect to their relevance across different personality disorders. Different motivations

may be related to different personality types: individuals high on neuroticism/emotionality (e.g., with borderline, dependent, avoidant, and obsessive-compulsive personality disorders) are more prone to affective instability and motivated to use substances for symptom relief (e.g., benzodiazepines, alcohol, opiates), whereas individuals high on impulsivity/disinhibition (e.g., with ASPD) are more motivated to use substances for positive-reinforcement motives (e.g., cocaine, amphetamines, ecstasy) (23,73,78). The three proposed pathways probably account for most of the observed comorbidity of personality disorders and SUD. The behavioral disinhibition pathway might account for the comorbidity of ASPD and, to some extent, BPD. The stress reduction pathway might account for the comorbidity of avoidant, dependent, schizotypal, and borderline personality disorder. The reward sensitivity pathway might account for the comorbidity of histrionic and narcissistic personality disorder.

Furthermore, specific substances may be chosen for specific psychological and pharmacological effects according to each abuser's needs; the most painful affect is likely to be what determines the choice of substance (4,107,108). For example, alcohol may be used to neutralize anxiety or for its relaxing properties, while hallucinogens appear to relieve boredom and stimulants are used to induce feelings of pleasure or to reduce internal stress. Consistent with this hypothesis, a recent study (109) reported that, when partialling out the impact of the comorbidity between alcohol and drug use disorders, alcoholism appeared to be primarily associated with negative emotionality but not with low constraint, whereas drug use disorders showed the reverse pattern. Interestingly, the self-medicating properties of alcohol appear to be related to individual differences in sensitivity to its effects (110), which in turn may be related to personality factors. Support for this hypothesis comes from studies demonstrating that individuals who score high on measures reflecting impulsivity/disinhibition seem to experience pronounced alcohol effects and may be more sensitive to alcohol than individuals who score low on these measures (111).

Consistent with the first two pathways (i.e., behavioral disinhibition and stress reduction), Cloninger (23) has proposed an alcoholism typology in which comorbid personality traits (i.e., temperamental factors), together with dependence characteristics, define two distinct etiological pathways. Type II alcoholics are characterized by an inherited predisposition toward antisocial personality traits, specifically high novelty seeking, low harm avoidance, and low reward dependence. Type I alcoholics are characterized by passive-dependent traits of low novelty seeking, high harm avoidance, and high reward dependence. However, it seems unlikely that the two types provide an exhaustive description of the total alcoholic population. For example, Koeter et al. (112) reported that, applying strictly the differential clinical features defined by Cloninger, only 7% of a sample of Dutch residentially treated alcoholics fulfilled the criteria for either Type I or Type II. Presumably, the failure to dichotomously classify individuals according to two or more characteristics is related to the relative independence of the defining features. This is certainly true when the defining characteristics include personality traits, especially when these traits are factor analytically derived and thus relatively independent of one another. Another example is the attempt of Cooper et al. (113) to classify their sample according to the two factors from their motivational model of alcohol use and abuse: only 25–30% of their sample could be successfully classified,

whereas the majority drank for neither or both reasons. In this case, the failure to classify subjects as either "copers" or "enhancers" was related to the correlation between the two scales for coping and enhancement drinking. From the above, we can learn that reality is better served by introducing relatively independent factors, which are allowed to occur simultaneously or be absent in individual cases. Distinguishing between relatively independent factors is also consistent with developmental models of addiction (73,114), which propose that the affective precipitants and consequences of alcohol abuse may change during the course of an individual's drinking career. Cox (73) argued that many male pre-alcoholics typically are not characterized by negative affective traits but, instead, by traits such as sensation and reward seeking, need for immediate gratification, impulsivity, and unconventionality. Hence, they will use alcohol initially to enhance their positive affect. However, as their drinking experiences continue, their chronic affect might change, and their motivation for using alcohol might change. As a result, alcohol's control of negative affect becomes progressively more salient (73).

A newer line of research focuses on the role of environmental etiological factors in the relationship between personality and addiction. For example, Brook et al. (115,116) found that the effect of parent-child mutual attachment was mediated through early adolescent personality attributes of greater responsibility, less rebelliousness, and intolerance of deviance. These non-drug-prone personality and behavioral attitudes, in turn, insulated the young adult from affiliating with drug-using peers, and these attitudes were related to less drug use during the individuals' early 20s and ultimately their late 20s. Another study reported that young adult neuroticism and agreeableness each, in part, mediated the effect of parental alcoholism on young adult alcoholism (117).

Common Factor Model

The common factor model assumes that both personality pathology and substance abuse are linked to an independent, third factor that contributes to the development of both disorders. This model is more likely for substance use and personality disorders that show relatively high joint comorbidity, i.e., both a high prevalence of SUD among the personality-disordered group and a high prevalence of personality disorder among the addicted group. Zimmerman and Coryell (35) found the lifetime prevalence of alcohol use disorders to range from 43 to 77% among various personality disorders. However, within substance abuse samples, a prevalence of 25% or higher is generally observed for ASPD and BPD only. Thus, if there are common etiological factors, we would most likely observe these for antisocial and borderline pathology. This hypothesis is consistent with the psychobiological perspective on personality disorders proposed by Siever and Davis (105), which suggests that BPD and ASPD are phenomenologically, genetically, and/or biologically related to Axis I impulse disorders such as substance abuse. Others have proposed that SUD and BPD and ASPD are impulse spectrum disorders (118,119).

Ideally, potential common factors should be associated prior to the onset of a disorder, and the association should persist during periods in which affected cases are asymptomatic (e.g., during periods of abstinence from drug or alcohol use). Therefore, the common factor model is often evaluated with regard to genetic factors and severe early childhood trauma. It is well known that genetic factors play an important role in

both alcohol and drug dependence (120,121). Of all personality disorders, ASPD, and to some extent BPD and schizotypal personality disorder, have been shown to have clear genetic determinants (122). In addition, there is some evidence of a relationship between childhood physical/sexual abuse and addictive problems (123). With respect to Axis II, BPD seems to be specifically related to early affective neglect and sexual and/or physical abuse histories (124), whereas ASPD seems to be related to various, nonspecific early family factors (41).

Family, twin, and adoption studies are generally considered most appropriate to evaluate whether a common risk factor is transmitted genetically or otherwise. Evidence from several adoption studies suggests that alcoholism and ASPD are genetically separate disorders (125,126). Furthermore, Loranger and Tulis (127) reported that family members of patients with BPD were at greater risk for alcoholism than those of schizophrenic or bipolaraffective patients, but when patients were further subdivided on the basis of their own level of alcohol consumption, family risk differences for alcoholism almost disappeared. A recent study reported that the shared genetic risk between major depression, alcohol, and marijuana dependence was largely explained by genetic effects on ASPD, which in turn was associated with increased risk of each of the other disorders (128). These data presented no evidence for cross-transmission of pure forms and no support for the shared-etiology model. However, the available studies do not preclude the possibility of common factors that, for example, are less specific to ASPD and play an important role in specific, homogeneous samples. For example, the population studied by Cloninger et al. (129) and Bohman et al. (130), in which petty criminality (i.e., a mild type of antisocial behavior) in biological fathers increased the risk for alcoholism in adopted sons, may be more homogeneous. Also, focusing on personality dimensions rather than Axis II diagnoses might help to disentangle the complex associations. For example, Slutske et al. (131) reported that genetic influences contributing to variation in behavioral undercontrol accounted for about 40% of the genetic variation in alcohol dependence and conduct disorder risk and about 90% of the common genetic risk for alcohol dependence and conduct disorder. This and other studies (e.g., Ref. 132) suggest that genetic factors contributing to variation in dimensions of personality, particularly behavioral undercontrol, account for a substantial proportion of the genetic diathesis for alcohol dependence and most of the common genetic diathesis for alcohol dependence and conduct disorder among men and women.

Another approach in the search for common factors has relied on high-risk strategies, with the aim of identifying markers of biological vulnerability for both conditions. A marker is a functional, structural, or behavioral variation associated with a biological vulnerability to a disorder. For example, reductions in the P3 component of the evoked response are observed in both alcoholic individuals and prepubertal boys of alcoholic fathers, as well as in nonalcoholic ASPD subjects (133), suggesting a shared genetic factor. A recent study revealed that a reduced P300 amplitude in men is strongly associated with a general tendency toward antisocial, defiant, and impulsive traits, which in turn increase the risk for alcohol abuse (134). Furthermore, some reviewers (70,105) have concluded that abnormalities in serotonergic function may form a biological substrate underlying both substance abuse and impulsive/aggressive behavior. In their study, Bernstein and Handelsman (70) found intriguing associations between biological

and behavioral factors in substance abusers, but the patterns of association appear to be complex and to differ importantly across subtypes of substance abusers. For example, in alcoholic individuals, *increased* serotonergic activity was shown to be associated with impulsivity/aggression whereas in cocaine abusers, *decreased* serotonergic activity was shown to be associated with impulsivity/aggression.

Comment on Causal Pathways

In summary, most evidence available to date strongly supports the primary personality disorder model, and a heuristic model of three developmental pathways has been proposed, i.e., the behavioral disinhibition, stress reduction, and reward sensitivity pathways. No data from prospective studies are available on the primary substance use disorder model, which has been relatively neglected in comparison with the other models. Bernstein and Handelsman (70) have proposed three mechanisms that can explain how personality disorder symptoms, such as paranoid ideation, suspicion, eccentric behaviors, and ideas of reference, and behavioral patterns such as interpersonal exploitativeness, manipulativeness, and passivity, might result from (chronic) substance abuse. To the extent that these mechanisms exist, the primary substance use disorder model accounts for part of the high prevalence of these Axis II characteristics. Finally, recent empirical findings with respect to the common factor model are quite intriguing and suggest a common diathesis for SUD and ASPD.

Although the issue of causality within individual patients is interesting and may have important treatment implications, retrospectively differentiating causal mechanisms is a complex task. Until now, two retrospective strategies have been proposed to distinguish between primary and secondary personality pathology. First, exclusion criteria have been applied using several assessment methods. It is, however, extremely difficult to separate substance-induced behaviors from persistent behavior patterns, particularly among individuals with chronic substance abuse histories (see further discussion of this issue in "Axis II Assessment in Substance Abusers," p. 288). Furthermore, some strategies do not exclude secondary personality pathology (i.e., enduring traits that persist beyond the period of alcohol and/or drug consumption) as such, but instead exclude only temporary behaviors that may mimic personality traits during an active abuse period but that disappear subsequent to cessation of substance use.

It is important to note that the different meta-models are not necessarily mutually exclusive. In any individual case, more than one model may have explanatory value (135). Furthermore, it is possible that one model best describes the initiation of a comorbid disorder, while another describes long-term maintenance of the same comorbid association. For example, a borderline patient may use stimulants to reduce feelings of boredom and use alcohol to regulate affective instability (affect-regulation model). After a while, the patient becomes addicted to both substances, which in turn aggravate the impulsivity and set the conditions for aggressive suicide attempts (neuropharmacological model). Simultaneously, the patient may get entangled with a deviant peer group, leading to both increased antisocial behavior (social learning model) and additional substance abuse (developmental behavior genetic model). This conjunction of models may be referred to as a *bi-directional model* (9). Another example of a bi-directional model is

suggested by Nace (28), who emphasizes personality regression with a weakening of ego functions and reinforcement of immature traits (e.g., impulsivity, decreased frustration tolerance) induced by the pharmacological effects of psychoactive substances, and predisposing in turn to substance abuse.

Personality pathology may also act as a modifier of symptoms, treatment response, outcome, and course of SUD, and thereby account for the strong association between both conditions. This possibility does not involve a causal relationship but may have important implications for treatment planning. The next section provides an overview of the empirical findings regarding course and outcome in comorbid patients.

TREATMENT OUTCOME

Response to Standard Substance Abuse Treatment

Personality pathology has been found to be significantly related to poor treatment response and outcome in patients with affective and anxiety disorders (136,137). In the early 1990s it was generally believed that the same applies to patients with SUD (9,17). However, the available studies at the time suffered from many methodological and interpretative problems, making it difficult to draw conclusions. For example, many studies consisted of small samples, used outcome measures uncontrolled for pretreatment status, or applied diagnostic measures of questionable value (48,94,138–141). Consequently, it was often unclear whether the reported effects on outcome were attributable to a poor treatment response of comorbid patients or to differences in pretreatment characteristics. In addition, some negative studies had been published. For example, the study by Nace and Davis (36,142) showed that personality-disordered substance abusers have worse pretreatment status and posttreatment outcome in terms of life satisfaction, but benefit from inpatient treatment about as much as substance abusers without Axis II comorbidity. Furthermore, the personality disorder group had significantly greater decreases in use of marijuana, amphetamines, and LSD, whereas the non-personality disorder group had greater decreases in alcohol use. In addition, Nace et al. (53,143) found that borderline alcoholic patients appeared to be more vulnerable to drug problems and disturbed relationships with their parents both before and following short-term, psychiatrically oriented alcoholism treatment than were nonborderline alcoholic patients. On the other hand, borderlines benefitted about equally from treatment and actually had fewer hospitalizations and better employment status following treatment than did nonborderlines. Other studies found the relationship between ASPD and poorer substance abuse outcome to be confounded by initial severity of substance abuse (144,145). Eight other studies published later revealed similar results, convincingly showing that personality pathology is associated with pre- and posttreatment problem severity but is not a robust predictor of the amount of improvement (146–152). Furthermore, some studies showed that Axis II comorbidity is not associated with premature drop-out or a shorter time-in-program (153–155), nor with less motivation to change (154). In the late 1990s, some authors therefore concluded that a close and critical examination of the available treatment outcome studies did not allow any firm

conclusions about the prognosis of substance abusers with personality disorders (e.g., Ref. 156).

Despite the obvious inconsistencies in clinical opinions, empirical findings, and treatment literature, a number of more recent studies have yielded results that provide somewhat more clarity (66,82). For example, two studies showed that Axis II disorders predict a shorter time to relapse after discharge (157), even when controlling for the baseline severity of alcohol problems (154). Therefore, although some studies show that substance-abusing individuals with Axis II disorders benefit as much as those without such comorbidity, other studies indicate that the "equal amount of improvement" does not resemble a similar risk of relapse. A possible explanation for this apparent discrepancy is that patients without personality pathology improve to a level of problem severity that no longer leaves them at risk for relapse, whereas patients with personality pathology stay at risk for relapse despite their improvement.

The importance of personality factors in the course of the addictive problems after discharge from treatment is also supported by studies focusing on "normal" personality traits. For example, it has been shown that low persistence is a strong predictor of the time to relapse (158–160). Interestingly, Meszaros et al. (161) found that novelty seeking is a strong predictor for relapse in detoxified male alcoholics. Finally, it was found that high neuroticism and low conscientiousness predicted the time to relapse after discharge, and that the combination of these two features was associated with the highest odds of relapse (162).

Early studies typically examined the impact of personality pathology separately from other patient characteristics, despite the fact that this approach might fail to identify possible interactions with other important characteristics. For example, one study examined motivation for change and time-in-program as potential moderators and mediators of the relationship between personality disorders and relapse (154). It appeared that, although motivation for change was unrelated to personality pathology, it moderated the relationship between Axis II and relapse so that personality pathology was a strong predictor of relapse among less motivated individuals but not among their more motivated counterparts. A similar relationship was observed for time-in-program. In addition, two studies suggest the importance of the patient-therapist working alliance as a potential mediator of the relationship between Axis II pathology and relapse (2,154). Finally, Pettinati et al. (163) found that the combination of Axis I and Axis II psychopathology was the best predictor of a return to substance use at one year posttreatment, compared to those factors alone.

An alternative explanation of the available data that seems to refute common clinical knowledge with respect to the prognosis of ASPD is that the ASPD criteria set identifies a heterogeneous group of patients that includes both individuals with only antisocial behaviors and individuals with antisocial or psychopathic personality traits such as shallow affect, grandiosity, and lack of empathy and remorse (146). The latter group is particularly at risk of poor treatment response and outcome. Consistent with this view, Woody et al. (164) have shown that opiate addicts with ASPD and a lifetime diagnosis of major depression were able to benefit about as much from individual psychotherapy as patients without ASPD. This is in comparison with "pure" ASPD subjects, who experienced very little benefit from psychotherapy. Another interesting study found that

antisocial patients who were able to form a working alliance with their therapists had better treatment response and outcome at follow-up than did antisocial patients who lacked this ability (2).

In summary, evidence from several studies indicates that, although substance abusers with comorbid personality disorders might benefit from treatment at least as much as those without such comorbidity, the patient's personality profile has a strong impact on the course of addictive problems after discharge. Evidence also suggests that the impact of the patient's personality on outcome might be partly mediated by its influence on certain aspects of the treatment process. Furthermore, some data suggest that personality traits interact with one another as well as other important patient characteristics such as motivation to change and Axis I disorders in their impact on treatment process and outcome. Finally, clinical heterogeneity among the categories on Axis II may mask subgroups with a particularly poor prognosis, such as psychopathic antisocial substance abusers.

Future studies should focus on identifying the specific personality traits that are most predictive of outcome, and the mechanisms underlying the process of change. Another fruitful line of future research is to extend the findings from studies examining the role of personality pathology as a potential matching variable (6,149,165–168). The findings of two studies, which indicate that antisocial substance abusers benefit most from a structured, behaviorally oriented treatment approach, are promising in that respect (167,168).

Response to Treatment Focusing on Axis II

Very few studies have investigated the effects on substance use outcome of treatments for Axis II disorders among substance abusers. We are aware of only four studies that provide relevant data on dialectical behavior therapy (169–171) and dual focus schema therapy (172). Dialectical behavior therapy (DBT) is a manualized 12-month treatment that combines four modules: weekly individual cognitive-behavioral psychotherapy sessions with the primary therapist, weekly skills training groups lasting 2–2.5 hours per session, weekly supervision and consultation meetings for the therapists, and phone consultation. Patients are encouraged to obtain coaching in the application of new effective skills by phoning their primary therapists either during or outside office hours. Individual therapy focuses primarily on motivational issues, including the motivation to stay alive and to stay in treatment. Group therapy teaches self-regulation and change skills, and self and other acceptance skills. Among its central principles is DBT's simultaneous focus on applying both acceptance and validation strategies and behavioral change strategies to achieve a synthetic (dialectical) balance in client functioning. Two randomized trials have shown that standard DBT, compared to treatment-as-usual (TAU), is effective in reducing severe borderline symptomatology in borderline patients without SUD (173), and that a modified version of this program (DBT-S) is effective in reducing substance abuse in borderline patients with SUD (169). For the latter study, standard DBT was extended and intensified with an added focus on substance abuse (DBT-S) (174), which includes all of the components of standard DBT plus the following elements: application of dialectics to issues surrounding abstinence, the application of a

specific pharmacotherapy module, a treatment target hierarchy relevant to substance abuse, a new set of attachment strategies designed to increase the positive valence of the therapy and the therapist as well as engaging difficult-to-engage and easily lost patients, the addition of six new and modified skills, an individual skills consultation mode, and increased emphasis on using natural and arbitrary reinforcers for maintenance of abstinence. Specific training of DBT therapists in the additional substance abuse module was a prerequisite. The subjects in Linehan's trial (169) who were assigned to DBT-S had significantly lower drop-out rates and showed significantly greater reductions in drug abuse throughout the treatment year and at 16-month follow-up compared to subjects in TAU. No differences were reported in the medical or psychiatric inpatient treatment received by DBT-S and TAU subjects, or on rates of parasuicidal behavior.

A later study investigated the effectiveness of standard DBT among 58 female borderline patients with or without substance abuse. The study showed that standard DBT can be applied in such patients, and that there were no major implementation problems (171). DBT resulted in a greater reduction of severe borderline symptoms than TAU, and this effect was not modified by the presence of comorbid substance abuse (170). However, standard DBT, as it was delivered in the study, had no effect on substance abuse problems (171).

Another interesting approach is dual focus schema therapy (DFST), developed by Ball and Young (175,176). DFST is a 24-week, manual-guided, individual therapy including both symptom-focused relapse prevention coping skills techniques for interpersonal, affective, and craving experiences (177–179) and schema-focused techniques for maladaptive schemas and coping styles (176,180,181). Cognitive-behavioral therapy appears to be an excellent choice for developing an integrated treatment strategy that has a dual focus on substance abuse and personality disorders. DFST interventions are focused on addictive behaviors and personality disorder symptoms through an integrated series of core techniques. For example, functional analysis is used to understand recent episodes of substance use and craving as well as maladaptive schemas and coping and their triggering events. Self-monitoring, problem solving, and coping skills training occur similarly for both the addiction and personality problems.

Ten individuals participated in a pilot-testing phase of a behavioral therapy development project funded by the National Institute on Drug Abuse (NIDA) that focused on the development and refinement of a treatment manual for personality-disordered substance abusers (Ball, personal communication). Two patients dropped out after 4 months of therapy and two were highly symptomatic and chaotic at baseline and dropped out after one appointment. The two patients with the best attendance were both employed full-time. Interestingly, the three patients with the lowest retention/attendance all had a primary Axis II diagnosis of avoidant personality disorder (with secondary ASPD). Because the two patients who dropped out after one appointment were discharged soon thereafter from the methadone treatment program and could not be located, these monthly follow-up assessments could not be completed. Although the monthly assessment results are biased because they exclude these two poor-outcome patients, they do provide a gross estimate of the effect of the psychotherapy being developed on those eight who received an adequate "dose." A visual inspection of the graphed aggregate data indicated that patients had decreases in the frequency of their

substance use, the severity of their psychiatric symptoms, and ratings of dysphoria. An observed increase in primary substance use frequency at month 6 was accounted for primarily by one of the patients who dropped out of the study after month 4 and resumed daily benzodiazepine use by the time of the termination assessment. Ratings of dysphoria (depression, anxiety, hostility) decreased by month 4 to the point of equaling positive affect ratings (which remained fairly stable across the study). Finally, although subjective in nature, all eight patients reported at study termination that they found the therapy very useful and were disappointed that it could not continue.

Furthermore, a randomized pilot study was completed, involving 30 methadone-maintenance patients, comparing individual manual-guided DFST to 12-step facilitation therapy (12FT) (182). Patients met structured interview criteria for an average of 3.3 personality disorders with ASPD present in over 70% of the cases, and BPD and avoidant personality disorder were present in over half of the cases. Paranoid and dependent personality disorder were present in over 10% of the cases, and the remainder of the Axis II disorders were less prevalent (172,183). Patients assigned to DFST reduced substance use frequency more rapidly over the 24-week treatment than did patients assigned to 12FT. Further inspection of the data suggested that a difference began to emerge at month 3, which corresponds to a point in the manual where the treatment is shifting from an assessment and education focus to an active change focus (172). Further-more, DFST patients reported an increase from a good early therapeutic alliance to a very strong alliance over the subsequent months of treatment, while 12FT patients demonstrated no such increase. Consistent with this finding, DFST therapists reported feeling as though they had a stronger working alliance with patients than did 12FT therapists.

Although the only Axis II-focused or dual focus treatments that have been evaluated for their impact on substance abuse outcome are DBT and DFST, several other Axis II-focused treatments may have some potential in this regard. In a formal meta-analysis of controlled effectiveness studies, Perry et al. (184) have shown that individuals with personality disorders improve over time and benefit substantially from intensive psychosocial interventions. For example, Bateman and Fonagy, in a controlled trial of 38 patients with BPD who were randomly allocated to a psychoanalytically informed day hospital or to treatment as usual, reported a substantial reduction in parasuicidal behavior, self-harm, and hospitalization over an 18-month period of treatment (11). The severity of self-reported psychiatric symptoms and social and interpersonal functioning also improved substantially, relative to the control group. Dropout was low (12%). Improvement occurred later in treatment, emphasizing that admission to day hospital needs to be for a relatively long period. Interestingly, the improvements were not only maintained but continued to develop over the 18-month follow-up period (185). A final report from this trial showed remarkable results in terms of the cost-effectiveness (186). Although borderline patients meeting formal criteria for SUD were excluded from this trial, periodic substance abuse was present among approximately half of the patients. It would be interesting to see whether borderline patients with SUD can benefit from this treatment as much as those without, especially because the trial by Verheul et al. (170) did not show differential effectiveness.

In summary, the only documented dual focus treatments are DFST and a modified version of DBT. Four studies support their efficacy. Although other treatment models

focusing on Axis II, such as psychoanalytically informed day hospital (11), have not yet been tested in substance abusers, it might be interesting to do so.

GUIDELINES FOR CLINICAL PRACTICE

Axis II Assessment in Substance Abusers

Since sampling accounts for only part of the variation in estimates of the prevalence of personality disorders among substance abusers, current epidemiological research and diagnostic practice are hampered by several unresolved issues concerning diagnostic criteria and assessment procedures. Until these issues are properly addressed, it is recommended that the diagnostic criteria and assessment procedures employed be carefully specified. An alternative approach is the inclusion of multiple criteria sets (e.g., with and without exclusion of substance-related pathology, with and without an early-onset criterion) and multiple assessments (e.g., both self-report and semistructured methods, replication of the assessments at another time of measurement). The guidelines described in this section might further direct epidemiological research and diagnostic practice. These recommendations are limited to issues that are more or less specific to Axis II assessment in substance abusers. Limitations in the reliability and validity of Axis II diagnoses have been summarized previously (58,187).

Assessment Method

Since the introduction of DSM-III in 1980, there has been an increased interest in the classification and diagnosis of personality disorders in research and clinical practice. This interest has fostered the development of semistructured interviews and self-report questionnaires for the assessment of DSM-IV personality disorders. These assessment methods provide diagnoses with reliability comparable to that of Axis I disorder diagnoses obtained using standardized procedures (188). However, diagnosis of personality disorders is constrained by poor agreement between data derived from different sources (e.g., patient vs. informant) and by poor inter-instrument agreement (58,187). Part of the disagreement between interviews and questionnaires might be the result of the high sensitivity and low specificity of the self-report approach in comparison with the interview approach. Although the issue of which method of assessment is more valid is not fully resolved, there is some consensus that self-reports overdiagnose personality disorders. This overdiagnosis may be especially prevalent in substance users since these instruments do not ask respondents to differentiate personality traits from the effects of substance abuse or other prolonged changes in mental status. Diagnostic interviews may have greater specificity because questions and answers can be clarified to tease out whether a symptom is chronic and pervasive or whether it is more situation-specific or related to substance abuse. Further clinical inquiry can also determine if there are other behavioral examples of the trait that are not specifically related to substance abuse. An interview also provides important behavioral observations of the patient's interpersonal style that may inform clinical judgment (187).

The available interview schedules differ in several respects. First, fully structured interview schedules should be distinguished from semistructured interview schedules. Fully structured interviews such as the CIDI (189) are significantly at variance with the DSM-IV general diagnostic criteria for Axis II disorders, particularly with respect to the operationalization and application of the timeframe requirements specified in DSM-IV. Timeframe refers to the required period in a person's life during which pathological traits must be present to be relevant for diagnosis. The DSM-III-R and its successor, the DSM-IV, stipulate three criteria in this regard (103). Traits or behaviors that are considered relevant for a personality disorder diagnosis should have an onset in adolescence or early adulthood (onset criterion), be characteristic of an individual's long-term functioning (duration criterion), including his or her recent functioning (continuation criterion). The CIDI does not require any timeframe criteria to be met. Therefore, we recommend caution when interpreting diagnoses made by the fully structured instruments. In our opinion, caution is also appropriate when using the distinction between current and lifetime ASPD diagnoses. From studies using this distinction (47,48,190), it remains unclear what timeframe requirements are applied for making current diagnoses. Furthermore, lifetime diagnoses are of unknown validity, as the duration criterion seems to be more or less ignored.

The PDI-IV (191), IPDE (192), SCID-II (52), and SIDP-IV (193) parallel the DSM-IV guidelines most closely. Therefore we strongly recommend using a semistructured interview schedule, both for epidemiological and clinical purposes. The choice between these instruments largely depends on the preferred level of detail and the preferred level of coverage of Axis II. For example, the IPDE includes item-specific anchor points for scoring, the PDI-IV is accompanied by the best manual containing helpful item-specific information (191), and the SIDP-IV provides the broadest coverage of Axis II including depressive, passive-aggressive and self-defeating personality disorder.

Exclusion of Substance-Related Pathology

Part of the reliability and validity issue for personality disorder diagnosis in substance abusers centers on whether to include or exclude Axis II symptoms that seem to be substance-related (i.e., behaviors directly related to intoxication and/or withdrawal, or other behaviors required to maintain an addiction). As discussed above, the magnitude of the effect of exclusion on the prevalence estimate seems partly attributable to the strategy used for exclusion. Measures with more stringent criteria exclude any symptom that has ever been linked to substance abuse and yield significantly reduced rates. Measures that exclude symptoms only if they were completely absent before substance abuse or during periods of extended abstinence show minimal effects on rates. It is important to realize that the more stringent strategy will probably exclude all secondary personality pathology, and may even exclude primary personality pathology. The less stringent strategy is meant to exclude behaviors and/or symptoms that do not persist beyond periods of abuse and do not qualify for a personality disorder diagnosis. Consequently, the less stringent approach will probably not exclude primary personality pathology and will have only a limited impact on secondary personality disorder.

Intuitively, one might suggest that excluding substance-related symptoms (at least

following the less stringent strategy) would result in more valid diagnoses. Diagnosing personality disorders independent of SUD is consistent with guidelines suggested by DSM-IV. However, the task of differentiating substance-related symptoms from personality traits is not easy for patients or clinical interviewers and thus may not be reliable. This task becomes almost impossible when the patient's entire adolescent and adult life is characterized by chronic abuse of substances. No one, not even the patient, may be able to predict how he or she would function without using drugs or alcohol. For example, when a 35-year-old drug-abusing patient notes that she has used hard-core drugs since the age of 15, the diagnostician is hard-pressed to view the patient's drug-related beliefs and actions as anything other than a major part of her personality. Furthermore, although most substance abusers can distinguish behaviors that are related only to substance intoxication or withdrawal, they have greater difficulty making the same distinction for other activities, such as lying or breaking the law, that may be related to obtaining substances. Such a distinction requires a high level of introspection and cognitive competence in making the judgment necessary to differentiate a trait from a situation or state. It also requires an empathic awareness of the impact of one's behavior on self and others and a willingness to accept responsibility for one's actions (187). Substance abusers may be particularly impaired in the skills necessary to make these distinctions. Depending on their stage of recovery and motivation, they may be more prone to make dispositional attribution for their behaviors or, in contrast, project responsibility for their negative traits onto others, the situation, or the effects of the substance. Consistent with this view, Rounsaville et al. (57) found that excluding substance-related symptoms reduced the reliability of ASPD diagnoses (but not of BPD diagnoses). Furthermore, they found that patients with independent diagnoses had a rather similar clinical profile to that of patients with substance-related diagnoses, thereby questioning the feasibility and clinical utility of exclusion.

If one chooses to exclude substance-related symptoms, several considerations are in order:

- It is probably more reliable to determine whether a symptom should be eliminated as substance-related on an item-by-item basis, and not wait until the end of the interview or until all items relating to a specific disorder are administered.
- Criteria in which substance dependence is an inherent part should be scored as due to substance abuse unless non-substance-related behavioral indicators of the trait (e.g., impulsivity, unlawful behaviors) are also present.
- When another Axis I disorder is suspected or present, the interviewer should periodically remind patients that questions refer to the way they are even when they are not symptomatic with either substance abuse or another Axis I disorder.

Time of Measurement

Test-retest reliability of Axis II assessment in substance abusers may be constrained because of the effects of intoxication, acute or protracted withdrawal symptoms, and other Axis I symptomatology. This contamination of trait measurement by state effects is likely to be stronger early in treatment. At that time, drug intoxication and withdrawal are characterized by marked changes in cognitive, emotional, and social functioning, which

may mimic many symptoms of personality disorders that do not accurately reflect baseline personality functioning. Due to the reduction of withdrawal symptoms over time, a substantial number of patients may lose their Axis II diagnoses. This hypothesis seems to be borne out, at least for personality disorders that consist of traits that closely parallel Axis I symptoms such as BPD and avoidant personality disorder (37). Some evidence suggests that self-report questionnaires are more susceptible to the confounding effects of state than semistructured interviews (194).

Withdrawal symptoms are strongest in the first week of detoxification and may be prolonged in a subacute manifestation for several weeks after (195). However, the first two weeks of treatment are also the time of greatest relevance from the standpoint of treatment planning. Although this problem can be partly overcome in inpatient settings by waiting for 2 weeks of abstinence, shorter inpatient stays greatly limit the clinical usefulness of this approach. Among outpatients, it is more difficult to ensure that a completely drug-free state has been achieved and maintained throughout the assessment period. Therefore, it may be preferable to interview a collateral informant in addition to the patient, to get valid information for diagnosis.

Other factors may account for the tendency to report more pathology on initial assessment and less pathology on follow-up interview. In our experience, the pathological traits reported by the patient may also reflect more generalized emotional distress or manipulative attempts to get help. Furthermore, the reduction of symptoms and impairment that occurs with time in treatment may also be attributed to a cognitive shift in which patients change from viewing themselves as completely troubled to believing they have completely recovered. This all-or-nothing view denies the persistence of symptoms, or minimizes their severity. In such circumstances, patients may no longer meet criteria for a personality disorder because a dramatic, defensive shift in self-assessment has occurred that is itself timelimited and not reflective of substantive changes in personality or poor reliability of the assessment methodology.

Summary of Recommendations

In conclusion, proper assessment of personality disorders in substance abusers requires the use of standardized assessment, including a semi-structured interview. Because the patient will sometimes appear to be unable to adequately or accurately answer the interview questions, it is recommended that data be obtained from multiple sources (e.g., patient interview, file information, staff observations, collateral informant interview). The best time of measurement in inpatient settings is after at least 2 weeks have elapsed and detoxification is complete. In outpatient settings, Axis II assessment should be avoided in clearly intoxicated patients, and at least some caution is appropriate when interpreting assessments of patients who are still actively using substances. Furthermore, in the absence of a clear consensus about the appropriate timeframe requirements and exclusion rules, the interviewer should be aware of the assessment problems and interpretative difficulties that may arise. Ideally, the results of the examination should be carefully documented and, if possible, supplemented with information about the diagnostic criteria employed and the theoretical orientation to the issue of the interrelationship between substance use and personality disorders.

Treatment of Substance Abusers with Axis II Comorbidity

As we have seen, substantial evidence indicates that comorbid personality disorders convey a poor treatment response and prognosis for SUD. However, the mechanisms of this effect are, for the most part, unknown. Comorbid individuals may precipitate more stressful life events by provocative or disagreeable behaviors, which in turn diminish social supports. Personality-disordered individuals are also especially vulnerable or sensitive to negative affect and interpersonal difficulties, two of the most common relapse precipitants. Finally, the effect may be related to the social isolation, dysfunctional attitudes, and maladaptive coping strategies of substance abusers with personality disorders. In short, a comorbid personality disorder tends to make substance abuse behavior patterns more rigid, compulsive, and difficult to treat. For these dually diagnosed patients, substance use seems to constitute a central part of an overall rigid defense system and a primary means of coping. Many of these patients struggle against compliance with their treatment plan and collaboration with their therapist. They place many demands and strains on therapeutic relationships, and require more time, energy, patience, and skill.

Phases in Treatment and Treatment Options

Effective treatment of substance abusers with personality disorders requires special and professional attention from the very beginning. Particular emphasis on motivational interviewing (196,197) during the admission phase and throughout the entire treatment process may be necessary with these dual-diagnosis patients. In addition to the regular program modules, intensive individual counseling is recommended to establish a working alliance and to prevent these patients from leaving treatment early. Direct therapeutic attention to maladaptive personality traits may increase cognitive and coping skills, which in turn may improve a comorbid Axis I condition (e.g., depression, anxiety, paranoia, all of which occur commonly among patients with substance abuse and Axis II disorders) and reduce the risk for relapse to substance abuse. Finally, such therapy may motivate these patients to participate in aftercare programs.

Although there has been an effort to treat the Axis I symptoms of substance abusers, patients with an Axis II dual diagnosis have not received the same specialized attention. Well-defined treatment approaches for these patients are limited, despite a richness of clinical knowledge in case reports and case histories. Psychiatry's historically most used treatment strategies (e.g., psychoanalysis) have little empirical support for their effectiveness in treating personality disorders. There is an extensive clinical literature on psychoanalytic and psychodynamic approaches, especially with borderline and narcissistic conditions. However, analytically oriented psychotherapy is generally regarded as being contraindicated for early-stage addiction treatment unless it is significantly modified to address substance abuse and acting-out behaviors. Among the more promising treatment approaches are cognitive or cognitive-behavioral therapy, and pharmacotherapy. These are discussed in more detail below.

Cognitive-Behavioral Therapy

Cognitive-behavioral therapy (CBT), in the form of relapse prevention (178) and coping skills therapy (179), has been evaluated in several well-controlled treatment outcome studies and has emerged as one of the most promising treatment approaches for substance abuse. As we have seen, the only documented integrated dual focus cognitive-behavioral treatment for the broad range of personality disorders is DFST. This treatment model is based on the idea that CBT for the two comorbid conditions shares several central intervention techniques, including self-monitoring, problem solving, assertiveness, managing thoughts and feelings, and assignment of homework. Schema-focused techniques include: 1) identifying, recording, hypothesistesting, coping with, and disputing maladaptive or dysfunctional thoughts, assumptions, and schemas; 2) imagery; 3) role play; 4) examining the therapeutic relationship; and 5) reliving and reattributing responsibility for past events. The relative balance of relapse prevention and schema-focused work would be based on the subject's abstinence from substances and readiness to change and work in a schema-focused model. During the earlier sessions, greater emphasis is placed on the establishment and maintenance of abstinence, but with a secondary focus on identification of and psychoeducation about maladaptive schemas. During later sessions, greater emphasis is placed on confronting and changing maladaptive schemas and creating alternative schemas. This treatment model assumes that a broad range of patients' difficulties (e.g., substance abuse, interpersonal dysfunction, depression, impulsivity) can be subsumed by a single or a few maladaptive schemas that organize these behaviors. As such, targeted change in a core schema can have a significant impact on a relatively broad range of behaviors. Preliminary outcome data indicate that DFST is a very promising outpatient treatment model (172) that is both feasible (i.e., relatively low-intensive and short-term) and "affordable" from a health insurance point of view.

Standard DBT, as compared to treatment-as-usual (TAU), has been shown to be effective in reducing severe borderline symptomatology in borderline patients without SUD (170,173). Standard DBT—although applicable to borderline patients with comorbid substance abuse problems—was not found to be more efficacious than TAU in reducing substance use problems (171). However, a modified version of DBT (i.e., DBT-S) has shown some promising results in a sample of borderline patients with SUD (169). In addition to DBT, which focuses on parasuicidal behavior, and DBT-S, which focuses on substance abuse, DBT has also been modified to focus on binge eating (198). The focus on one target behavior seems to be a common characteristic of the different DBT programs (174,199), each of which requires additional or separate clinical training. This approach might not be very useful for common clinical practice, which includes patients who suffer from multiple symptoms. Therefore, we agree with Bosch et al. (171) that it would be worthwhile to examine the possibility of an integrated, multi-targeted DBT program, rather than separate symptom-specific programs. This implies that therapists are trained to address a range of symptomatic manifestations of personality pathology in the impulse control spectrum, including suicidal and self-damaging behaviors, binge eating, and substance abuse.

Pharmacotherapy

Some evidence suggests that pharmacotherapy might be a helpful addition to psychotherapy in those individuals with personality disorders who are very symptomatic or exhibit behaviors that interfere with psychotherapy, such as suicidality or severe impulsivity (200–203). Little is known about which particular drug treatments are most helpful for which particular personality disorders, and no studies have focused on the treatment of comorbid substance use and personality disorders.

Low doses of antipsychotics have been reported to be associated with a range of beneficial effects in patients with borderline, schizotypal, or paranoid personality disorders as well as with a decrease in craving in cocaine-dependent patients (200,204–207). However, recent trials do not support the anti-craving or abstinence-promoting effect of neuroleptics (e.g., Ref. 208).

Furthermore, selective serotonin-reuptake inhibitors (SSRIs) have been shown to reduce aggression/impulsivity in borderline and antisocial patients and may have some positive effect on substance abuse in alcohol-and cocaine-dependent patients (200,209–211). However, a recent study showed that fluvoxamine, as compared to placebo, produced a robust and long-lasting reduction in rapid mood shifts in female borderline patients, but no effect on impulsivity or aggression (212). Interestingly, another study by the same authors strongly suggested that fluvoxamine treatment is effective only in female borderline patients with a history of sustained childhood abuse (213).

Lithium and other mood stabilizers (e.g., carbamazepine, divalproex sodium) have been reported to reduce aggressive and violent behaviors in antisocial prison inmates and to decrease "within-day mood fluctuations" in borderline patients (214–218). Early anecdotal reports and a small, double-blind, placebo-controlled study also suggested that lithium may be efficacious in the treatment of alcohol dependence. However, a large VA study showed no benefits of lithium over placebo for alcohol-dependent patients with or without depressive symptoms (219). Similar negative findings are now available for the treatment of cocaine dependence with mood stabilizers (220).

Benzodiazepines are generally contraindicated as an anxiolytic for alcohol- and drug-dependent patients with personality disorders, because of the risk of addiction and of paradoxical reactions involving disinhibition with an increase in behavioral dyscontrol (214). In contrast, the partial serotonin agonist buspirone seems to combine a lack of abuse potential with a positive effect on social phobia and avoidant personality disorder (221) and a delay in the return to heavy alcohol consumption in anxious alcohol-dependent patients (222). Various stimulants, including methylphenidate, pemoline, dexamphetamine, and levodopa, have been reported to reduce impulsivity in borderline and antisocial patients with a history of ADHD. It has been claimed that childhood hyperactivity and a history of drug abuse are predictors of a favorable response to both psychostimulants and monoamine oxidase inhibitors among personality-disordered patients (223). However, stimulants are known for their addictive and abuse potential, and restraint should be used in prescribing these drugs. Finally, it has been shown that the opioid antagonist naltrexone is effective in the treatment of alcohol and opiate dependence as well as in the prevention of self-mutilation in a borderline patient (224–

227).

Together, these examples indicate that pharmacotherapy may have an important role in the treatment of comorbid substance abuse and certain personality disorders. Medications may ameliorate some personality-disorder symptoms while simultaneously improving the outcome of SUD. It should be noted, however, that the co-occurrence of these disorders is also associated with high rates of noncompliance and an increased risk of lethal overdose, as well as the potential for dependence on the medication.

Treatment Matching Implications

It is highly unlikely that the same treatment approaches are suitable for all Axis II dual-diagnosis patients. Strong evidence suggests that the practice of matching specific patients to specific treatments will enhance treatment effectiveness (16). An empirically based understanding of the efficacy of psychotherapy for personality disorders with or without substance abuse is in its early stages. There is some evidence that structured coping-skills therapy works better than interactional therapy with antisocial substance abusers (167,168). Furthermore, Woody et al. (164) found that depressed antisocial opiate abusers in methadone maintenance responded better to CBT or supportive-expressive therapy than did nondepressed antisocial patients, although both did worse than patients without ASPD.

Furthermore, it can be hypothesized that an alcohol-dependent patient with a co-existing cluster C personality disorder needs a different interpersonal approach (e.g., directive, supporting) and a distinct pharmacological (e.g., buspirone) and psychotherapeutic treatment (e.g., individual social-skills training) than a cocaine-dependent patient with a cluster B disorder (e.g., SSRI together with individual or group CBT). Ultimately, the most suitable and effective treatment package for a particular dual-diagnosis patient can be derived using both general evidence from empirical studies and specific clinical knowledge regarding the unique etiology of the patient's psychopathology and environment.

Whether the assumed causal direction between personality disorder and substance use disorder should affect the treatment approach in these dual-diagnosis patients depends on both general treatment principles and individual patient characteristics. For example, even in cases in which substance abuse is primary, focusing only on the initiation and maintenance of abstinence is usually unsuccessful. The secondary personality problems often persist as major relapse vulnerabilities and need to be addressed for both how they impact on others and how they maintain and protect a substance-abusing lifestyle. Likewise, even when a personality disorder is primary, focusing on personality pathology before addressing the substance abuse problems is unlikely to succeed. Ongoing substance abuse is likely to reduce retention, motivation, and the cognitive-emotional stability needed to address long-standing personality problems. In general, we advocate a simultaneous focus on both the substance abuse and personality disorder symptomatology and their etiological and pathogenetic interrelatedness. This approach does not require an immediate effort to change long-standing dysfunctional personality problems. In most cases, treatment begins by trying to empathize and understand the normal and abnormal personality traits of the patient and by using supportive, limit-setting techniques to

contain or reduce acting-out and relapse risk. As Beck et al. (4) have suggested, attention to the patient's dysfunctional views of self and others increases trust and the therapeutic alliance, which facilitates treatment for the substance abuse problem. Once abstinence has been maintained for several months, personality problems that persist can be addressed more directly in ways that call on the increased capacity of the patient to tolerate and work for change.

Challenges to the Working Alliance

Many of the pathological traits of Axis II dual-diagnosis patients are in the interpersonal realm and cause significant distress to others, including therapists. Personality-disordered patients are likely to act out their chronic, maladaptive interpersonal patterns with particular intensity in the therapeutic relationship, and are more likely than other substance abuse patients to elicit negative feelings and reactions from the therapist. In our clinical experience with personality-disordered substance abusers, particularly borderline and antisocial patients, we have found that the following interpersonal patterns place significant burdens on the therapeutic relationship.

First, substance abusers with personality disorders are more likely to present at either extreme of the dependency-avoidance continuum or to move between these two extremes. Many behaviors during therapy may be efforts to maintain distance or regulate the intimacy of the therapeutic relationship.

Second, personality-disordered substance abusers are more prone to impulsive, volatile, self-damaging, attention-seeking, and manipulative acting-out. In a similar vein, the emotional lability and volatility of substance abusers is usually more exaggerated and problematic when there is a comorbid personality disorder. Intense anger, anxiety, and sadness may alternate with periods of grandiosity, confidence, and imperturbability. These split emotions may also be expressed in the form of splitting the therapist (overidealized and devalued) and a tendency to move rapidly from hopeful abstinence to hopeless relapse.

Finally, the antisocial traits of substance-abusing patients pose significant difficulties for developing a therapeutic alliance. Their tendency to treat others as objects to be won over or destroyed may be carried out with the therapist. Antisocial patients may present as unfeeling, insensitive, and indifferent to the rights and needs of others and lacking in empathy, remorse, or guilt for the harm, lying, or manipulations for which they have been responsible. They may view treatment providers as an extension of the legal system that is trying to oppress them, or as an agent of society's values, which they do not respect (228).

Unless the interpersonal styles of personality-disordered substance abusers are monitored, reality-tested, gently confronted, or interpreted in an ongoing way, they have the potential to reduce therapist efficacy and lead to poor treatment outcome. All treatment activities should be tailored to the specific interpersonal style of the personality-disordered patient, and the therapist should be constantly aware of specific forms of transference and countertransference.

According to the interpersonal theory of personality pathology, paranoid, narcissistic, and antisocial patients evoke hostile-dominant behaviors and reactions in the therapist,

which in turn will lead to continuing conflicts and a high probability of early dropout (229). Therefore, the self-importance of the narcissistic or antisocial patient should not be confronted directly; rather, the therapist is advised to cooperate with, or at least condone, the patient's need to be admired and regarded as a special case (230). In addition, it seems most effective not to prescribe any particular treatment to these individuals, but to let them make their own choice from a number of possible treatment alternatives proposed by the therapist (231).

Histrionic and borderline patients need reassurance and explicit validation of their current suffering (229). However, these implicit demands may lead to an overinvolvement of the therapist and to excessive feelings of responsibility for the patient's wellbeing. In order to establish an effective working alliance and to prevent early dropout, the therapist has to find a subtle balance between both emotional validation and the need for behavioral change and between personal commitment and professional distance (232). Interpersonal theory predicts that patients with avoidant or dependent personality disorders will evoke dominant and caring reactions in the therapist. To get the treatment started, the therapist may have to respond to this implicit invitation for action with clear proposals for limited behavioral changes and individual social-skills training activities in a supporting, nonconfrontive environment, a strategy consistent with the therapeutic principles of motivational interviewing (196). However, with both avoidant and dependent patients, the therapist should not push matters too hard or too fast, and group therapy should be avoided in the early phase of treatment because group sessions may evoke unnecessary feelings of embarrassment and anxiety, and ultimately noncompliance and dropout (231). Conversely, such active attitudes are generally counterproductive in the treatment of narcissistic, paranoid, or passive-aggressive patients.

Overall, initiating and maintaining complete abstinence is very difficult and usually not accomplished in a first treatment episode for personality-disordered substance abusers. With some persuasion, many patients will agree to work on their substance abuse, but eliciting their collaboration to work on personality problems is more difficult. As therapists, we are essentially asking them to examine and change who they have been for as long as they can remember. This is obviously very anxiety-provoking and elicits defensive maneuvers and produces an increased risk of relapse (228).

Appropriate Treatment Goals

There is consensus between psychoanalytical and cognitive-behavioral theories that the treatment of personality-disordered individuals can be a very long-term process. The added problems of limited treatment retention and compliance associated with substance abuse raises questions of what are appropriate treatment goals and who is most appropriate for treating a personality-disordered substance abuser. In most cases, the goal of psychotherapy for the personality-disordered substance abuser will not be to accomplish deep and permanent change in personality structure within a relatively short-term treatment. Rather, a more practical aim may be to improve substance abuse treatment outcome by explicitly addressing the personality functioning of patients. In addition, psychotherapy with personality-disordered substance abusers probably should

not be provided as a standalone treatment. Psychotherapy is likely to have greater success if it is provided in the context of a relatively long-term treatment program that provides sufficient structure and safety (e.g., a residential treatment or methadone maintenance program).

Substance abusers with severe personality disorders are commonly seen in treatment programs and consume a disproportionate amount of staff time. They tend to be admitted into treatment repeatedly and exhaust the resources of one counselor after the next. Although no studies have defined the optimal treatment of substance abusers with severe personality disorders, it may not be group counseling or psychoeducation by drug counselors with limited training and supervision. Therapists treating these dual disorders probably should be professional or highly skilled therapists with extensive education and training in psychotherapy, personality theory, psychopathology, and, specifically, personality disorders. Given the challenges of treating this population, all therapists should have some forum for supervision.

EPILOGUE

As has been stated before, one should also realize that comorbid substance abusers often meet criteria for more than one personality disorder. This finding applies to both substance-abusing populations (32) and psychiatric populations (233–235), and may be interpreted in different ways. First, specific combinations of personality disorders may have different treatment implications. For example, a substance abuser with BPD and dependent and/or avoidant personality disorder (i.e., strong affective lability and problems with trusting friends and partners; moderate impulsivity) may benefit more from cognitive therapy or CBT, whereas a substance abuser with BPD and ASPD and/or narcissistic personality disorder (i.e., strong impulsivity and aggressiveness; moderate affective lability and problems in relationships) may benefit more from a structured coping-skills therapy or reinforcement contingency-based approach. Second, the phenomenon of overlapping disorders—the absence of clear boundaries between personality disorders as defined by the leading classification systems—might be taken as an argument for replacing or supplementing the current categorical approach by a dimensional or hierarchical approach. Dimensional systems of classification are recognized as presenting more flexible, specific, and comprehensive information, while categorical systems tend to be procrustean, lose information, and result in many classificatory dilemmas when patients do not meet criteria for any category or meet criteria for two or more (mutually exclusive) categories (236,237).

However, even within a dimensional approach, it might be useful not to limit personality assessment to personality disorder diagnosis, but to expand the DSM classification of abnormal personality with additional measures of normal personality, such as the dimensional approach based on the five-factor model (238) or interpersonal models (239). The assessment of underlying normal personality dimensions may yield a fruitful, additional approach to treatment planning, including matching strategies. For example, a diagnosis of ASPD with a higher score on neuroticism may be a less stable diagnosis (or one more amenable to change) than a diagnosis of ASPD with higher scores

on impulsivity and aggression. Furthermore, Annis and Chan (240) found that intensive group therapy with a confrontational content tends to have a positive effect on substance-abusing offenders with a good self-image, but a clear negative effect on substance-abusing offenders with a poor self-image.

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10
Comorbidity of Eating Disorders and Substance-Related Disorders

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OVERVIEW

The relation between eating disorders and substance-related* disorders is somewhat unique in psychiatry in that a complete explication of the relation requires exploration of three distinct domains. First, an explication of the prevalence of substance-related disorders in women with eating disorders necessitates information gleaned from epidemiological and genetic epidemiological designs. The latter approach also gives insight into the etiological relation between these disorders. Although critical for understanding etiology, these data do not necessarily reflect the clinician's concerns regarding the frequency with which eating disorders and substance abuse

* Both the eating disorders and substance use disorders literature have been plagued by frequent changes in terminology and diagnostic labels for the disorders under focus. In this chapter we have used the DSM-IV (1) terms bulimia nervosa, anorexia nervosa, eating disorders, and substance-related disorders when speaking generally and attempted to utilize the terms and diagnostic labels used by the original authors when discussing specific studies.

co-occur in the clinic. The second domain therefore requires an exploration of the prevalence and pattern of comorbidity of eating disorders and substance-related disorders in clinical samples. The third domain is unique to eating disorders. This domain addresses the use and abuse of substances associated with purging (i.e., laxatives, diuretics, and emetics) or decreasing appetite (i.e., amphetamines and other "diet pills"). Although the abuse of these substances may be integral to the eating disorder, the pattern of self-administration is often phenomenologically similar to the use of more traditional substances of abuse.

This chapter focuses on these three domains as they pertain to bulimia nervosa, anorexia nervosa, eating disorder not otherwise specified, and related subthreshold forms of eating disorders.

THE GENETIC EPIDEMIOLOGY OF EATING DISORDERS AND SUBSTANCE-RELATED DISORDERS

In samples drawn from treatment settings, certain eating disorders often occur in combination with dependence on drugs or alcohol (reviewed later in this chapter). The purpose of this section is to consider and to review the mechanisms by which eating disorders and substance-related disorders might co-occur.

The notion that bulimia nervosa and substance-related disorders are causally related is commonly held. These two classes of disorders have been conceptualized as manifestations of an underlying "addictive" trait (reviewed by Wilson (2)). Indeed, certain treatment strategies (e.g., Overeaters Anonymous) conceptualize various forms of eating-related pathology as closely akin to substance abuse. These assumptions are based primarily on phenomenological similarities and are premature. The observed co-occurrence of eating and substance-related disorders could result from a number of other, non-causal processes.

Methodological and Theoretical Issues

First, a key weakness of the literature on this topic has been the general reliance on clinically referred samples of individuals with eating disorders. Clinical samples are not necessarily representative of all those afflicted with an eating disorder. In order to become part of a clinical sample, individuals must pass through a series of "referral filters" (3) that can substantially bias the composition of the resulting group. Indeed, individuals with two co-existing disorders may be much more likely to seek treatment. If individuals with both disorders are more likely to be referred for treatment, the two disorders will appear to be related in clinical samples when in fact they are not (4).

Two studies have addressed the issue of referral bias directly. Fairburn et al. (5) compared a clinical series and a community sample of women with bulimia nervosa (6). The two groups were substantially different in a number of respects, although the authors presented no data concerning the prevalence of psychoactive substance dependence. A more direct comparison was applied in New Zealand by Bushnell et al. (7) who compared a clinical series and a random community sample of women with bulimia (8). Women with bulimia from the clinic clearly had symptoms of alcohol use disorder of greater severity than women with bulimia from the community. In summary, the observed associations between eating disorders and substance-related disorders in clinical samples may in part be an artifact of the referral process.

Second, the existing studies are plagued by recurring methodological deficiencies that compromise interpretability. These deficiencies include: the use of unstructured or "semi-structured" diagnostic procedures of unknown reliability and validity; the lack of interviewer blinding; small sample sizes with limited statistical power to detect differences of meaningful size; and inappropriate comparison or control groups. For some family studies, there has been a general reliance on the proband's report of the psychiatric status of her relatives (9) (instead of more effortful personal interviews) despite the problematic nature of this method (10,11).

Third, several theoretical issues concerning the co-occurrence of eating disorders and substance-related disorders remain inadequately explored. An observed association between two disorders could result from numerous processes (12,13). It is critical to note that not all of these processes represent causal associations—for example, an observed association between two disorders might merely be due to chance or to biased sampling procedures. More interesting models are possible (13) and result from the interplay of one or more underlying liability dimensions. For example, an eating or a substance use disorder may be alternative forms originating from a common liability dimension. Alternatively, the existence of several liability dimensions can result in complex interrelations between two conditions. The details of these models are technical and beyond the scope of this chapter but are, in principle, amenable to formal hypothesis testing.

Epidemiological Studies

A key question is whether eating disorders and substance-related disorders co-occur at a rate greater than chance. The gender imbalance in eating disorders is perhaps more skewed than for any other major psychiatric syndrome, with women being afflicted 9–10 times more frequently than men (1). Therefore, the majority of studies that have explored the comorbid relation between eating disorders and substance use disorders have focused on females. Four large community-based studies have addressed this issue directly. Kendler et al. (14) studied an epidemiological sample of 2163 female twins with a structured diagnostic interview. Using modified DSM-III-R (6) criteria, they found that 5.7% met lifetime criteria for "broadly" defined bulimia. Of these women, 15.5% met lifetime criteria for "alcoholism" and there was a significant association between bulimia and alcoholism (odds ratio 3.23, 95% CI 1.55–6.73), indicating that the presence of one disorder was associated with an approximately threefold increase in the risk of the other. In a separate paper from the same sample, Walters and Kendler found no significant association between anorexia nervosa and "alcoholism" (15). Garfinkel et al. studied a large community sample in Ontario; 2.4% met lifetime criteria for a broad definition of bulimia nervosa (16). Of these women, 30.9% met lifetime criteria for alcohol dependence, considerably more than a comparison group of women without bulimia nervosa (5.0%). Dansky et al. (17) reported the prevalence of bulimia nervosa to be 2.4% in a large community sample of women (n=3031). The prevalence of alcohol dependence was significantly higher in women with bulimia than in women without bulimia nervosa (13.2% vs. 6%). Only when the presence of major depression and post-traumatic stress disorder were controlled was the prevalence of alcohol abuse higher in women with bulimia nervosa (than in women without bulimia nervosa or binge-eating disorder).

In a community ascertained study by Welch and Fairburn (18), rates of drug and alcohol use were compared across women with bulimia nervosa (n=102) and two control groups—one control group without any psychiatric disorders (n=204) and a second control group comprising individuals with other psychiatric disorders but not eating disorders (n=102). Individuals with bulimia nervosa were more likely to have had episodes of drinking eight or more units of alcohol per drinking episode than the psychiatric controls (but not the healthy controls). Also, a larger proportion of the bulimia

nervosa group reported a past history of high alcohol consumption than healthy but not psychiatric controls. Overall, individuals with bulimia nervosa were more likely to have used illicit drugs than either healthy or psychiatric controls.

The available epidemiological data are limited but suggest the presence of an association between bulimia nervosa and alcohol dependence. No such association was evident for anorexia nervosa. These correlational data cannot be used to infer a causal relationship between bulimia nervosa and alcohol dependence, as more sophisticated strategies are required.

Family Studies

The majority of family studies of bulimia nervosa have documented an increased lifetime prevalence of alcohol abuse and dependence in the relatives of women with bulimia (19–23), with few exceptions (24). However, these findings may not be relevant to the issue of the nature of the association between bulimia and alcohol use disorders because these findings could merely be due to the high prevalence of alcohol use disorders in clinical samples of women with bulimia and the familial transmissability of alcohol use disorders.

Family studies can, however, be used to evaluate the hypothesis of whether two co-occurring disorders result from a common transmissible familial factor (which can be genetic or environmental in origin). The logic runs as follows: if disorder X and disorder Y are co-existing but separate disorders, then disorder Y should be elevated in the relatives of probands with disorder X co-existing with disorder Y, but not in the relatives of probands with disorder X alone. Kaye and colleagues (25,26) have conducted a methodologically sound study of the comorbidity of bulimia nervosa and psychoactive substance use disorders. They found that the first-degree relatives of substance-dependent bulimic probands had significantly higher lifetime prevalence of alcohol or drug dependence (38%) than relatives of non-substance-dependent bulimic probands (10%) or relatives of community controls (18%). Their results provided no support for the hypothesis that these disorders result from a common transmissible familial factor. Similar results were reported in a smaller study by Bulik (27).

Schuckit et al. (28) employed the reverse design and reported the prevalence of eating disorders in relatives of alcohol-dependent male and female probands. The data did not reveal a significantly higher rate of eating disorders among the relatives of alcoholic probands than among the relatives of comparison probands. Although intriguing, given the low baserate of eating disorders in the population, it would be expected to be more difficult to detect eating disorders in family members of alcoholic probands than detecting alcohol-related disorders in the family members of probands with eating disorders. Moreover, an assessment of continuous measures of eating disorders-related pathology may be more revealing than an exclusive focus on diagnostic criteria.

Twin Studies

Twin studies represent a powerful method by which to delineate the genetic and environmental etiological relations between two disorders (29). We are aware of one twin study that has attempted to explain the causes of association between eating disorders and

alcohol use disorder. Kendler et al. (30) investigated the interplay of genetic and environmental causal factors simultaneously for six psychiatric disorders (including broadly defined bulimia and alcoholism) in a genetic epidemiological study of 2163 female twins. In this sample, the genetic or environmental risk factors for bulimia and alcoholism were quite distinct. Similar to the family studies, there was little evidence in support of a causal association between these disorders.

Are Eating and Substance-Related Disorders Causally Related?

In conclusion, the widely held notion that eating disorders and substance-related disorders are causally related has little empirical support. The observed comorbidity between bulimia and alcohol use disorders in clinical and epidemiological samples does not appear to represent a causal process. However, this notion has been incompletely evaluated. The existing studies have mostly looked at bulimia and alcohol use disorders and have not studied other eating disorders (i.e., anorexia nervosa and eating disorder NOS) or other psychoactive substances (e.g., cannabinoids, opioids, and nicotine). In addition, the focus of family and twin studies has been limited to transmissible familial factors and some causal associations could exist that do not involve these mechanisms.

PREVALENCE OF SUBSTANCE-RELATED DISORDERS IN CLINICAL SAMPLES OF WOMEN WITH EATING DISORDERS

Estimates of the prevalence of comorbid substance abuse and/or dependence in clinical samples of women with bulimia nervosa have varied widely. The prevalence of comorbid substance abuse or dependence ranges between 3% and 50%. In a review of 25 studies of the prevalence of alcohol abuse or dependence in women with bulimia nervosa in clinical samples, Holderness et al. (31) calculated a median prevalence of 22.9%. Parameters affecting the estimates range from the nature of the clinical service (inpatient vs. outpatient), the definition of and assessment procedures for both eating disorders and substance dependence, whether current or lifetime diagnoses are assessed, the distorting effects of any exclusion criteria for clinical trials, and the age of patients seen.

Table 1 presents studies that have examined the prevalence of substance abuse and/or dependence in women with eating disorders. Overall, the majority of studies have observed an elevated prevalence of substance-related disorders in clinical samples of women with bulimia nervosa. Most studies have observed comorbidity that exceeds that expected in the general population of women of similar age. Hudson et al. (32) found significantly

Table 1 Clinical Samples of Prevalence of Substance-Use Disorders in Women with Eating Disorders

	Diagnostic instruments	Prevalence of substance use disorders	Prevalence of other comorbid

Authors	Subjects				psychopathology
Mitchell et al., 1985 (97)	DSM-III	Eating-history questionnaire and interview	23.0% history of alcohol abuse		—
	275 bulimia		17.7% history of treatment for chemical dependence		
Hudson et al., 1987 (32)	DSM-III	Diagnostic Interview Schedule	Alcohol abuse/ dependence	Other abuse/ dependence	Affective disorders most frequent comorbid condition in bulimic women (70%)
	70 bulimia				
	29 major depression		B: 36%	36%	
	28 controls		D: 8%	21%	
			C: 11%	7%	
Bulik, 1987 (21)	DSM-III	Diagnostic Interview Schedule	Alcohol abuse	Alcohol dependence	Major depression most frequent comorbid condition: B (60%), C (8.9%)
	35 bulimia				
	35 controls		B: 48.6%	22.9%	
			C: 8.0%	0%	
Kassett et al., 1989 (23)	DSM-III-R	Research Diagnostic Criteria/Schedule for Affective Disorders and Schizophrenia	Substance abuse		58% of bulimic women and 0% of controls had a history of major affective disorder
	40 bulimia nervosa		BN: 55%		
	24 controls		C: 0%		
Leassle et al., 1989 (43)	DSM-III	Composite International Diagnostic Interview and Diagnostic Interview Schedule	Alcohol abuse/ dependence	Drug abuse/ dependence	Affective disorders (58%) and anxiety disorders (57%) more prevalent comorbid conditions
	21 anorexia nervosa—restricting		AN-R: 0%	4.8%	
	20 anorexia nervosa—bulimic		AN-B: 20%	0%	
			BN: 13%	21.7%	
	23 bulimia with history of anorexia		BN-hx-AN:	25.9%	
	27 bulimia		18.5%		

Authors	Subjects	Diagnostic instruments	Prevalence of substance use disorders	Prevalence of other comorbid psychopathology

Herzog et al., 1992 (33)	DSM-III-R 41 anorexia nervosa 98 bulimia nervosa 90 anorexia and bulimia	EAT—Schedule for Affective Disorders and Schizophrenia	Lifetime alcohol use disorders AN: 5% BN: 19% AB: 20%	Lifetime drug use disorders 7% 12% 17%	At least one affective disorder (63%) more frequently comorbid and at least one anxiety disorder (17%) equally comorbid
Braun et al., 1994 (34)	DSM-III-R 34 anorexia nervosa—restricting 22 anorexia and bulimia nervosa 31 bulimia nervosa 18 bulimia nervosa with history of anorexia	Structured Clinical Interview for DSM-III-R	Alcohol dependence AN-R: 5.9% AN-B: 27.3% BN: 41.9% BN-hx-AN: 27.8%	Alcohol/drug dependence 11.8% 36.7% 51.6% 38.9%	62.9% of entire sample had an affective disorder; 37% had substance or alcohol dependence; 37% had a lifetime anxiety disorder
Brewerton et al., 1995 (143)	DSM-III-R 59 bulimia nervosa	Structured Clinical Interview for DSM-III-R	Any substanceabuse disorder 20%		Any affective disorder (75%) and any anxiety disorders (36%) more frequently comorbid
Bulik et al., 1997 (53)	DSM-III-R 114 bulimia nervosa	Structured Clinical Interview for DSM-III-R	Lifetime alcohol dependence 47%		Any affective disorders (75%) and any anxiety disorder (64%) more frequently comorbid

greater prevalence of alcohol abuse in DSM-III bulimic (36%) than depressed (8%) patients; however, few other studies have compared directly the frequency with which

substance use disorders co-occur with bulimia relative to the frequency of their co-occurrence with other major psychiatric conditions. Thus it remains to be determined whether the prevalence of substance-related disorders in women with bulimia is specific to the disorder or part of a general pattern of elevated comorbidity in treatment-seeking samples with other psychiatric disorders.

The consistently observed co-occurrence of substance-related disorders in women with bulimia nervosa warrants routine screening for their presence in situations in which women with bulimia nervosa are assessed. The screening would ideally address both current and lifetime presence of alcohol and other drug use disorders as well as an in-depth understanding of the behavioral relation between the eating disorder and substance use.

Substance-related disorders appear to be much less frequent in women with the restricting subtype of anorexia nervosa than in other subtypes of eating disorders (33,34). The distinction between current anorexia nervosa with or without current bulimic symptomatology has been codified in the DSM-IV (1) into "restricting" and "binge-eating/purging" types. Stern et al. (35) examined lifetime prevalence of substance use disorders in 34 women with anorexia (Feighner criteria) and 34 controls. They found a prevalence of 15% in women with anorexia and 3% in controls, which was not significantly different. With one exception, substance use disorders were confined to women with the bulimic subtype of anorexia. Across studies, the prevalence of substance-related disorders in women with anorexia with bulimic features appears to be comparable to or to exceed those of women with normal weight bulimia nervosa (33,34,36–39).

In a comprehensive study of 229 outpatients with DSM-III-R eating disorders using structured diagnostic methodology, Herzog et al. (33) compared comorbidity in 41 women with anorexia nervosa, 98 women with bulimia nervosa, and 90 women with anorexia and bulimia nervosa. Examining the prevalence of *current* substance use disorders (including alcohol and other drugs), 0% of women with anorexia, 5% of women with bulimia nervosa, and 8% of women with both anorexia nervosa and bulimia nervosa met diagnostic criteria. For *lifetime* alcohol use disorders, 5% of women with anorexia nervosa, 19% of women with bulimia nervosa, and 20% of women with both anorexia nervosa and bulimia nervosa met diagnostic criteria (p=0.07). Lifetime prevalence of any substance use disorder varied similarly: 12% for women with anorexia, 31% for women with bulimia, and 37% for those with both anorexia and bulimia (p=0.07).

In a 10-year prospective longitudinal study of 95 consecutive admissions for the inpatient treatment of anorexia nervosa, Strober et al. (40) found that women with anorexia nervosa who reported binge-eating at admission were 5.8 times more likely to develop later substance use disorders than women without binge-eating.

Bulik et al. (39) examined prevalence of alcohol and drug use in 42 women with DSM-III bulimia (including those with and without concurrent anorexia nervosa) and 27 women with the restricting subtype of anorexia nervosa (i.e., no binge-eating). Significantly more bulimic women than anorexic women reported the regular use of alcohol, the consumption of larger quantities of alcohol, and more severe consequences from drinking (i.e., blackouts).

Wiederman and Pryor (41) reported the prevalence of substance use in 134 patients

who met DSM-III-R criteria for anorexia and 320 individuals who met DSM-III-R criteria for bulimia nervosa. The respondents indicated how frequently they had used alcohol, amphetamines, barbiturates, hallucinogens, marijuana, tranquilizers, cocaine, and cigarettes. The prevalence of use for all eight substances was significantly higher in individuals with bulimia nervosa than in individuals with anorexia nervosa.

A Swedish study by Clinton and Glant (42) assessed alcohol and drug abuse in 86 cases of DSM-III-R eating disorders. Sixty-five percent of women had bulimia nervosa, 20% atypical eating disorders, 9% restricting anorexia nervosa (including individuals who vomited as a form of purging), and 6% both anorexia and bulimia nervosa. "Overdrinking" (defined as more than two bottles of wine per week or the equivalent) was found in 12.5% of restricting anorectics, 22.2% of women with bulimia, 23.5% of those with atypical eating disorders, and 60% of women with both anorexia and bulimia.

In summarizing the data regarding the prevalence of substance-related disorders in clinical samples of women with eating disorders, several issues must be considered. First, although the prevalence of comorbid substance-related disorders is high, they are not the most frequently diagnosed comorbid conditions. Most studies have reported more frequent lifetime comorbid affective disorders and some have reported the co-occurrence of anxiety disorders to be more common as well (see Table 1). Thus, comorbidity of a range of disorders, not just substance-related disorders, would ideally be considered in the optimal treatment of women with eating disorders.

In addition, with some exceptions (e.g., Refs. 34,43), the majority of studies have been cross-sectional, determining the eating disorder diagnosis based on current clinical presentation. This approach is conceptually problematic as the boundary between anorexia and bulimia nervosa is often fluid. Although a percentage of women with the restricting subtype of anorexia never binge or purge, between 37 and 48% of clinical samples of women with anorexia nervosa display features of bulimia nervosa at some point during their illness (44–48). To date, we are unable to predict accurately which women are likely to recover, maintain a chronic course of restricting anorexia, or develop bulimia nervosa. Thus, when examining the prevalence of substance-related disorders in women with eating disorders, one must be mindful that the clinical features on which groups are defined are protean and that a cross-sectional examination of the same sample at a later date may yield quite different groupings and thus different estimates of the prevalence of comorbidity.

Eating Disorders and Substance-Related Disorders in Adolescents

The majority of studies of comorbidity of eating disorders and substance abuse and dependence have been on adults. Only recently, has research emerged exploring the relation between eating disorders and substance use in adolescents—which is a critical developmental period for the emergence of both eating and substance-related problems. Ross and Ivis (49) studied a student population in Ontario (1068 female and 934 male students) aged 10 to 20 years. In this study, the symptom of binge-eating was significantly related to substance use in the past year in both males and females. Individuals who reported both binge-eating and compensatory behaviors had the highest reported use of cannabis and other drugs (excluding alcohol and tobacco). This study

identified groups based on the presence of binge-eating and compensatory behaviors and did not utilize full diagnostic criteria.

A study by Stice et al. (50), which explored the relation between early menarche and several psychiatric disorders in a sample of 496 adolescent girls (ages 11–15) from public and private middle schools in a large metro politan area of the United States, also provided prevalence estimates of comorbidity of substance use in adolescents with eating disorders. A total of 4.64% (37 individuals) of this sample met broad diagnostic criteria for an eating disorder. Of these 37 girls, 14 (37.8%) also met broad diagnostic criteria for a substance use disorder, suggesting elevated rates of comorbidity in individuals with an eating disorder.

Wiederman and Pryor (51) studied 117 adolescent girls (12–17 years) who met diagnostic criteria for anorexia nervosa (n=59) or bulimia nervosa (n=58). Similar to the adult studies, girls with bulimia nervosa had higher rates of substance use than girls with anorexia nervosa. This pattern held for the use of alcohol (29.3% vs. 1.7%), amphetamine (12.1% vs. 0), barbiturates (6.9% vs. 0), hallucinogens (8.6% vs. 0), marijuana (31.0% vs. 8.5%), tranquilizers (3.4% vs. 0), cocaine (8.6% vs. 0), and cigarettes (29.3% vs. 13.6%).

Although only a few small studies have been reported, it appears that the associations observed between eating disorders in adolescents parallel those observed in adults; namely, higher rates of use and abuse in girls with disordered eating in comparison with controls, and higher rates in girls with bulimia nervosa or bulimic symptoms than in those with anorexia nervosa.

HOW WOMEN WITH BULIMIA WITH AND WITHOUT SUBSTANCE-RELATED DISORDERS DIFFER

Given the frequent co-occurrence of bulimia nervosa and substance-related disorders, how do bulimic women with and without comorbid substance abuse differ?

Chronology of Eating Disorders and Substance-Related Disorders

Studies of women with bulimia nervosa with comorbid alcohol use disorders have often used retrospective interviews to determine the chronology of onset of the disorders. Specker et al. (cited in Ref. 52) reported that two-thirds of 70 women with this comorbid pattern reported the onset of their eating disorder to predate the onset of their substance use problems.

We examined lifetime prevalence of alcohol dependence in 114 women with DSM-III-R bulimia nervosa presenting for an outpatient clinical trial of cognitive-behavioral therapy (53). Forty-seven percent of women had met criteria for alcohol dependence at some point in their lives. Examining those with the comorbid pattern, alcohol dependence began before bulimia nervosa in 28%, at approximately the same age in 38%, and later in 34%.

No consistent pattern has emerged with reference to the chronology of onset. Future studies should address how differences in the first disorder affect clinical course and outcome.

Clinical Features of Bulimia Nervosa

Several investigations have found no differences in the core clinical features of bulimia nervosa (i.e., frequency of binging and purging) in women with or without comorbid alcohol dependence (53–55).

Hatsukami et al. (56) compared clinical characteristics of women with DSM-III bulimia only, bulimia plus affective disorder, and bulimia with substance abuse. Individuals with both affective and substance use disorders were excluded from the investigation. Bulimic women with comorbid substance abuse showed greater use of diuretics, greater disruption in financial and work areas, more stealing, more suicide attempts, and had more inpatient treatment.

Dansky et al. (17) studied the comorbidity of bulimia nervosa and alcohol use in a national household probability sample of 3006 women. They found that women with bulimia and alcohol abuse were more likely to report a history of vomiting and laxative abuse than women with bulimia without alcohol abuse.

Although there were no differences in frequency of binging and purging, we also found that women with bulimia nervosa and lifetime comorbid alcohol dependence reported greater laxative use and greater food restriction than bulimic women with no alcohol dependence (53). There were no observed differences in body mass index, depression, global functioning, and no differences on any scale of the Eating Disorders Inventory (57), with the exception of impulse regulation, which was higher in women with comorbid alcohol dependence. Women with bulimia nervosa and substance dependence also had higher novelty seeking and lower cooperativeness on the Temperament and Character Inventory (58), elevated scores on all subscales of the Baratt Impulsivity Scale (59), and utilized more immature defenses on the Defense Style Questionnaire (60). Overall, women with bulimia nervosa and alcohol dependence exhibited a pattern of greater impulsiveness across a broad array of response domains.

These findings dovetail with a series of studies conducted by Lacey et al. (61,62) focusing on a subgroup of bulimic women who exhibit “multi-impulsive bulimia,” defined as a combination of bulimia plus other impulsive behaviors such as excessive alcohol use, regular street drug use, stealing, overdosing, self-harm, and sexual promiscuity. Approximately 40% of bulimic women seen in their clinics displayed alcohol or drug abuse, stealing, overdosing, or self-harm (61). Fifteen of the 112 patients displayed a pattern that included five of the targeted impulsive behaviors. Although alcohol abuse is not a necessary component of “multi-impulsive bulimia,” they consider this subgroup of bulimic women to be particularly problematic in terms of prognosis and frequency of parasuicide.

Fichter et al. (63) examined clinical characteristics and prognosis in 32 women who met DSM-IV criteria for bulimia nervosa (purging type) and who presented with three or more impulsive symptoms. Consistent with other research, the core symptoms of bulimia nervosa did not differ between those with and without an impulsive behavioral pattern. By the end of treatment, however, the “multi-impulsive bulimics” were more anxious, depressed, and demoralized, showed greater anger and hostility, had higher rates of borderline personality disorder, obsessive-compulsive disorder, alcohol abuse and dependence, more inpatient treatment, and greater psychoticism and paranoid ideation.

In a study in Japan, Suzuki et al. (64) compared 22 DSM-III-R bulimic women with alcoholism to 22 bulimic women without alcoholism. There were no differences between groups on prevalence of other Axis I diagnoses. Individuals with bulimia nervosa and alcoholism more often had borderline personality disorder, somatic disorders, stealing, suicide attempts, and heavier body weights.

Lilenfeld et al. (65) compared 20 women meeting criteria for DSM-III-R bulimia nervosa with a lifetime history of alcohol and/or drug dependence to 27 bulimic women without a history of alcohol and/or drug dependence and to 44 healthy control subjects. The women with bulimia with a lifetime history of alcohol and/or drug dependence had significantly higher rates of social phobia, conduct disorder, cluster B, and cluster C personality disorders than both the bulimic women without substance dependence and the controls. In addition, substance use disorders, social phobia, panic disorder, and cluster B personality disorders were significantly more prevalent in relatives of bulimic probands with substance dependence than in relatives of bulimic women without substance dependence or relatives of controls.

Wiseman et al. (66) compared comorbidity patterns in 218 female patients (109 with an eating disorder and substance dependence and 109 with an eating disorder without substance dependence). Of those with substance dependence, 34.8% reported that the onset of the substance dependence preceded the onset of their eating disorder and the remainder reported that their eating disorder preceded the onset of their substance abuse. Individuals in the group who developed substance dependence first were likely to be dependent on a significantly greater number of substances, and were also more likely to have cluster B personality disorders than those who reported the onset of their eating disorder to be first and those with no comorbid substance use disorders. Individuals in the group who reported onset of eating disorders first reported the greatest number of comorbid diagnoses and were significantly more likely to have panic disorder and social phobia than the other two groups.

In summary, the core clinical features of the eating disorder (i.e., frequency of binging and purging) do not appear to differ significantly whether substance abuse or dependence is present. Individuals with the comorbid pattern do appear to display more frequent impulsive behaviors, use of other drugs, laxative abuse, and possibly more Axis II pathology. These data suggest that impulsivity may underlie the development of both eating disorders and substance abuse in this group of women.

Strober et al. (40) have posited an alternative but compatible explanation for the development of binge-eating and substance use disorders in some women with anorexia nervosa. Severe dieting and weight loss associated with the onset of anorexia nervosa may precipitate appetitive phenomena in individuals at greater risk for substance use disorders (i.e., those with a positive family history). Stated differently, individuals who develop the restrictive eating pattern associated with anorexia nervosa who have a positive family history of substance abuse may be more likely to develop both binge-eating and later substance-related disorders as rebound appetitive phenomena secondary to food deprivation and weight loss.

Indeed, this interpretation is in line with extensive animal data documenting increased self-administration of psychoactive substances under conditions of food deprivation and weight loss (67). Although this is a near-universal phenomenon in animals, its expression

in humans has been less consistently observed and the behavior may be moderated by temperament and cognitions (68–73). Integrating these two hypotheses, it is clear that dieting is often the behavioral precursor to the development of eating disorders (74) and that many women with bulimia nervosa pass through a phase of anorexia nervosa or subthreshold anorexia before developing bulimia. According to these theories, those individuals who enter a phase of restrictive dieting associated with threshold or subthreshold anorexia nervosa who also have a positive family history for substance abuse may be genetically at greater risk for the activation of appetitive phenomena (i.e., binge-eating and substance abuse), either directly or via a temperamental predisposition such as high novelty seeking or impulsivity.

Effect of Comorbidity on Treatment Outcome

Several studies have suggested that the presence of comorbid substance-related disorders does not adversely affect treatment outcome for bulimia nervosa. Mitchell et al. (54) examined 91 female outpatients with DSM-III bulimia who presented for a cognitive-behavioral psychotherapy trial. The outcome of treatment was similar between those with or without a history of substance abuse. Likewise, the use of alcohol or other drugs did not escalate after treatment for bulimia nervosa, although 34% of those with bulimia and substance abuse increased their caffeine consumption after bulimia treatment.

Strasser et al. (55) examined the effect of prior substance abuse on outcome of a six-week desipramine trial for DSM-III-R bulimia nervosa. Nineteen subjects reported past substance abuse, although those individuals with evidence of substance abuse in the prior year were excluded from the trial. Following treatment, the substance abuse group had significantly lower scores on self-reports of eating symptomatology, were more responsive to treatment, and displayed a better response to desipramine. There were no post-treatment differences between groups in actual binge and purge frequencies. Thus, in some respects, those with a history of substance abuse responded better to treatment.

Collings and King (75) performed a 10-year follow-up of participants in a clinical trial of mianserin for bulimia nervosa. Comorbidity at presentation did not adversely affect outcome at follow-up. It is important to note that individuals with current alcohol abuse had been excluded at entry to the trial.

Although further studies are required to examine the effect of *current* alcohol use disorders on treatment outcome for bulimia nervosa, the studies performed to date suggest that *past* substance-related disorders do not adversely affect treatment for bulimia. It is possible that some of the components of treatment, either psychological or pharmacological, generalize beyond the treatment of eating disorders and have beneficial effects on substance use problems as well.

PREVALENCE OF EATING DISORDERS IN SUBSTANCE-RELATED DISORDER TREATMENT SAMPLES

The flurry of research documenting the high prevalence of substance-related disorders in eating disorder samples has been mirrored by a parallel body of research examining the

prevalence of eating disorders in women with a primary diagnosis of substance dependence. Studies examining prevalence of eating disorders in substance dependence treatment samples have used both questionnaire and interview designs. With some exceptions (76), the prevalence of bulimia nervosa is elevated in women presenting for treatment of substance dependence (28,77–84).

Lacey and Moureli (77) determined that 40% of 27 women with alcoholism exhibited a past or present history of binge-eating. For the majority, binge-eating began before problem drinking. The characteristics of the bulimic alcoholics included younger age at presentation, onset of problem drinking at an earlier age, higher self-report scores on eating pathology, and heavier weight.

Jonas et al. (85) surveyed 259 callers to a National Cocaine Hotline (122 men and 137 women) via structured telephone interview and found that 20% of callers met DSM-III criteria for bulimia, 7% for anorexia and bulimia, 2% for anorexia nervosa, and 9% met criteria for bulimia plus vomiting. Among female callers, 23% met criteria for bulimia and 13% met criteria for bulimia with purging.

Hudson et al. (84) examined 243 male and 143 female inpatients in an alcohol and drug abuse treatment center. Fifteen percent of women and 1 % of men had a lifetime DSM-III-R eating disorder (primarily bulimia nervosa) as assessed via questionnaire. The eating disorder occurred before the substance abuse in 50%, in the same year in 14%, and greater than one year after in 36% of participants. It was notable that individuals with eating disorders were significantly more likely to use stimulants and significantly less likely to use opioids.

Grilo et al. (86) addressed the question of whether eating disorders were more prevalent in psychiatric inpatients with or without substance dependence. They compared the prevalence of eating disorders in 67 female psychiatric inpatients with substance use disorders and 69 patients with no substance use disorders. DSM-III-R eating disorders were significantly more prevalent in the psychiatric inpatients with substance abuse (31.3% vs. 14.5%). There was no difference in the distribution of bulimia and anorexia across groups; however, inpatients with substance abuse were significantly more likely to receive a diagnosis of eating disorder not otherwise specified.

The presence of disordered eating behavior in treatment-seeking alcoholic samples is not limited to Western countries. Higuchi et al. (87) studied 3592 patients in the National Institute on Alcoholism in Japan. Eleven percent of female patients were identified as suffering from DSM-III-R eating disorders. Eating disorders were particularly prevalent in younger women, as over 70% of female patients under 30 had eating disorders. In almost all cases, the eating disorder occurred first, followed by alcoholism on average 4.5 years later.

In summary, eating disorders and disordered eating appear to be overrepresented in clinical samples of women presenting for treatment of substance-related disorders. Further studies are required to assess how the presence of an eating disorder affects treatment for substance dependence and how best to integrate treatment for those suffering from both conditions.

USE AND ABUSE OF SUBSTANCES ASSOCIATED WITH DIETING AND PURGING

The third aspect of substance use, essential to understanding women with eating disorders, is that of pharmacological agents ingested for the purpose of weight loss, appetite suppression, and purging. Among these drugs are prescription and over-the-counter diet pills, laxatives, diuretics, and emetics. Nicotine and caffeine (21,88–91) must also be considered when assessing substance abuse in women with eating disorders. Comprehensive reviews of the types of agents abused, and their toxicity and detection, tolerance and withdrawal, and effects on appetite and weight can be found in Bulik (92) and Mitchell et al. (93).

Laxatives

Between 38% and 75% of women with bulimia nervosa use laxatives as a method of purging (19,39,94–98). Laxative use can exist as the sole method of purging, or as an auxiliary method to vomiting. Bulimic women who abuse laxatives often believe that they lose a significant amount of calories via this method of purging. Bo-Linn et al. (99) found that high doses of a stimulant laxative decreased caloric absorption by only 12%. Although laxatives lead to the loss of water and electrolytes, they do not substantially affect caloric absorption and hence are ineffective weight loss agents.

Mitchell et al. (100) suggested that women with bulimia who abused laxatives may be more severely psychiatrically disturbed than those who do not. Women who abuse laxatives were also found to use more pharmacological agents such as diuretics, emetics, and diet pills, as well as using saunas and enemas, and to engage in self-injurious behavior and suicide attempts. In a clinical sample of 76 women with bulimia nervosa (101), laxative abuse was observed almost exclusively in patients with comorbid personality disorders.

Several different types of over-the-counter laxatives exist, which vary greatly in their mechanisms of action, side effects, and potential to cause medical complications. Perhaps most concerning is the use of stimulant laxatives containing phenolphthalein, which acts directly on intestinal smooth muscle to increase peristaltic activity (102,103). The most common side effects of stimulant laxatives are diarrhea, weakness, abdominal cramping, nausea, vomiting, dehydration, and hypokalemia. More severe complications can occur and occasionally lead to “cathartic colon” and loss of normal bowel function. Individuals who abuse laxatives may start with the recommended dose, then escalate this dose rapidly as they develop tolerance to the cathartic effect. Ingestion of as many as 50 to 100 stimulant laxatives per day has been observed. The pattern of laxative abuse is either doses after meals or binges, or large doses at the end of the day. Individuals with eating disorders also experience laxative withdrawal, such as severe constipation, rebound edema, and “craving” for the drugs.

Studies have not been performed to determine the optimal treatment for laxative abuse. Although consensus exists that laxatives should be discontinued and if necessary replaced with a high fiber diet and possibly bulk forming agents, the optimal way to achieve that

goal is unknown. Rapid discontinuation of laxatives ("cold turkey") can cause severe discomfort, rebound edema, bloating, and strong urges to ingest more laxatives. A more gradual discontinuation regimen, coupled with an increase in dietary fiber and fluid consumption, is generally more acceptable to patients.

Diuretics

Diuretic use has been reported in between 1 and 33% of women with eating disorders. It appears to be more common in bulimic than anorexic women (39). Many more women experiment with diuretics than use them on a regular basis. Individuals with eating disorders may request diuretics from their general practitioners or gynecologists for the management of premenstrual water retention and then use the prescription medication for purposes of purging. Alternatively, over-the-counter diuretics containing combinations of pamabron, caffeine, and ammonium chloride are available. The toxic profile from diuretics varies according to the type and mechanism of action. Tolerance does develop to prescription diuretics (104–106). Ongoing use can lead to a vicious cycle of diuresis and reflex water retention. Mitchell et al. (93) suggest tapering diuretics in conjunction with a sodium-restricted diet to limit water retention. Depending on the type of diuretic used and the side effect profile, potassium replacement may also be required.

Emetics

Although most bulimic women self-induce vomiting, some will self-administer syrup of ipecac. Pope et al. (107) found that 28% of bulimic women reported using ipecac at least once. Bulik et al. (39) found similar numbers, with 26% of bulimic women and 4% of anorexic women experimenting at least once. In an extensive study of 851 consecutive outpatients presenting to an eating disorders clinic, Greenfeld et al. (108) found that 7.6% of all patients reported some use or experimentation with ipecac and that 8.8% of those presenting with a diagnosis of bulimia reported chronic ipecac use.

Ipecac (emetine, cephaline, and psychotrine) produces emesis peripherally through its action on the gut, as well as centrally. Emetine is cleared from the body very slowly. Repeated self-administration of the drug increases potential toxic reactions. Toxicity from cumulative small doses and single large doses are comparable. Gastrointestinal, neuromuscular, and cardiac complications are common and the presenting complaints of individuals who use ipecac are often nausea, vomiting, and muscle weakness.

Ipecac is an extremely dangerous method of weight control. Screening for its use is important although it runs the risk of introducing it as an alternative method of purging. Although we do not advocate asking younger patients specifically about their use of ipecac, we do routinely inquire whether they have ever used any chemicals to help themselves vomit or lose weight.

Other Agents and Medication Manipulation

In addition to laxatives, diuretics, and emetics, women with eating disorders also use diet pills (often containing ephedrine, caffeine, or phenylpropanolamine) or become

dependent on amphetamines for the combined effect of increasing energy and decreasing appetite and weight. Reports have also cited use of thyroid hormone (39,109–111), fluoxetine (112), paracetamol (113), potassium (114), licorice (115), tobacco (116), sorbitol (117), enemas (118), bran (119), orlistat (120), dextromethorphan (121), topiramate (122), and heroin (123) either for their weight loss effects or ability to induce emesis. Similarly, "insulin purging" or the manipulation of insulin to achieve weight loss in diabetic patients has been noted in both insulindependent (124–128) and non insulin-dependent samples (129).

In summary, drugs related to purging, such as diuretics, laxatives, and emetics, have been shown to be ineffective and even dangerous methods of accomplishing weight loss or maintenance. The literature suggests that, like more common drugs of abuse, tolerance and withdrawal occur with laxatives, diuretics, and possibly diet pills and emetics (92).

Although the development of this sort of drug use in women with eating disorders may begin with experimentation, with the intent of relieving perceived constipation or bloating, the ability of these substances to create a "sense" of weight loss increases the likelihood of further use. With laxatives, over time, their use may become less associated with the postbinge state and may develop into a dependency that is self-perpetuating. It has been noted that not only can individuals become dependent on laxatives for normal bowel function, but they can also begin to "crave" the specific effects and sensations associated with laxative self-administration (130). In such instances, as with more common drugs of abuse, the positively reinforcing aspects of these drugs may serve to maintain their use.

A critical message for clinicians is that women with eating disorders will often go to quite dangerous extremes to lose weight and a comprehensive assessment must document the individual's full repertoire of weight loss behaviors. Clinicians must also be mindful of excessive consumption of sugar substitutes (e.g. Nutrasweet, saccharin) and fat substitutes (e.g. Olestra), as the long-term effect of consumption of large quantities of these substances in humans has yet to be determined.

TREATMENT OF COMORBID EATING DISORDERS AND SUBSTANCE-RELATED DISORDERS

No controlled trials have yet been conducted to determine the optimal intervention strategy for women with comorbid eating disorders and substance-related disorders. Few specialist services exist that are designed to treat eating disorders and substance abuse concurrently. Although intuitively appealing, it remains to be determined whether concurrent treatment is indeed preferred. In the absence of such services, staff on specialty services for substance use or eating disorders should have specific training in dealing with individuals with this particular pattern of comorbidity.

Assessment

Prior to engaging in any intervention, a thorough clinical assessment is required. This includes a full diagnostic interview, focusing on both current and lifetime diagnoses.

Even though a patient may not be suffering from an eating disorder currently, a history of bulimia or anorexia could become a factor in the successful treatment of her substance-related disorder or vice versa. Clinical interviews can also be supplemented with structured eating disorders interviews such as the Diagnostic Schedule for Eating Disorders—Revised (131) or the Eating Disorders Examination (132). A number of medical investigations might be warranted, depending on the findings on physical examination and based on the nature and severity of the substance-related disorder.

Once the co-occurrence of an eating and substance-related disorder has been established, then a complete behavioral analysis can be informative if consistent with the philosophy and approach of the treatment service. The critical questions to be addressed in this portion of the assessment include foods and substances of choice, high risk times and situations for engaging in disordered eating and substance abuse behaviors, and the nature, pattern, and interrelationship of disordered eating and substance use. Examples of appropriate areas of inquiry are: what sorts of situations could prompt the patient to diet/binge/drink? What times of the day are high risk times for each behavior? What are the cues that prompt disordered eating behavior or substance use? In addition, one must address how dieting and binging are related to substance abuse. For example, does she drink or use drugs in order to curb appetite when dieting? What is the effect of drinking on eating behavior? Does alcohol disinhibit eating? From the patient's perspective, do binging and drinking serve similar or different "functions" for her?

Intervention

Once diagnosis has been established and the behavioral parameters identified, Marcus and Katz (133) outline three potential approaches to the treatment of the individual with eating disorders and substance-related disorders. First, both disorders can be treated concomitantly on a unit specializing in this particular pattern of dual diagnosis. Second, detoxification and treatment for substance-related disorders can be completed first, followed by specialized treatment for the eating disorder. Third, specialized treatment for the eating disorder can be followed by specialized treatment for the substance-related disorder.

There are several factors that can dictate which of these approaches is followed; however, no empirical data exist to inform the decision. Specialty services for dual-diagnosis patients are scarce and hence the opportunity for concurrent treatment is limited. In the absence of such a service, one must attempt to address the question as to which disorder is currently primary and requires the most immediate attention. Although, for some individuals, detoxification is an essential first step, perhaps the most important treatment goal is for the patient to be encouraged to *complete* treatment for both disorders and that this be emphasized throughout the treatment process. In addition, whichever treatment approach is chosen, the other disorder cannot be compartmentalized and ignored. It is critical to address the presence of the eating problem, for example, even if the substance-related problem is the initial target of treatment. Failure to integrate treatment leads to the "ping pong" phenomenon where patients bounce back and forth between eating and substance-related disorder treatment services, never addressing the relation between the two disorders. Katzman et al. (134) have documented the re-

emergence of binge-eating following detoxification from opiates. We have observed similar behavior following detoxification from alcohol. We have also noted clinically that the frequent behavioral pairing between disordered eating behaviors and substance abuse can lead to a situation in which relapse in one domain fuels relapse in the other. Thus an integrated relapse prevention plan which acknowledges the similarities and differences in relapse risk for each behavior is essential.

Katz (135) has highlighted that individuals with eating disorders who are being treated in substance abuse units be expected to participate fully in the substance abuse program but that their treatment be augmented with nutritional consultation, the setting of a goal weight range, and observations at and between meal times for disordered eating behaviors. If sufficient numbers of women are available on a substance abuse service who present with eating disorders or disordered eating behavior, special eating disorders psychoeducation or basic cognitive-behavioral strategy groups can be used to augment the substance abuse treatment plan.

The available literature supports the inclusion of women with past or current mild or moderate substance-related disorders in eating disorders treatment programs. In our randomized clinical trial of cognitive-behavioral therapy for bulimia nervosa, we have observed that successful treatment of bulimic symptoms with core cognitive techniques such as psychoeducation, identification of automatic thoughts, thought restructuring, chaining, and relapse prevention often generalizes, insofar as patients are able to apply the techniques to their alcohol and drug use as well as to their binging and purging (136).

Treatment of individuals with severe substance-related disorders and eating disorders poses a more significant clinical challenge. Although empirical data are lacking, individuals who fail to benefit from traditional cognitive behavioral approaches and who find 12-step approaches beneficial in controlling their drinking or drug use may respond to 12-step programs that focus both on eating and substance use. Traditionally, the 12-step approach of Overeaters Anonymous (OA) focuses on abstinence from high risk foods (i.e., sugar, wheat) which are believed to have the ability to trigger a binge. In direct contrast, the cognitive-behavioral approach emphasizes empowerment over food and minimizes avoidance, often incorporating exposure techniques to precisely those foods from which OA would encourage abstinence. An ongoing concern is that although alcohol and drugs can be abstained from, it is virtually impossible to abstain from certain foods, given the frequency with which high-risk foods are encountered in daily life. An integrated 12-step-CBT model could encourage patients to abstain from high-risk behaviors (i.e., dieting or binging) rather than high-risk foods. Empirical data are required to substantiate the efficacy of this approach; however, for those individuals who find a 12-step approach beneficial and who see similarities between their disordered eating and substance-related problems, it holds intuitive appeal.

Pharmacological approaches to treatment may also be considered. The selective serotonin-reuptake inhibitor fluoxetine has been shown to be of some efficacy in the treatment of bulimia nervosa (137), although its specific efficacy in individuals with comorbid substance use disorders has not been documented. The opiate antagonist naltrexone has been approved by the Food and Drug Administration in the United States for the treatment of alcohol dependence because of its efficacy in reducing alcoholic relapse (138,139), and it appears to decrease the reinforcing efficacy of alcohol (140).

Preliminary data suggest that naltrexone may decrease the frequency of binging and purging and the preoccupation with food in women with bulimia (141). The possible utility of naltrexone in the treatment of individuals with comorbid bulimia nervosa and alcohol dependence is an empirical question worthy of further investigation. Although empirical data are lacking, Ziedonis and Brady (142) note the short-term efficacy of the selective serotonin reuptake inhibitors in the treatment of bulimia nervosa and that these medications may be helpful with the dually diagnosed.

CONCLUDING REMARKS

Eating disorders and substance-related disorders co-occur frequently in treatment settings, posing a significant treatment challenge to clinicians in both eating disorders and substance abuse treatment centers. Despite the frequency with which this pattern of comorbidity is observed in the clinic, genetic epidemiological data do not suggest an etiological link between the two disorders. Alcohol and drug dependence are more often associated with the presence of bulimia nervosa than with the restricting subtype of anorexia nervosa. In addition to alcohol and drug dependence, women with eating disorders often utilize a broad array of pharmacological agents to induce purging and decrease appetite and weight. The use of these substances parallels the abuse of more traditional substances phenomenologically, although their use tends to be confined to the clinical course of the eating disorder. No clinical trials exist which identify the optimal approach to the treatment of comorbid eating disorders and substance-related disorders; however, the past or current presence of mild or moderate substance abuse or dependence does not appear to adversely affect treatment outcome for eating disorders. Clinical trials are required to determine the most effective approach to individuals who present with severe comorbid eating and substance-related disorders.

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11
Attention-Deficit/Hyperactivity Disorder and Substance Abuse

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INTRODUCTION

Awareness by mental health professionals and the lay public of attention-deficit/hyperactivity disorder (ADHD) and its impact on functioning in childhood and adulthood has grown rapidly since 1990. This is reflected in the proliferation of self-help books (1–3), documentaries, and television programming (4,5), and an exponential increase in the prescription of psychostimulants (6). These developments have been controversial, as the validity of the diagnosis, particularly in adults, has been questioned (7,8).

Adding to the complexity is the high rate of comorbidity of ADHD with a number of psychiatric conditions including mood and anxiety disorders, conduct/antisocial behavioral disorders, learning disabilities and neuropsychological impairments, and substance use disorders (9–12). The co-occurrence of ADHD and substance use disorders has received considerable attention in recent clinical and scientific investigations (5,13–15). Prospective follow-up studies of ADHD children into adulthood, as well as retrospective studies of referred and non-referred ADHD adults, have documented increased risk for substance use disorders in ADHD patients (13,16,17). Initially, the risk for substance use disorders in ADHD patients was attributed to psychiatric comorbidity. Recent research suggests that ADHD increases the risk for substance use disorders, independent of psychiatric comorbidity (14).

ADHD and substance use disorders are linked to one another in a variety of ways. The core symptoms of ADHD may be mimicked by the effects of psychoactive substance use, which make it difficult to diagnose one disorder in the presence of the other. The treatment of patients with substance use disorders is also complicated by the presence of ADHD. Individuals with ADHD may demonstrate earlier onset and a pattern of more frequent or intense use of substances (18). The symptoms of ADHD, including inattention and impulsivity, often hinder treatment efforts directed at the concurrent substance use disorder. Thus, understanding the relationship between substance use disorders and ADHD should permit the development of more focused treatments aimed at

each of these disorders when they occur together.

In this chapter, we discuss 1) relevant issues regarding ADHD across the lifespan, 2) the relationship between ADHD and substance use disorders, 3) assessment/differential diagnosis of ADHD in substance, abusing populations, and 4) treatment issues relevant to both disorders.

Attention-Deficit/Hyperactivity Disorder Across the Lifespan

ADHD is the most common emotional, cognitive, and behavioral disorder treated in youth (6,19). Epidemiological studies indicate that ADHD is a prevalent disorder, affecting 4–5% of children in the United States, New Zealand/Australia, Germany, and Brazil (20). A child with ADHD is characterized by a considerable degree of inattentiveness, distractibility, impulsivity, and often hyperactivity that is inappropriate for the developmental stage of the child. Other common symptoms include low frustration tolerance, shifting activities frequently, difficulty organizing, and daydreaming. While symptoms are usually pervasive, they may not occur in all settings. Children whose predominant symptom is inattention may have difficulties in school and in completing homework but may not manifest difficulties with peers or family. Conversely, children with excessive hyperactive or impulsive symptoms may do relatively well in the structured setting of school but may have difficulties at home or in situations with less guidance and structure (12).

The concept of ADHD has undergone a number of changes over the past several decades. Initially, ADHD was characterized as a disorder of hyperkinesis or overactivity. Currently, inattention and hyperactivity are equally emphasized as important core features. Three subtypes of ADHD are currently recognized, with diagnostic criteria described in the DSM-IV (21): predominantly inattentive, predominantly hyperactive-impulsive, and a combined subtype (Table 1). The combined subtype is the most commonly represented subgroup, accounting for 50–75% of all ADHD individuals, followed by the inattentive subtype (20–30%) and the hyperactive-impulsive subtype (less than 15%) (22–25). Children, adolescents, and adults with the inattentive subtype of ADHD have fewer other emotional or behavioral

Table 1 Diagnostic Criteria for Attention-Deficit/Hyperactivity Disorder

A. Either (1) or (2)

(1) six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Inattention

(a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities

(b) often has difficulty sustaining attention in tasks or play activities

(c) often does not seem to listen when spoken to directly

(d) often does not follow through on instructions and fails to finish school work, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)

(e) often has difficulty organizing tasks and activities

(f) often avoids, dislikes, or is reluctant to engage in tasks that require substantial mental effort (such as school work or homework)

(g) often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)

(h) often easily distracted by extraneous stimuli

(i) often forgetful in daily activities

(2) six (or more) of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactivity

(a) often fidgets with hands or feet or squirms in seat

(b) often leaves seat in classroom or in other situations in which remaining seated is appropriate

(c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)

(d) often has difficulty playing or engaging in leisure activities quietly

(e) often "on the go," or often acts as if "driven by a motor"

(f) often talks excessively

Impulsivity

(g) often blurts out answers before questions have been completed

(h) often has difficulty awaiting turn

(i) often interrupts or intrudes on others (e.g., butts into conversations or games)

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.

C. Some impairment from the symptoms is present in two or more settings (e.g., in work [or at work] and at home).

D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.

E. The symptoms do not occur exclusively during the course of a pervasive developmental disorder, schizophrenia, or other psychotic disorder, and are not better accounted for by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, or a personality disorder).

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problems than individuals with the other subtypes. Youth with prominent problems of inattention as part of their ADHD (combined or inattentive subtype) have greater academic impairment than those with predominant hyperactivity/impulsivity. The combined-type ADHD individuals have more co-occurring psychiatric and substance use disorders and are the most impaired overall (12).

Adult ADHD

Early formulations of ADHD viewed it as a childhood disorder that disappeared during adolescence (26). Since the early 1970s, there have been publications in the medical/psychiatric literature questioning the view of "hyperactivity" as strictly being a childhood disorder (27,28). Wender and colleagues (29–32) have been instrumental in reviewing the sources of evidence and the reasoning that led to the awareness of residual ADHD in adult life. Studies (16,33–35) of ADHD children followed into adult life have provided persuasive evidence that some children do not outgrow ADHD. Family studies (36,37) have revealed higher incidences of ADHD, alcoholism, and sociopathy in parents of ADHD children, providing further support for the existence of adult ADHD. A final line of evidence came from reports of successful stimulant drug treatment of adults meeting provisional operational criteria for the ADHD-residual type diagnosis (31–33).

Despite the emerging and growing support for the existence of adult ADHD, its diagnosis remains controversial. Some researchers (7) have asserted that ADHD usually remits in adulthood and should be rare and of little concern to the practicing clinician. Others have stressed the diagnostic continuity of ADHD throughout the life span and asserted that adults seen clinically have the same well-validated syndrome as that seen in pediatric cases (38,39). Faraone et al. (8) recently examined the validity of adult ADHD, utilizing the requirement proposed by Robins and Guze (40) that the validity of any psychiatric disorder derives not from a single study, but from a pattern of consistent data obtained from multiple sources. Table 2 summarizes their review of a wide range of studies that strongly suggests that adult ADHD is a valid disorder.

Clinical correlates of ADHD are similar for children and adults. ADHD adults are impulsive, inattentive, restless, and, like their childhood

Table 2 Summary of Evidence for the Validity of Adult Attention-Deficit/ Hyperactivity Disorder (ADHD)

Domain	Score	Comments
ADHD symptoms	++	Adults show core symptoms of inattention, impulsivity, and hyperactivity, but, hyperactivity may diminish with age
Psychiatric comorbidity	+	Substance use disorder is more common among, adults
Impairment	++	ADHD adults show functional impairments in, multiple domains
Gender difference	+	Greater male prevalence of ADHD is less evident, for adults than for children

Family history of ADHD	+	ADHD appears to be more prevalent when there, is an affected adult in the family
Treatment response	++	Medications with documented anti-ADHD, activity in children work equally well in adults
Molecular genetics	+	The D4 dopamine receptor gene has been, implicated in both childhood and adult ADHD
Neuropsychology	++	ADHD children and adults show impaired, vigilance, motoric inhibition, executive, functions, and verbal learning and memory
Neuroimaging	?	Not enough comparable data between children, and adults
Course and outcome	?	The persistence of ADHD into adulthood ranges, from 4% to 80%, depending on the definition, of persistence

++=results strongly support the validity of adult ADHD; +=results support the validity of adult ADHD; ?=results are equivocal.
Source: Ref. 8.

counterparts, suffer from higher rates of antisocial, depressive, and anxiety disorders. ADHD adults show evidence of clinically significant impairments in histories of school failure, occupational problems, and traffic accidents. Studies of treatment response show that medications used to treat childhood ADHD are equally effective for adult ADHD.

Review of family studies provides strong support for the validity of adult ADHD (8). Adult relatives of ADHD children have higher rates of ADHD, and the child relatives of ADHD adults have a higher risk of ADHD. Assessment of neuropsychological functioning reveals a characteristic profile of deficits in both childhood and adult ADHD. Neuroimaging findings implicate prefrontal dopaminergic hypoactivity in adult ADHD, consistent with the putative role of dopamine in the etiology of ADHD (41). However, further research is necessary to determine the evolution of dopamine abnormalities in ADHD from childhood to adulthood.

While these convergent lines of evidence provide support for the validity of ADHD in adults, areas of ambiguity remain. For example, psychiatric comorbidity among ADHD adults can lead to false positive diagnoses, hence there is a need to validate appropriate diagnostic criteria for adult ADHD (8). Although false positive diagnosis is an issue for all disorders, the problem may be more significant for adult ADHD. Many adult ADHD patients are self-referred, which may in part be due to the high rate of media attention to adult ADHD. Many individuals attempt to attribute their life problems to an ADHD diagnosis and see themselves as suffering from ADHD-like symptoms. Clinicians need to take extra care to evaluate the presence of childhood onset, chronicity of symptoms, and functional impairment secondary to ADHD symptoms in self-diagnosed referrals.

The question of what constitute appropriate diagnostic criteria for adult ADHD is complex. Currently, the DSM-IV requires that ADHD should have an onset by age seven (21), though the validity of this age-of-onset criterion (AOC) has been challenged (42). DSM-IV field trials (43) showed that many subjects meet symptom criteria for ADHD but do not satisfy the AOC criterion. Requiring an AOC of seven years reduced the

accuracy of identifying currently impaired cases of ADHD and reduced agreement with clinician judgments. Applegate et al. (43) identified three alternative strategies for the diagnosis of ADHD: 1) drop the AOC; 2) drop the requirement that symptoms at the AOC are "impairing"; or 3) keep the impairment criterion but raise the AOC. They also suggested that a separate AOC rule be considered for the diagnosis of the inattentive subtype of ADHD (43).

Further complicating the diagnosis of adult ADHD is the question of what symptom thresholds are necessary to define cases. Longitudinal studies have found highly variable rates of persistence of ADHD symptoms into adolescence (50–75%) (44–46) and adulthood (40–60%) (34,47). This ambiguity is, in part, due to differences in how researchers have defined the persistence of ADHD in adults. Barkley (48) argued that, depending on the methodological approach used, 30–68% of those with childhood ADHD might also have adult ADHD. Barkley (48) has emphasized the problem of "developmentally insensitive" diagnostic criteria for adult ADHD. As a consequence, patients seem to outgrow the childhood criteria used to make the diagnosis while ostensibly retaining the disorder. When developmentally appropriate criteria are used, such as those based on the DSM-III-R, prevalence rates tend to be substantially higher, ranging up to 75% in young adulthood (49,50). These studies show the persistence of ADHD into adulthood, including symptoms of inattention, disorganization, distractibility, and impulsiveness, along with academic and occupational failure. Barkley (48) has suggested that ADHD be recast as a "norm-referenced" rather than a "criterion-referenced" diagnosis.

THE RELATIONSHIP BETWEEN ADHD AND SUBSTANCE USE DISORDERS

With the recognition of adult ADHD as a unique diagnostic entity, there has been converging evidence that the overlap between ADHD and substance use disorders is greater than that expected by chance alone. This association has been found in primary substance abusers and those initially diagnosed with ADHD (12,13). While the two disorders differ in their developmental expression (ADHD begins at a younger age than do substance use disorders), they share several important characteristics. Both ADHD and substance use disorders occur predominantly in males, have familial aggregation, and may be genetically influenced. Further complicating their relationship is the high rate of psychiatric comorbidity. Antisocial personality disorder, conduct disorder, anxiety disorders, and mood disorders commonly co-occur in both substance use disorders and ADHD. Despite the high degree of symptom overlap between ADHD, substance abuse, and other disorders, Milberger and colleagues (11) found that ADHD is not an artifact of symptoms shared with other psychiatric disorders, and that comorbid conditions are not an artifact of the presence of ADHD.

Research on ADHD and Substance Abusing Populations

During the past decade the link between ADHD and substance abuse has been examined

with an increasingly sharper focus (15). Adults with ADHD have consistently been found to have elevated rates of lifetime substance use disorders compared to the general population (8,10,13,14,51). Studies have demonstrated that approximately 33% of adults with ADHD have histories of alcohol abuse or dependence, and approximately 20% have histories of other drug abuse or dependence (10,13).

Prospective studies of children with ADHD show that they are at greater risk for comorbid conduct disorder and substance use disorders in adolescence, as well as antisocial personality and substance use disorders in adulthood (15). While a history of childhood ADHD is associated with a higher rate of adult substance abuse, this risk is further increased if ADHD symptoms persist into adulthood (16,52). There is also a higher rate for antisocial personality disorder among those with ADHD. Mannuzza et al. reported that 50% of probands with continuing ADHD symptoms had a substance use disorder, while 30% had antisocial personality disorder (34). In a large study of adults with childhood ADHD, Wilens and colleagues (18) found that ADHD was associated with earlier onset of substance use disorders, an effect that was independent of psychiatric comorbidity. Conversely, the offspring of parents with substance use disorders are at increased risk, not only for adolescent and adult substance use disorders, but also for cognitive and behavioral abnormalities. These include shortened attention span, impulsivity, aggressiveness, and elevated rates of ADHD, compared to the offspring of control parents (53,54). ADHD has also been implicated in the transitions from substance abuse to dependence and between different classes of abused substances. For instance, Biederman et al. (52) found that subjects with ADHD, compared to those without ADHD, were significantly more likely to make the transition from alcohol abuse to drug abuse (hazard ratio=3.8) and showed a significantly higher rate of persistent substance abuse following a period of dependence (hazard ratio=4.9).

While research shows that individuals with ADHD exhibit higher rates of substance use disorders, the reverse is also true, as individuals presenting for substance abuse treatment show elevated rates of ADHD. This has been reported in clinical samples of alcoholics (55–58), opiate and cocaine addicts (11,59–61), and adolescent substance abusers (62). Prevalence rates of childhood ADHD have ranged from 17 to 50% in alcoholics (58,63,64) and 17 to 45% in cocaine and opioid abusers (13), compared to 2–9% in the general population (9). Clinical studies have also shown that rates of nicotine dependence are substantially higher among ADHD adolescents and adults (40%) than among the general population (26%) (65). Recent work suggests that ADHD youth disproportionately become involved with cigarettes, alcohol, and then drugs (52,66).

Clinical research has been directed toward identifying particular vulnerabilities in the ADHD population that may explain the elevated rates of substance use disorders, including nicotine use found in adults who have persistent ADHD symptoms. Early studies postulated that ADHD individuals abused stimulants preferentially in an effort to "self-medicate" their symptoms (59,67). Research has also suggested that nicotine may have a therapeutic effect on some of the symptoms of ADHD, such as inattention and hyperactivity (15,68), thus resulting in higher rates of daily smoking in individuals with ADHD compared to controls (35% to 19%) (69). While there has been some support for the self-medication hypothesis, recent investigations (70–72) have demonstrated that adults with ADHD have elevated rates of substance abuse across several different classes

of drugs regardless of whether the abused drug normalizes ADHD symptoms. Clure et al. (71) recently examined the issue of drug choice among those with ADHD and substance use disorders. They found no significant differences in ADHD prevalence by substance of choice. The finding is consistent with the work of other investigators who have concluded that ADHD represents a broad vulnerability to substance abuse. Vulnerabilities particular to this population include impulsivity, poor choice in peer groups, impaired occupational and social functioning, and the desire to get "high," as well as efforts at self-medication (16).

The association between adult ADHD and substance use disorder is complex and varied. Some investigators have reported that more severe hyperactive symptoms in childhood predict a more severe form of alcoholism (73–75), but others have challenged this claim. Longitudinal studies of ADHD children have provided evidence that conduct and antisocial disorders are significant mediating factors between substance use disorders and ADHD (76,77). Recent studies have provided further evidence (78,79) that conduct disorder or "some form of psychopathology" likely existed in adolescents and/or adults prior to their substance use disorders. In a rare prospective study, Linskey and Fergusson (80) found that conduct problems at age eight were associated with a twofold increase in the amount of alcohol, tobacco, and illicit drugs used at age 15. The relationship between ADHD at age eight and later substance abuse disappeared when the intervening effect of conduct problems was removed. In contrast, Moss and Lynch (81) found evidence that implicated both conduct disorder and ADHD in the development of substance use disorders.

Biederman and associates (52) have proposed an ADHD-specific sequence to the development of substance use disorders. They found a threefold greater risk for developing a drug use disorder among ADHD adolescent subjects who abused alcohol (52). Biederman and his colleagues (82) found that history of medication use is an important modifier of the relationship between ADHD and substance use disorders. Results revealed that although risk for substance use disorders was indistinguishable in ADHD vs. non-ADHD youth, when the ADHD group was stratified by medication use history, subjects who did not receive pharmacological treatment were at a significantly increased risk for substance use disorder. This was true even after controlling for the presence of conduct disorder.

ADHD and Substance Abuse Disorders: Common Pathophysiology?

ADHD is among the psychiatric disorders for which a genetic basis is best established (83). Family, twin, adoption, and segregation analysis studies suggest that the familial aggregation of ADHD has a substantial genetic component. Family studies have also demonstrated an association between ADHD and substance use disorders (10,13,84,85). Initial family studies of ADHD children (36,37) found a greater frequency of alcoholism, as well as depression and sociopathy, among the parents of hyperactive children than among the parents of healthy control subjects. Half-sibling, twin, adoption, and segregation analysis studies have also confirmed a greater prevalence of alcoholism, sociopathy, and hyperactivity in biological parents and relatives of ADHD children. Clinical studies have confirmed the epidemiological finding that the children of

alcoholics have higher rates of ADHD than the offspring of control parents (53,54). Rates of ADHD are also elevated in the offspring of opiate-dependent individuals (86). Adolescent and adult offspring of parents with substance use disorder are at increased risk for cognitive and behavioral deficits, such as higher levels of impulsivity, aggressiveness, reduced attention span, and elevated rates for both ADHD and substance use disorders. These findings suggest a common pathophysiology for ADHD and alcohol/drug abuse, which may have its basis in common genetic loading.

The high levels of comorbidity of ADHD with conduct, anxiety, and mood disorders have been interpreted as possibly reflecting genetic heterogeneity (85). Early studies showed that adult psychiatric disorders were more commonly associated with childhood conduct disturbance than with ADHD. Clinical and etiological studies have shown that conduct and antisocial personality disorders result in a heightened risk for drug and alcohol addiction (87,88). In a series of studies, Biederman and colleagues (85,89–91) have addressed the proposed genetic heterogeneity in ADHD by stratifying ADHD probands on the basis of the presence or absence of other psychiatric disorders, particularly conduct and antisocial personality disorders. In a large family study (85), they found that brothers but not sisters carried an increased risk for ADHD, but only among siblings from families exhibiting antisocial disorders. In non-antisocial families, brothers and sisters were at equal risk for ADHD. The findings support the hypothesis that the combination of ADHD and antisocial disorders represents a distinct subtype of ADHD, placing children (especially boys) at especially high risk for substance abuse and other psychopathology.

The precise neural and pathophysiologic substrate of ADHD remains unknown, and this is true for substance use disorders as well. The behavioral and cognitive difficulties that are pathognomanic of ADHD have long been ascribed to anomalies in brain function (92), specifically dysfunction of frontal regions and connections to the striatum (93–95). Functional neuroimaging studies, using single photon emission computed tomography (SPECT) and positron emission tomography (PET), have identified anomalies of frontal metabolic activity indexed by diminished cerebral blood flow or glucose metabolism (95–97). Consistent with this, Giedd et al. (98) reviewed structural neuroimaging studies that identified morphologic differences in frontal and striatal structures of ADHD individuals compared to matched controls. In addition to dysfunction of frontal-striatal circuitry in ADHD, there is a growing literature that suggests that there is differential involvement of right hemispheric mechanisms specialized for behavioral regulation and attention (99). The clinical relevance of the frontal and striatal structures is supported by neuropsychological studies indicating that ADHD is commonly associated with impaired performance on measures of executive functioning and working memory (100,101), consistent with frontal lobe dysfunction. Moreover, hypofunction of frontal striatal pathways rich in dopaminergic innervation is compatible with the dopamine-enhancing action of medications found to be successful in the treatment of ADHD.

Considering the enormous complexity of the distributed neural network that mediates diverse aspects of attention-related behavior, the neural pathophysiology of ADHD would be expected to involve more than deficits in frontal lobe functioning. Yet, frontal lobe deficits appear to mediate the pathophysiology of both ADHD and substance use disorders. There is evidence of deficient frontal functioning in individuals at high risk of

alcoholism, compared with those at low risk for the disorder (102). Further evidence for the role of deficits in frontal lobe function in alcohol abuse has been provided by research showing that desynchronized EEG in frontal areas (a potential marker for frontal dysfunction) is related to a greater likelihood of relapse in alcoholics (103). Cocaine abusers have also been found to have structural deficits in frontal areas believed to be involved in decision-making and behavioral inhibition (104). These studies emphasize the importance of examining the pathophysiological substrates that may be shared by individuals with either ADHD or substance abuse.

Studies in molecular genetics have uncovered promising clues into the potential nature of the common underpinnings of the frontal-striatal deficits seen in both ADHD and substance abuse (15). For instance, because frontal-striatal areas are rich in dopaminergic neurons, it stands to reason that deficits in these areas may be mediated by deficits in dopaminergic function (15). Molecular genetic studies have found evidence of the involvement of several genes that encode dopamine system proteins in the etiology of ADHD, including the genes encoding the D_2-receptor, the dopamine transporter, and dopamine-beta-hydroxylase (105). More importantly, studies of these dopaminergic genes also suggest a possible locus for shared vulnerability for drug abuse and ADHD. Considerable attention has been focused on the A1 allele of the dopamine D_2 receptor gene (genetic locus DRD2), the prevalence of which has been reported to be significantly increased among individuals with ADHD (106), as well as those with polysubstance abuse, but not in individuals with only alcohol abuse (107). Studies of DRD2 have also suggested a possible locus for a shared vulnerability to drug abuse and to ADHD. Prevalence of the A1 allele at this locus has been found to be elevated in severe alcoholics (108), individuals with polysubstance abuse (107), and cocaine addicts (109). However, these reported associations between dopamine receptor marker alleles and severity and kind of substance dependence have been challenged in a later study which failed to replicate the finding of significant differences in allele frequency between cocaine-dependent and control subjects in samples from either European-American or African-American populations (110).

The gene of the dopamine D4 receptor (genetic locus DRD4) occurs significantly more frequently in children with ADHD than among matched controls (111). Given that DRD4 mediates a blunted cellular response to dopamine, its overrepresentation in the ADHD population is consistent with the hypothesis that ADHD symptoms are related to hypodopaminergic function, and are thus ameliorated by drugs that increase synaptic dopamine. Thus, genetic factors in the etiology of ADHD that are present in affected individuals may represent particular vulnerabilities for substance use disorders (111). For instance, most abused drugs increase dopamine in the nucleus accumbens, implying increased activity of this area, which has major projections to the frontal cortex. It is theoretically possible that abused substances (cocaine, nicotine, alcohol, stimulants) will enhance frontal cortical functioning through this pathway. This effect could then become additive to the rewarding effects of abused substances in ADHD individuals.

Summary

Research suggests that while ADHD and substance use disorders are distinct diagnostic

entities, there is nevertheless a high degree of etiologic and phenomenologic overlap between the disorders. Prospective studies of children with ADHD whose symptoms persist into adolescence and adulthood show that these individuals are at increased risk for substance abuse. Children with ADHD and comorbid conduct disorder appear to be at particularly high risk for substance abuse. Gonversely, retrospective studies of adults currently diagnosed with substance use disorders reveal a higher occurrence of ADHD in childhood. The co-occurrence of the two disorders suggests that they may share common etiological pathways.

The presence of a common pathophysiology between ADHD and substance use disorders is supported by evidence obtained from a variety of sources. Family studies point to a close genetic association between the two disorders, as children of parents with ADHD and/or substance abuse are at increased risk for both disorders. Although the precise neural substrates of ADHD and substance use disorders remain unknown, neuropsychological and neuroimaging studies point to the presence of common abnormalities in frontro-striatal networks for both disorders. These shared frontro-striatal deficits may be related to shared abnormalities in dopaminergic function. Some recent studies in molecular genetics show allelic association of genetic loci that mediate the expression of dopaminergic function and both drug abuse and ADHD. Taken together, these data are consistent with a possible common pathophysiology for both disorders, and continued research in this area is needed to validate and extend these findings.

ASSESSMENT/DIFFERENTIAL DIAGNOSIS

The assessment of ADHD relies heavily on the clinical expertise of the diagnostician. Diagnosing ADHD in childhood can be difficult. Since the diagnosis becomes more complicated as the individual ages, diagnosing ADHD in late adolescence and adulthood, in particular, is not an exact science (112). There is no single neurological or psychological test battery that can conclusively determine whether ADHD is present. The diagnostic task is complicated by the limited amount of controlled research with adults, the likelihood of comorbid psychiatric conditions, including substance abuse, the variety of other diseases and environmental stressors that can mimic ADHD, and the fact that almost everyone at times experiences some of the symptoms of the disorder. The diagnostic process is further complicated by the fact that the DSM-IV criteria (21) were derived from childhood behaviors and can be difficult to translate into adult behaviors.

As now defined, adult ADHD is a continuation of a disorder that has its origins in childhood. Strictly speaking, one cannot make a diagnosis of ADHD in an adult without a positive childhood history of disruptive attentional difficulties and/or impulsivity and hyperactivity (21). Clinicians assessing ADHD in a substance-abusing client need to assess the history of functioning prior to the initiation of substance use/abuse. However, it can be difficult to elicit an accurate childhood history with any degree of confidence. The task may be relatively simple when objective records are available that document social, psychological, and academic problems, with a diagnosis of hyperactivity and treatment with medication. However, many adults presenting for substance abuse treatment attended school before ADHD was commonly recognized or effectively

diagnosed. Their behavioral characteristics may not easily translate into current ADHD constructs, rendering records of limited benefit. Female substance abusers with ADHD are less likely than males to have a previous ADHD diagnosis or treatment history because of their lower rates of conduct and oppositional disorders. Yet, research indicates that ADHD females share prototypical features of the disorder with their male counterparts, including high rates of school failure and comorbid disorders (12).

While ADHD and substance use disorders can be assessed simultaneously, the initial focus should be on the client's substance use. The first rule of thumb for the clinician is to accept the validity of the ADHD diagnosis and be open to its potential comorbidity with substance abuse. In doing so, the clinician should assess the substance abuser's preferences for and reactions to substances. For example, ADHD substance abusers sometimes report paradoxical reactions to cocaine or stimulant use, including an increased ability to focus, a less euphoric response, and sedation. Other inquiries regarding self-medication with substances can be helpful. For example, a college student may report that he gets himself intoxicated the night before a day of rigorous studying because a hangover improves his ability to sustain his attention and concentration. Assessing primary symptoms of inattention, impulsivity, and hyperactivity during either extended periods of abstinence from substance use or during withdrawal may assist in clarifying the clinical picture. The clinician should also give special attention to the possibility of psychiatric and cognitive disorders not directly related to the substance use disorder. As an example of one functional approach, Rounsaville et al. (87) suggest that psychiatric symptoms in substance abusers should be considered valid unless they occur only during a period of marked change (increase or decrease) in the use of the abused substance.

Clinical judgment is needed as to when to conduct a more formal ADHD assessment in the substance-abusing adult. It has been recommended that a client who is actively using alcohol or drugs be interviewed at least 5 to 7 days after termination of substance use to minimize the impact of the effects of prior use or withdrawal symptoms on the information provided (87). We, like others (13), have found that the assessment of ADHD symptoms is more accurate as the client remains in treatment and abstains from psychoactive substance use for a longer period of time (e.g., 2–3 months). Yet, clinicians specializing in addictions and ADHD may find that timely ADHD intervention—earlier than previously recommended—can help stabilize recovery rather than jeopardize it (113).

AACAP Practice Parameters for ADHD

Clinicians interested in assessing ADHD in their substance-abusing clients should familiarize themselves with the practice parameters established by the American Academy of Child and Adolescent Psychiatry (AACAP) (114). These empirically based guidelines for the assessment, treatment planning, and treatment of children, adolescents, and adults with ADHD may be obtained from the American Academy of Child and Adolescent Psychiatry's WebPages at www.aacap.org. To date, AACAP's guidelines are the only ADHD practice parameters for adults. They were developed by the Work Group on Quality Issues of AACAP and are based on an exhaustive review of the literature.

Table 3 summarizes the recommended assessment procedures.

AACAP (114) provides several caveats that are helpful in the assessment of ADHD. If ADHD was not identified when the client was a child, it is often missed in adulthood. Adults with ADHD may not have been diagnosed with ADHD in childhood for a number of reasons.

Table 3 AACAP Recommended Assessment Procedures for ADHD

1. Patient interview to obtain developmental history, psychiatric history and past treatments, present and past DSM-IV ADHD symptoms, impairment history (including the domains of school, work, family, and peers), differential diagnosis of alternate and/or comorbid DSM-IV disorders, an assessment of strengths, talents, and abilities, and mental status examination
2. Standardized rating scales completed by the client, client's parent (when available), or significant other
3. Medical history
4. Family history
5. Interview with significant other or parent, if available
6. Physical evaluation (if not completed within the past year)
7. School information
8. Referral for additional evaluation if indicated (e.g., neuropsychological, psychoeducational or vocational evaluations)

Source: Ref. 114.

A comorbid condition may have clouded the picture (e.g., a chaotic school, substance-abusing parents, comorbid anxiety, or early substance abuse). On the other hand, as a child the adult may have been extremely bright, compliant, had consistent discipline at home, an accommodating school, or interpersonal charm that allowed him or her to compensate for the symptoms of ADHD. This scenario is particularly true of the ADHD, predominantly inattentive type (114). Thus, AACAP recommends that the clinician assess the adult from a developmental perspective, which might include a history of childhood underachievement or having been considered undisciplined, unmotivated, or "spacey." It is also important to evaluate the role of substance use in the household of origin as part of the developmental history.

The AACAP practice parameters also take into consideration the fact that many adults with ADHD have limited insight into their difficulties and may be poor informants. Under-reporting of childhood ADHD symptomatology has been well documented (31,115). Wender and colleagues (31) found poor agreement between the recollections of adult clients and their parents about the clients' ADHD symptoms during childhood. Parental recall was a more valid measure and a better predictor of treatment response. On the other hand, Biederman and colleagues (10,116) have demonstrated that a reliable and valid clinical diagnosis of childhood ADHD can be made on the basis of self-report, even

among clients with comorbid substance use disorders. Thus, AACAP's practice parameters note that current information from spouses or significant others, employers, and retrospective reports from parents, is important. School records and past psychiatric reports can make a major contribution to the assessment, as can a medical history and recent physical examination. Psychological or neuropsychological testing may be indicated but are not required (114). This multi-modal approach to ADHD assessment has been advocated and examined in the childhood literature for several years (117). As Conners and Erhardt note, "the major problem with these multilevel assessments is how to integrate information across informants and domains in such a way that the needs of both diagnosis and treatment formulation are served" (Ref. 117, p. 505).

The AACAP (114) practice parameters also state that standardized rating scales may be useful. We find that they are useful and important tools when used in conjunction with the categorical diagnostic system of the DSM-IV (21). Rating scales provide an alternate method of establishing which symptoms go together, how prevalent the symptoms are in the normal population, and what level of a specific dimension is statistically abnormal. Some advantages of a dimensional measurement are that it is empirically derived and cost-effective, and that it covers a broad range of behaviors. Also, it yields quantitative information for group comparisons and measures of change, as well as normative comparisons with age- and gender-matched peers.

Diagnosing ADHD/Differential Diagnosis

In order to make a diagnosis of ADHD in an individual with a substance use disorder, the clinician must assess the presence and history of ADHD symptoms and the extent to which symptoms cause impairment, as well as differentiate it from other comorbid disorders that can result in ADHD-like symptoms. Creating a time line of an individual's ADHD symptoms and substance use history, anchored by significant life events, can make assessment easier. It is also important to keep in mind that intoxication or withdrawal from substances may produce inattention and that intoxication, cravings, or withdrawal from certain substances (e.g., stimulant or alcohol intoxication, cocaine cravings, alcohol withdrawal) can involve hyperactive or impulsive behavior.

A DSM-IV diagnosis of ADHD (21) requires not only the presence of symptoms, but also evidence of impairment in two or more domains of functioning (such as home, work, school, social, and personal/self-esteem), with significant impairment in at least one domain. Unfortunately, the DSM-IV (21) provides no operational guidelines for determining impairment, nor does it provide a complete list of settings. Adults with chronic substance abuse or dependence are likely to be impaired across the same domains that are impaired in ADHD. Therefore, it is the clinician's responsibility to determine if impairment in functioning is due to ADHD or substance use. If one is not sure, it may be better to err on the side of caution and withhold a diagnosis of ADHD until such time as impairment can be re-assessed independently of substance use (e.g., after sustained abstinence).

The differential diagnosis of ADHD in a substance-abusing adult is challenging. An adult with ADHD is likely to have a comorbid psychiatric condition and the same diagnoses that are common in childhood ADHD appear to be common in adult ADHD

(9). In cases of adult ADHD, depression is reported to co-occur in 15–75% of cases, anxiety in 25% of cases, antisocial personality disorder in 30–50% of cases, substance use disorders in 30–50% of cases, and learning disabilities in anywhere from 10–90% of cases (9). Consequently, one must not only determine whether ADHD exists, but also assess any co-occurring psychiatric conditions. The differential diagnosis of ADHD in adulthood is difficult due not only to comorbidity, but also to a host of other conditions that may include attention or organizational deficits (see Table 4).

Table 4 Conditions that May Include Attentional or Organizational Deficits

Psychiatric	Medical
Schizophrenia	Head injury
Bipolar disorder	Dementia
Cyclothymia	Delirium
Major depression (with agitation)	Tumors—frontal, parietal, and temporal regions
Anxiety disorders	Tourette's syndrome
Antisocial personality disorder	Stroke
Borderline personality disorder	Hyperthyroidism
Histrionic personality disorder	Hypothyroidism
Alcohol intoxication or withdrawal	Renal insufficiency
Other substance use disorders	Hepatic insufficiency
Intermittent explosive disorder	Anoxic encephalopathy
Dissociative disorders	Vitamin deficiency states
Post-traumatic stress disorder	Chronic obstructive pulmonary disease
Conduct disorder	Multiple sclerosis
Learning disorders	Seizures/epilepsy
Age-appropriate high activity	Sensory deficits (e.g., hearing loss)
Mental retardation	Drug side effects
Stress/environmental	Neurological disorders of vigilance

Source: Adapted from Refs. 4,48,118–120.

Application of ADHD Practice Parameters

We recommend that the assessment of ADHD in a substance-abusing adult adhere to the format recommended by the AACAP practice parameters (114). In our clinics, clients referred for an ADHD assessment complete a package of assessment materials to assist in the diagnostic process. The assessment package is provided during the initial intake and includes a cover letter with an explanation of the assessment process, a request for past

records from school, psychological or medical evaluations, and/or work reports, and multiple assessment instruments including the following:

1. A structured developmental history form that requires written responses from the client, detailing the chronology of life experiences from gestation to current adult functioning: The structured interview includes questions about a variety of childhood risk factors for ADHD as well as elements of the family, gestational, medical, academic, psychiatric, and interpersonal histories. One example of such a history form was developed by Johnson and colleagues in an effort to create a comprehensive developmental history for diagnosing adult ADHD (Conners' Adult ADHD Diagnostic Interview for DSM-IV [CAADID]) (121). At the time of the next meeting the clinician has the completed materials and is able to focus on relevant areas of concern or risk.
2. Self and collateral ADHD behavioral rating scales, which assess for the presence and disruptiveness of current ADHD symptoms and related behaviors: Numerous rating scales are available in the literature or for purchase. These include the Conners' Adult ADHD Rating Scales (CAARS) (122), Brown Attention-Deficit Disorders Scales for Adults (123), and Barkley and Murphy's Current Symptoms Scale—Self and Other Report Form (124). The use of rating scales is particularly useful for adults who are not accompanied by a significant other due to issues of conflict or confidentiality.
3. Self and collateral ADHD behavioral rating scales which retrospectively assess for signs and symptoms of ADHD in childhood function (ages 6–10): Consistent with Wender's research (31), we have found it useful to have the client's parent complete one of these rating scales. Retrospective rating scales include the Conners' Parenting Rating Scale—Revised, Long Form (CPRS-RLF) (125), Wender Utah Rating Scale (126), and Barkley's Childhood Symptoms Scale—Self and Other Report Form (124).

In the diagnostic session, the client also completes a computerized version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (127). The interview requires the client to answer yes or no to questions related to past and current psychiatric difficulties including mood, anxiety, substance use, psychotic, somatization, and eating disorders. This relatively brief (30-minute) process screens for the presence of psychiatric comorbidity. Results of the diagnostic interview are combined with data from the rating scales and structured history form allowing for a thorough review and amplification when meeting with the client. More systematic assessment of the diagnostic criteria for ADHD is also undertaken with the use of interviews such as the Conners' Adult ADHD Diagnostic Interview for DSM-IV (121) or Schedule for the Assessment of Conduct, Hyperactivity, Anxiety, Mood, and Psychoactive Substances (CHAMPS) (128). A physical/medical evaluation may be recommended, particularly if there are concerns that a medical condition is contributing to the client's complaints. Collateral information obtained via interview of a parent, spouse, co-worker, or treatment provider (including substance abuse clinicians) provides greater validity to the self-reported symptoms.

In our clinic, clients are often assessed with a brief battery of neuropsychological tests that are sensitive to executive functions and anterograde memory. The battery includes a computerized Continuous Performance Test (CPT) that assesses attention, vigilance, and impulsivity. CPTs are the only neuropsychological instruments specifically developed for the identification of ADHD. CPTs can be administered repeatedly to monitor treatment

outcome, and are designed to provide objective measurement of the ability to maintain attention while inhibiting impulsive responses over time. Available CPTs include: the Gordon Diagnostic System (GDS) (129), Test of Variables of Attention (TOVA) (130), and Conners' Continuous Performance Test (CPT) (131). With this method, the individual receives feedback about test results, referrals as necessary, and psychoeducational materials and resources within 2–3 hours.

In an effort to guard against over-diagnosis of ADHD, Murphy (132) recommends the following: a) Keep the primary symptoms of inattention, impulsivity, and hyperactivity in the forefront. Secondary symptoms such as procrastination, chronic lateness, or underachievement do not necessarily indicate ADHD; b) Be aware that some adults may be looking for "performance enhancement," or may have something to gain by securing an ADHD diagnosis, such as qualifying for special accommodations on professional licensing examinations or obtaining stimulant medication for recreational use; c) Pay careful attention to other diagnoses that may account for the symptoms, especially depression, anxiety, substance abuse/ dependence, or antisocial personality disorder.

Neuropsychological Assessment

Research on children (50) and adults (10,133,134) indicates that neuropsychological deficits are part of ADHD. A large body of research has examined neuropsychological functioning in children diagnosed with ADHD by comparing specific domains of impairment in test performance of ADHD children to that of non-ADHD children. In these studies ADHD children do not perform as well as non-ADHD children on tests of neuropsychological functioning, motoric inhibition, and verbal learning and memory (135). However, while ADHD children as a group do not perform as well as a non-ADHD comparison group, there is much variability within the ADHD group so that no one test is sensitive and specific for all ADHD individuals. Nevertheless, the most frequently cited areas of neurocognitive deficits are inattention, poor motivation, inability to respond to behavioral consequences, and deficient response inhibition (136). While no consensus exists regarding which deficit is primary, recent theories focus on response inhibition (136). Barkley (137), for example, links poor inhibitory functioning to the inability to prioritize and execute four critical executive functions: 1) nonverbal working memory; 2) internalization of self-directed speech; 3) self-regulation of mood, motivation, and level of arousal; and 4) reconstitution or the ability to break down observed behaviors into component parts. According to Barkley, the inability to perform these executive functions leads to ADHD behaviors.

Numerous neuropsychological studies support the hypothesis that ADHD children have inhibitory deficits. However, only a handful of such studies have been conducted on adults, and fewer still that utilized DSM-IV criteria (21) to identify individuals with ADHD. In a recent study (136), 25 ADHD adults, 15 anxiety-disordered adults, and 30 normal adults completed three neuropsychological tests of response inhibition: the Conners' Continuous Performance Test, the Posner Visual Orienting Test, and the Stop Signal Task. ADHD adults demonstrated response inhibition performance deficits when compared to both normal and anxiety-disordered adults on the CPT only. In another study by the same authors (135), 45 ADHD adults and 38 normal adults were administered a

battery of tests assessing verbal learning and memory, psychomotor speed, and sustained attention. ADHD adults demonstrated verbal and nonverbal memory deficits and decreased psychomotor speed compared to normal controls. Differences between ADHD and non-ADHD adults were not found on traditional measures of executive functioning (135).

The aforementioned areas of neuropsychological impairment have associations with frontal lobe functions. Consequently, the cause of ADHD has been conceptualized in at least three different ways: 1) frontal lobe dysfunction; 2) delayed frontal maturation functioning; and 3) subcorticalfrontal motor subsystems dysfunction (135). Beyond neuropsychological test scores, other problems have been documented, such as academic underachievement, greater prevalence of learning disabilities, relative impairments on intelligence testing, and poorer executive functions (10,138). Indeed, "executive dysfunction" (138) has been described as the neuropsychological weakness in ADHD adults, with capacities in selective and sustained attention, inhibition of verbal and nonverbal responses, organization, self-monitoring, planning and sequencing of complex behaviors, and management of time and space often being affected. While adults with executive dysfunction may be very intelligent, they are inefficient and often go through their day in a nonproductive manner.

Newly abstinent substance abusers are often impulsive, distractible, and inattentive learners who are unable to focus on important tasks or to display adequate sequential organizational problem-solving skills (139). These impairments are similar to the deficits described in ADHD and have been found to persist in post-withdrawal alcoholics (140), but with significant variability. Childhood hyperactivity, as a premorbid risk factor, has been found to correlate with the persistence of a performance decrement in substance abusers (55,134). In a population of mildly-to-moderately alcohol-dependent outpatients, we found significant neurocognitive differences after 5 days of abstinence, based on the presence or absence of a childhood history of hyperactivity (134,141). Subjects without a childhood history of hyperactivity performed significantly better on the Shipley Full Scale IQ, Trail Making Test, Stroop Color-Word Interference Test, and Verbal Fluency Test (141).

For the clinician assessing a substance-abusing patient for ADHD, neuropsychological evaluation in close proximity to substance use is unlikely to assist in differential diagnosis. Neuropsychological evaluation after a period of abstinence (e.g., 3–6 months) is more likely to be helpful in differential diagnosis, as well as to provide information about strengths and weaknesses useful in the development of a treatment plan.

No definitive test battery has been developed to assess for the neuro psychological impairments associated with ADHD. Empirical research is emerging, but remains quite limited. The clinician should be flexible in his or her approach to testing. The best strategy is to develop a battery of tasks that will allow assessment of attentional, memory, and executive functions, which have been implicated most often as the deficits associated with ADHD (10,138,139). While deficits in general intellect do not appear to be part of the ADHD syndrome, its measurement allows one to rule out a lack of ability as a cause for unsuccessful school or work experiences, and it aids in the interpretation of scores obtained on other measures. If learning disabilities are suspected, broad-based assessment of academic skills should be pursued.

Although assessing a client's quantitative performance is useful, qualitative assessment is often more revealing. The clinician should observe the client for signs of ADHD manifested in short latency responses, uncritical and careless performance with frequent false starts, off-task behaviors, and concentration problems (142). Listening to how a person answers an openended question can provide insight into the person's ability to organize his or her thoughts in an economic and productive manner. Clinicians should also observe for distractibility, alteration in work style, test anxiety, and mental fatigue.

Conclusion

Adult ADHD is a diagnostic orphan. It is important for clinicians in substance abuse settings to accept ADHD as a valid disorder with a high rate of comorbidity. By doing so, an appropriate assessment will allow for the confirmation or disconfirmation of comorbid ADHD. While the initial focus of assessment and treatment should be on the client's substance use disorder, evidence of childhood and adult ADHD should be sought, using the guidelines set out by AACAP (114). The clinician's insight and observations play a special role in the diagnosis of adult ADHD. The goals of assessment include formulation of a differential diagnosis and development of a treatment plan to reduce the morbidity associated with both disorders. Providing an accurate diagnosis of adult ADHD in adults who were not identified in childhood as having the disorder can be therapeutic in and of itself. These individuals often report immediate relief once they have a framework in which to explain their lifelong difficulties. As will be discussed in the treatment section, understanding ADHD in the context of substance use has therapeutic implications related to the type of medication prescribed, the need for additional support, and the impact on one's involvement in 12-step and other group experiences common in substance abuse treatment.

TREATMENT

Overview

Understanding the relationship between ADHD and substance use disorders is important for two reasons: 1) to design efforts for preventing substance use disorders in children and adolescents who have ADHD; and 2) to develop therapeutic interventions for these clients. It is evident that ADHD symptoms complicate the treatment of substance use disorders. Substance-abusing clients with ADHD may demonstrate earlier onset of substance use and a pattern of more frequent or intense use. ADHD clients being treated for a substance use disorder have more treatment difficulties, with poorer outcome and greater risk for relapse than clients diagnosed with substance use disorders alone (14,15). While ADHD and substance use disorders should be addressed simultaneously in treatment, the initial focus should be on the client's substance use (13). Treatments for ADHD should not be solely relied on to ameliorate the behavioral patterns of substance abuse (13). These clients often have poor self-esteem, risk-taking behavior, and difficulty sitting through 12-step programs and psychotherapies. It may be helpful for the therapist

to use structured and goal-directed sessions that enhance the client's knowledge about ADHD and substance abuse. This strategy can assist the client in examining false beliefs about the history of his or her difficulties, which may serve as the framework for an effective intervention (13,143). Lengthy and unstructured verbal exchanges, extended group therapy, and overstimulating environments should be avoided, as they overtax the ADHD/substance-abuse client. Use of modalities other than auditory/verbal ones may also be helpful in this population. It is imperative that clients be assigned to therapists who are knowledgeable about ADHD and substance use disorders.

The initial task of treatment involves education about ADHD, which in and of itself may bring great relief from psychic pain and a dramatic reduction in symptoms (48,145). The use of self-help books and attendance at ADHD support groups help clients learn about their condition. Structured and directive interventions to resolve interpersonal and system problems associated with ADHD can be delivered simultaneously with traditional substance abuse treatment. Because frequent reassessments may detect the emergence or disappearance of other psychiatric and cognitive disorders as abstinence is maintained, reassessments should form the basis of a multimodal treatment plan. A clinician who is experienced in ADHD treatment can best deliver the needed interventions.

As the client maintains a period of abstinence, consideration of pharmacotherapy is warranted. Recent multisite studies suggest that medication management of ADHD is the most important variable in outcome in the context of multimodal treatment (144,145). Use of psychostimulants and other pharmacological agents may reduce the core symptoms of ADHD and other concurrent psychiatric disorders and thus enhance the treatment of substance use disorders (146). We, as well as others (147), have found that psychostimulants may be safely administered to many adults with comorbid ADHD and substance use disorders, without abuse of the stimulant. In addition to improving the primary ADHD symptoms, psychostimulants may enhance clarity of thinking, reduce craving for substances, reduce impulsivity, and promote greater awareness of the client's problematic pattern of substance use.

Clinicians treating clients with comorbid substance abuse and ADHD are often confronted by a dilemma. On the one hand, psychostimulants are often considered to be contraindicated for use by substance abusers because of concerns regarding increased risk for relapse, perhaps triggered by medication-induced craving or discriminative stimulus mechanisms (148,149). On the other hand, there is a growing literature supporting the use of psychostimulant medications in ADHD patients with active substance use disorders (150,151). Both uncontrolled and controlled trials suggest that judicious use of psychostimulants may be safe and effective in individuals with comorbid ADHD and either alcohol or stimulant abuse/dependence (147,150,151).

Judicious use of psychostimulants involves understanding the main pathways to the development of substance use disorders in adult ADHD patients. One pathway involves conduct disorder as a mediating factor in the emergence of substance use disorders in adolescents and adults with ADHD. This is consistent with features of the "Type II" alcoholic described by Cloninger (152) and with similarity to alcoholic subtypes identified by others (55,153). Type II (152) alcoholics are predominantly male, with an early onset of substance use, a more severe abuse history, and a strong family history of substance abuse and antisocial disorders. Type II clients should be prescribed

psychostimulants and/or other pharmacotherapeutic interventions with extreme caution. These clients are often coercively mandated to substance abuse treatment facilities, where they show poor compliance and treatment outcome. Such clients are less likely to use substances for self-medication and report less guilt and demoralization associated with their history of substance abuse and ADHD problems. These factors increase the risk that prescribed medications will be abused (e.g., used for recreational purposes, shared, or sold). While representing a minority of clients in treatment for substance abuse, this population highlights the need for early prevention/intervention programs that target the behavioral difficulties associated with ADHD, as is stressed by Biederman and associates (82). The aim of this approach is the prevention of conduct disturbance and psychoactive substance use disorder.

A second pathway from ADHD to substance use disorder is found in older individuals who develop substance abuse after their attempts to self-medicate symptoms and stress associated with ADHD and associated difficulties (154). It is not surprising that such individuals exist, since the syndrome of ADHD persisting into adulthood is known to be associated with morbidity, disability, chronic failure, and demoralization (14). This "self-medicated" population is akin to the Type I (152) alcoholic subtype. These clients are likely to profit from the appropriate assessment, as well as behavioral and pharmacological treatment of ADHD, with less risk for abuse of prescribed medications.

Pharmacotherapy

There is a vast literature documenting the efficacy of stimulants for treatment of the core features of ADHD (motor overactivity, impulsiveness, and inattentiveness). These medications also have beneficial effects on cognition, social functioning, and aggression (155). Although there are relatively few controlled studies, pharmacotherapy for ADHD in adults has been shown to be effective (156). First-line agents for treatment of ADHD in both children and adults are the psychostimulants. These agents have response rates of up to 80% when used at medium to high doses (157). Despite concerns over the potential for stimulant abuse in substance-abusing clients, there are reports that describe the efficacy of these medications among clients with active substance use disorders (147,150). Uncontrolled trials suggest that psychostimulants are safe and effective for individuals with comorbid ADHD and substance abuse, with respect to both alcohol and stimulant abuse/dependence. Two double-blind, placebo-controlled trials assessing the efficacy of methylphenidate in adults with ADHD included a small number of substance abuse patients (158,159). Both studies found that substance abusers receiving methylphenidate were more likely to have a reduction in ADHD symptoms than those receiving placebo. However, neither study reported whether methylphenidate produced changes in drug use (70).

Potential pharmacological strategies designed to treat both substance use and ADHD have focused primarily on individuals with cocaine dependence (15). This appears to be driven by the hypothesis that ADHD and cocaine dependence may be linked by a need for dopamine stimulation. That is, the use of cocaine may serve the purpose of increasing dopamine activity for individuals with ADHD (i.e., the self-medication hypothesis) (151). Levin and colleagues (147) conducted an initial clinical trial that assessed the efficacy of

methylphenidate for the treatment of adult ADHD and cocaine abuse. Significant improvements in ADHD symptoms as well as a significant decrease in cocaine use were reported. A subsequent double-blind, placebo-controlled trial comparing methylphenidate with placebo revealed significantly greater ADHD symptom relief associated with methylphenidate but no group differences on self-reported cocaine use, urinalysis results, or cocaine craving (151).

While methylphenidate is the best-studied stimulant (160), clinical trials of the mixed amphetamine compound Adderall (161) and magnesium pemoline (162) have proven to be efficacious in the treatment of adult ADHD. Magnesium pemoline (Cylert) has less abuse potential and longer action than many of the stimulants. However, administration of magnesium pemoline has been associated with rare hypersensitivity reactions, with elevations in liver function studies (ALT and AST) after several months of treatment (163). Thus, baseline and repeat liver studies are recommended. The FDA is now recommending biweekly liver function monitoring when magnesium pemoline is used (163).

Long-acting medications provide treatment throughout the day. These extended-release preparations greatly reduce untoward effects of stimulants, such as headaches and moodiness, which commonly occur as blood levels of short-acting medications peak. They also have the advantage of minimizing afternoon wear-off and rebound (163). Recently released preparations of methylphenidate include Concerta, Metadate CD, and Ritalin LA. These agents have an immediate onset of action and a duration of 8–12 hours. Adderall XR is designed to provide effective amphetamine treatment for 12 hours. Extended-release preparations may be of utility in treating adult ADHD patients with substance use difficulties, as there is a reduced peak effect and thus less potential to induce craving. Atomoxetine (Strattera) is a noradrenergic compound recently approved for the treatment of ADHD in children, adolescents, and adults. Atomoxetine is not a stimulant and has little or no abuse potential. As such, it may be a safe agent to use in a substance-abusing population, particularly among individuals with a history of cocaine or stimulant abuse.

In addition to the psychostimulants, noradrenergic and dopaminergic antidepressants such as certain tricyclic antidepressants (TCAs) and bupropion have been found to be superior to placebo for treatment of ADHD (163). These compounds have a long duration of action, little symptom rebound or insomnia, and minimal risk of abuse or dependence. Studies of the TCAs have shown both short- and long-term positive effects on ADHD symptoms (163). It has been suggested that antidepressant medications such as bupropion should be reserved for stimulant non-responders or for those who have concomitant depressive or anxiety syndromes.

As detailed throughout this chapter, substance abusers with ADHD represent a heterogeneous population. We (164) have recommended the use of psychostimulants in adult ADHD substance abusers who have a definite childhood history of ADHD and who have been abstinent for more than one month, but who do not have antisocial personality disorder or a history of stimulant (including cocaine) abuse. Antidepressant medications such as bupropion might be a reasonable initial choice for clients with persistent depression or anxiety during one month of abstinence. In contrast, antisocial individuals with a questionable history of ADHD, or who have abused stimulants, are unlikely

candidates for stimulant medications. Depending on the clinical circumstances, especially duration of abstinence, use of atomoxetine or antidepressants may be a suitable alternative, since they have low abuse potential.

When medications are used to treat ADHD symptoms in adult substance abusers, close monitoring and follow-up are indicated. If stimulants are provided, prescriptions should be written for the smallest reasonable amount. Unlimited refills are contraindicated. Risks for diversion to other individuals, increased cocaine craving, and significant cardiovascular effects should be assessed. Discontinuation of the medication should be considered if the clinician suspects that it is being diverted. With fastidious diagnosis, assessment, attention to prognostic factors, and close monitoring, adult ADHD substance abusers should receive the same consideration for pharmacological treatment as non-substance-abusing adults with ADHD. With attention to the issues discussed in this section, treating one disorder may have beneficial effects on the other, resulting in improved outcomes.

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12
Co-Occurring Schizophrenia and Addiction

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OVERVIEW OF THE PROBLEM

Substance use disorders are common among individuals with schizophrenia, and the comorbidity of the two disorders presents special challenges for diagnosis and treatment. Schizophrenia occurs in about 1–2% of the population; however, this disorder is much more common among patients receiving treatment in mental health settings, where having a co-existing substance use disorder is the rule and not the exception. Co-occurring schizophrenia and addiction is a great public health concern. The combination of disorders increases the cost of care and is associated with poor clinical outcomes, medication noncompliance, higher rates of hospitalization and emergency room visits, more violence and criminal activity, higher rates of HIV, hepatitis C, and greater risk of suicide.

Schizophrenia and substance dependence each have an associated set of impairments in cognitive, interpersonal, affective, and biological functions. When these disorders occur together, the interaction of these impairments leads each disorder to be more intractable. In addition, interactions occur among the underlying neurobiology, psychopathology, social correlates, treatment strategies, and health care systems associated with the two individual disorders. Hence, substance-abusing individuals with schizophrenia do not generally respond well to treatment approaches designed for patients with schizophrenia only or for patients with substance abuse only. The most successful treatment for comorbid schizophrenia and substance use disorders combines medications with a psychosocial therapy that utilizes both mental health and addiction approaches. This type of co-occurring disorder is best treated in a mental health setting that is capable of managing co-occurring disorders.

In this chapter, we describe the interacting impairments seen among patients with

comorbid schizophrenia and substance use disorders as they relate to the tasks of assessment, pharmacotherapy, and psychotherapy. This chapter describes the Motivation-Based Dual Diagnosis Treatment (MBDDT) and Dual Recovery Treatment models, which offer an approach to modifying and integrating traditional substance abuse treatment into mental health treatment. There are numerous models that describe how to adapt mental health system programs to address co-occurring alcohol, tobacco, and other drug use disorders. This chapter reviews many of the recent studies in this population, including new medication options.

Assessment Issues

Substance abuse and psychosis commonly occur together. In the Epidemiologic Catchment Area study, lifetime substance use disorders were found in about 47% of the individuals with schizophrenia, including 34% with an alcohol use disorder and 28% with a drug use disorder (1). Mental health treatment settings report rates of current substance use disorders in this population to be 25–75% (2). Recent data indicate that the amount of substance use among patients with schizophrenia may be increasing over time (3). However, these epidemiological findings represent a best guess about comorbidity, given the challenges of diagnosing substance abuse in the presence of schizophrenia and the problems of diagnosing schizophrenia in the context of substance abuse. In addition, about 70–85% of individuals with schizophrenia are nicotine dependent (4,5). Smokers with schizophrenia smoke a large number of cigarettes and are efficient smokers who are effective at inhaling a high percentage of the nicotine in cigarettes. About 44% of all cigarettes smoked in the United States are used by individuals with mental illness or addiction (6).

A diagnostic evaluation of schizophrenia assesses the presence of psychotic symptoms, including positive symptoms (e.g., hallucinations and delusions) and negative symptoms (e.g., flat affect, amotivation, poor attention, anhedonia, and asociality). Medical conditions and substance abuse can cause or exacerbate psychotic symptoms. Mood instability and cognitive impairment are common in the context of psychosis. The addition of chemical substances often increases and exacerbates these symptoms. Among patients with schizophrenia, even relatively small amounts of substances taken over a brief period of time may result in an exacerbation of psychiatric problems, loss of housing, frequent use of emergency room services, or an increased vulnerability to exploitation within the social environment (e.g., sexual, physical, or other abuse). Perhaps because of this sensitivity to substances, individuals with schizophrenia appear to progress quickly from substance use to dependence.

Two scenarios described below are often problematic for clinicians in establishing a diagnosis of schizophrenia and/or a substance use disorder. In the first scenario, the clinician is evaluating a new patient who presents with both psychotic symptoms and substance abuse. In the second scenario, the clinician is re-evaluating a known psychiatric patient with schizophrenia who presents with symptoms of an undiagnosed substance use disorder.

Scenario #1: Diagnosing Schizophrenia During Periods of Active Substance

Use

In the first scenario, the clinician attempts to differentiate schizophrenia from a substance-induced psychotic disorder. This task is not easy, especially when the patient's chronic psychiatric history is unknown. For example, intoxication from cocaine, amphetamines, PCP, marijuana, or formaldehyde can mimic the psychotic symptoms of schizophrenia or other psychiatric symptoms such as depression, anxiety, and mania. Breathing in formaldehyde via cigarettes or marijuana dipped into the chemical (often called "wet" on the streets) can cause a toxic delirium, rhabdomyolosis, and psychotic symptoms that can last six months. In addition, misuse of prescription drugs can produce symptoms of intoxication. Medication side effects can be mistaken for negative symptoms, and negative symptoms can be mistaken for depression. Substance abusers can also be poorly compliant in taking their medication, and relapse may be due to noncompliance.

In a longitudinal diagnostic study of 165 patients with chronic psychosis and cocaine abuse or dependence, a "definitive diagnosis" could not be established in 93% of the cases (7). To establish a definitive diagnosis of schizophrenia, the researchers required that a patient had to meet diagnostic criteria for schizophrenia at some point after six weeks of abstinence from substances. The patients were interviewed at multiple points over time (using the Structured Clinical Interview and DSM criteria) (8). Using these strict criteria, the primary reasons for not reaching a diagnosis were insufficient abstinence (78%), poor memory (24%), and/or inconsistent reporting (20%). A review of hospital records and collateral information addressed the problems of poor memory and inconsistent reporting, leaving insufficient abstinence as the primary barrier to establishing a diagnosis. The finding that most patients continued to use substances reflects the difficulty of treating this subtype. Often, clinical decisions must be made in the context of diagnostic uncertainty.

A study of cocaine-induced psychosis by Satel and Lieberman (9) suggests that a psychosis persisting for more than several days is most likely to represent an underlying primary psychotic disorder. However, patients who inhale or inject high doses of amphetamines or who smoke large amounts of the combination of marijuana and formaldehyde ("illy" or "wet") may develop psychotic symptoms that last for 3–6 months.

In the context of trying to establish a diagnosis to explain the psychotic symptoms of a new patient, clinicians can improve their diagnostic efforts by gathering information from all available sources, including patient interviews, hospital records, and collateral informants. A review of hospital records and collateral information can reduce the problems of poor memory and inconsistent reporting, yet insufficient abstinence continues to be the primary barrier to establishing a diagnosis. Ongoing longitudinal assessments can assist the clinician in making decisions about the use of antipsychotic medications in the context of diagnostic uncertainty.

From clinical experience, there is a group of patients that has chronic psychotic symptoms and actively abuses stimulants. These individuals can be extremely difficult to diagnose. Some have prominent affective symptoms and might have had a primary affective disorder if substance-free. There may be a strong family history of affective disorders (depression or bipolar disorder), onset of depression at an early age, and/or

stimulant abuse during the onset of psychotic symptoms. The treatment should address all problems through the use of lower dose atypical antipsychotic medication with consideration for an extended medication-free period after several months of abstinence.

Cravings and Relapse

Craving for alcohol or other drugs, particularly cocaine, can also complicate the diagnostic picture and is often accompanied by acute affective symptoms. These symptoms remit a few weeks after the last use. However, cravings can lead to relapse and continued negative consequences secondary to use. Carol et al. (10) compared cocaine craving among individuals with schizophrenia and cocaine dependence to cocaine-dependent individuals without schizophrenia. Their results suggest that the individuals with schizophrenia and cocaine dependence had significantly more cocaine craving than cocaine addicts without schizophrenia in regard to intensity, frequency, and duration of craving. In a follow-up study, Smelson and colleagues (11) again found that individuals with comorbid schizophrenia and cocaine dependence had significantly more cue-induced cocaine craving than cocaine-dependent subjects without schizophrenia. Their study used a cue-exposure laboratory, which is a method of inducing cocaine craving in a controlled laboratory setting by exposing the individual to a standard set of drug cues. Furthermore, 97% of the individuals with schizophrenia and cocaine dependence had an increase in craving following the presentation of the cocaine cues versus approximately 50% of those without schizophrenia. These findings suggest that cocaine craving is an especially important barrier to recovery for individuals with schizophrenia. Therefore, assessment of cravings is an important component of the evaluation process for these individuals at baseline and throughout the treatment process. We suggest the use of a craving scale that asks questions specific for each drug used. Unfortunately, many of these scales have not been standardized for use with individuals with schizophrenia. However, there has been a variety of studies that have used the Voris Cocaine Craving scale in this population. This scale is a short 4-item instrument (craving intensity, mood, energy, and overall feeling sick) that has shown good reliability and validity among cocainedependent patients without schizophrenia (12,13).

Scenario #2: Assessing Substance Use and Misuse Among Individuals with Known Schizophrenia

In the second scenario, individuals treated for schizophrenia have not been carefully screened for substance use and substance-related problems. Mental health staff may have limited training in identifying and treating the patient with co-occurring schizophrenia and addiction. A number of studies have demonstrated that mental health clinicians continue to under-recognize substance abuse in patients diagnosed with schizophrenia (14). Establishing a substance use diagnosis in psychiatric patients can be complicated, especially if the patient minimizes his or her substance-related problems and attributes those problems to other causes. Psychiatric patients tend to have more severe consequences from smaller amounts of substance use when compared to nonpsychiatric patients, and clinicians may be lulled into a false sense of security by focusing only on

the amount of substance use reported. Carey and Correia (15) make several suggestions regarding the assessment of substance use among individuals with schizophrenia. In an effort to increase the accuracy of self-reported substance use, they recommend making the assessment at a time when the patient is not under acute psychiatric distress and when not intoxicated as confirmed by urine and breath screens, if possible. In addition, it is important to be aware of circumstances that might motivate the patient to be deceptive, such as housing or other positive reinforcers being contingent on sobriety.

An initial assessment of alcohol, tobacco, and other drug use should be completed on every patient in mental health treatment settings. Co-occurring addiction among individuals with schizophrenia can usually be detected by asking patients about their use of substances, talking with significant others (family, friends, residential counselors, etc.), obtaining urine toxicology screenings, and utilizing substance abuse screening tools. The use of standard substance abuse screening instruments can be helpful in this population; however, the CAGE questionnaire did not do as well as in the general population (sensitivity of 0.6 and specificity of 0.7) (16–19). Studies vary in regard to the degree of accurate self-reporting that individuals with schizophrenia provide. In many addiction or integrated co-occurring disorder treatment studies, where patients are presumably motivated, laboratory tests and clinical examinations added little incremental predictive value to the self-report measures (20). This may not be the case in clinical situations with patients who are less motivated. One of the more promising instruments that is being designed to screen substance abuse among psychiatric patients is the Dartmouth Assessment of Lifestyle Instrument (DALI). The DALI was found to have an overall classification accuracy of 0.83 (0.85 specificity and 0.80 sensitivity) as an alcohol use disorder screen and 0.88 (0.80 specificity and 1.00 sensitivity) as a screen for drug (i.e., cannabis and cocaine) use disorders (21).

Urine toxicology and alcohol breathalyzer tests are invaluable tools, as denial of substance use among individuals with schizophrenia is common among the majority of less motivated patients. One study found that one-third of the individuals with schizophrenia who came to the emergency room were recent cocaine users. Of this group, 50% reported that they had not used cocaine recently (14). It is important, however, to recognize that urine drug screens are more likely to yield false negatives than false positives because of rapid excretion of some substances and high thresholds for drug detection (22).

A patient's smoking status can be a clue to a hidden substance use disorder. As with the general population, cigarette smoking is associated with other substance use among individuals with schizophrenia. Heavy smokers (more than 25 cigarettes per day) have rates of substance abuse three to four times that of nonsmokers (4,23).

Other screening clues for a substance use disorder include the occurrence of the common consequences of substance abuse. These consequences include episodes of homelessness, legal problems, verbal threats, violence, treatment noncompliance, need for a higher dosage of antipsychotics, multiple medical problems, frequent emergency room visits or hospitalizations, and suicidal ideation or attempts (24–26). It should be noted that the consequences of substance use among individuals with schizophrenia may be different than those among the general population. These differences are important to consider if one is using substance use screening measures developed for the general

population that focus on negative consequences or social functioning (15).

As in other substance abuse assessments, one should ask schizophrenic patients about their patterns of use (specific amounts, frequency, last use, route of administration), consequences of use, past treatment history, severity of symptoms, family history of both mental illness and substance abuse, perception of the benefits of continued use, as well as reasons and motivation to quit using each substance. The patient's motivation to quit and enter dual-diagnosis treatment is important for treatment planning.

Motivation to quit using substances is most commonly defined by Prochaska et al.'s five-stage motivational scale (precontemplation, contemplation, preparation, action, and maintenance) (27). Using these stages to evaluate a sample of 295 individuals with both schizophrenia and a substance use disorder, approximately 77% were assessed as having low motivation (precontemplation or contemplation), with the motivation varying according to the specific substance used and the presence or absence of polysubstance abuse. Low motivation was assessed in 53% who abused alcohol, 65% who abused cocaine, and 73% who abused marijuana (28). A simpler five-point Likert scale of current motivation for treatment was able to predict dually diagnosed patients' ability to become abstinent (29).

TREATING THE INDIVIDUAL WITH SCHIZOPHRENIA AND ADDICTION

Understanding the multidimensional aspects of schizophrenia helps researchers and clinicians develop treatment approaches for this unique dual-diagnosis subtype. Individuals with schizophrenia present with a number of pervasive and chronic vulnerabilities in the cognitive, emotional, interpersonal, and biological domains (30,31). These vulnerabilities impede traditional approaches to addiction treatment. Therefore, the goal of integrating mental health and addiction treatment is to modify addiction models to accommodate the needs of schizophrenic patients. Significant behavioral changes in individuals diagnosed with schizophrenia have been associated with integrated interventions based on a biopsychosocial model, i.e., psychotropic medications (biological intervention), social skills development (psychosocial intervention), and family therapy (psychosocial intervention) (32). Treating patients with comorbid schizophrenia and addiction requires both medications and psychosocial interventions.

We will now review the medication treatments for this population and the current understanding of the underlying neurobiology of schizophrenia and addictions. Subsequently, we will review the psychosocial interventions and how the biological, cognitive, affective, and interpersonal vulnerabilities inherent to schizophrenia must be considered in modifying traditional treatments for substance use disorders.

THE NEUROBIOLOGY AND PHARMACOTHERAPY OF SCHIZOPHRENIA AND CO-OCCURRING SUBSTANCE ABUSE

Interactions Between the Neurobiology and Pharmacology of Substance Abuse and Schizophrenia

Prior to discussing medication treatment strategies, we will briefly review the overlapping neurobiology of addiction and schizophrenia. This may partially explain why substances of abuse may be especially reinforcing to individuals with schizophrenia, through the combined mechanism of stimulating the brain reward center and ameliorating deficits in brain functioning (33). There are five primary findings from the literature on the interaction between disorders, substances, and medications: 1) both schizophrenia and addiction appear to have a primary neurobiological defect in the mesolimbic system; 2) substance abuse is generally associated with a more severe clinical profile, including functional impairment, psychiatric symptoms, and cognitive impairment; 3) some substances can impact the metabolism of medications and reduce the therapeutic effect; 4) there are some perceived positive effects of substance use that are reported by some patients; and 5) substances may be more frequently used by the higher prognosis patients.

Neurobiology

A central reward pathway is associated with the dopamine pathway that includes the ventral tegmentum area, the nucleus accumbens, and the prefrontal cortex. The ventral tegmental area is linked to the prefrontal cortex, which, some research has hypothesized, may be hypoactive in schizophrenia (23). Therefore, substances may be especially reinforcing in individuals with schizophrenia due to the combined stimulation of subcortical brain reward mechanisms and the hypoactivity of the prefrontal cortex.

Pharmacology

Each substance of abuse acts upon a variety of receptors in a unique manner, and has a unique pharmacological effect that modifies cognition, thought, and mood. Many substances (including caffeine, nicotine, marijuana, and cocaine) have a direct impact on dopamine and other neurotransmitters important in schizophrenia. The addition of substances often worsens the positive and negative symptoms of schizophrenia. Even relatively small amounts of substances taken over a short period of time may result in substantial biological, psychological, social, and spiritual problems. Individuals with schizophrenia appear to progress rapidly from substance use to abuse or dependence.

In addition, substances can interact with psychiatric medications used to treat the negative and positive symptoms of schizophrenia. The interactions are both pharmacokinetic (because of the drug's effect on the body) and pharmacodynamic (at the drug's site of action in the brain or body). Most substances of abuse interact with psychiatric medications and reduce their effectiveness; some can alter medication blood levels and increase side effects. For instance, coffee and tea, like cigarettes, are known to

interfere with the absorption and metabolism of some psychiatric medications as a function of their effects on liver enzyme (e.g., cytochrome P450 1A2 isoenzyme) activity. Cigarette smoking modifies the metabolism of psychiatric medications, including their potential side effects and effectiveness. The "tar" (polynuclear aromatic hydrocarbons) rather than the nicotine in cigarettes causes this interference (34). Smoking is known to decrease the blood levels of haloperidol, fluphenazine, thiothixene, olanzapine, and clozapine (35–39). Abstinence from smoking increases antipsychotic medication blood levels, and smokers are usually prescribed about double the dosage of traditional antipsychotic medications as compared to nonsmokers (4). The impact of smoking on the metabolism of antipsychotics is important in making treatment decisions with the hospitalized patient whose smoking habits were curbed and with the patient who is attempting to quit smoking.

About 25% of individuals with schizophrenia who are treated with traditional antipsychotic medications develop the side effects of a movement disorder (parkinsonism or tardive dyskinesia), and there is no effective treatment for tardive dyskinesia (40). Substance abuse may be associated with earlier and more severe cases of tardive dyskinesia (41–44). However, other studies have found that substance abuse had no effect on movement disorders when important covariables are considered (4,37,45).

The Negative Impact of Substance Use on Schizophrenia

Beyond just the pharmacological impact of the substance, the development of a substance use disorder results in negative medical, legal, vocational, social, family, and psychological consequences. Schizophrenia, in itself, profoundly affects an individual's ability to carry out day-to-day functioning in an industrialized society. Substance use may have a deleterious impact on the course of schizophrenia, but studies report that effects vary according to the type of substance used and the severity of the problem (46–49). As with all individuals, the impact of substances varies with the route of administration and the state of use—intoxication, acute withdrawal, protracted withdrawal, acute use, or chronic use. Moreover, the patient's psychiatric presentation may vary according to the type(s) of substance use and state of use. Depending on the type of substance used and the state of drug use, patients can demonstrate symptoms of mania, psychosis, depression, anxiety, cognitive impairment, or personality disorder. For example, cocaine withdrawal may appear similar to clinical depression in terms of dysphoric mood, suicidal ideation, nightmares, and psychomotor changes (50). Alcohol-abusing individuals with schizophrenia are more likely to manifest hostile threats, paranoia, incoherent speech, depression, and suicidal thoughts than non-alcohol-abusing individuals with schizophrenia (5).

Unfortunately, the picture is complicated by the fact that 35% of cocaine addicts have had an affective disorder during their lifetime (1). Among treatment-seeking cocaine addicts, 30% have a current affective disorder, and 62% have a lifetime history of an affective disorder (52). Other studies have shown that 20–50% of cocaine addicts have a lifetime history of depression (1,53,54) and 28–53% have concurrent depression (55). One method of teasing out whether the affective disorder is related to the recent use of alcohol or cocaine or a separate and discrete comorbid condition is to examine the

chronicity of the disorder, the precipitating factors, and whether it was present during periods of sobriety. Unfortunately, this requires that the individual be a good and reliable historian. Consequently, family or other collateral informants may be necessary to tease out these issues.

Individuals with comorbid schizophrenia and substance abuse have a poorer prognosis than those with schizophrenia only (56). Problems associated with this comorbidity include increases in hospitalizations, resource consumption, medication dosages, vulnerability to social dysfunction, and suicide attempts. People with this dual-diagnosis subtype also have more hospital emergency room visits, psychosocial problems, housing problems, financial problems, periods of homelessness, and nutritional deficiencies than the non-dually-diagnosed (18,19,57,58).

Cognition is another important factor that can significantly impact the functional outcome in this population. Among non-substance-abusing individuals with schizophrenia, greater cognitive deficits result in poorer prognoses and these individuals utilize more mental health services (59). Among non-substance-abusing individuals with schizophrenia, the literature supports a consistent pattern of neurocognitive impairment in executive functioning (60), attention, visuospatial skills, motor skills, and memory (61). These deficits result in significant functional impairments, with these individuals reporting difficulty in focusing their attention, filtering out distracting and irrelevant details, and concentrating on aspects of their environment or interactions that interest them (31). Chronic abuse of alcohol can result in substantial cognitive difficulties as well, especially on complex tasks that require simultaneous consideration of several elements. The severity of these deficits relates to the quantity of alcohol intake and the duration of the drinking problem (62). Because cognitive impairment can be a consequence of substance abuse and is a finding in schizophrenia, there is concern that cognitive impairment is compounded in patients with comorbidity.

There is also a growing body of evidence suggesting cognitive deficits in individuals who use cocaine. Cocaine addicts without schizophrenia show a diffuse and inconsistent pattern of impairment in attention (63), concentration (64), memory (65), concept formation (65), visual spatial ability (66), and perceptual motor speed (67). Unfortunately, many of the existing studies failed to match on age, education, and socioeconomic status, all of which could affect cognition. A recent study comparing cocaine abusers to age- and educationally matched controls showed that cocaine addicts did worse on tasks involving attention, concentration, and perceptual motor speed (68).

Researchers have recently begun to examine the impact of stimulant abuse on cognition among individuals with schizophrenia. The neuropsychological studies that have compared individuals with comorbid schizophrenia and cocaine dependence to individuals with schizophrenia alone have shown inconsistent results. For example, several studies suggest that those with schizophrenia and cocaine dependence have impairments in memory, verbal learning, executive functioning, and recall (68–70). Several other studies have shown contradictory results across neurocognitive domains. For example, several studies have shown that individuals with schizophrenia and cocaine dependence performed better on tests measuring attention and psychomotor speed, but significantly worse than those without cocaine dependence on tests measuring conceptual encoding and memory (68,71). Nikou et al. (72) used a brief computerized

neuropsychological test battery and found that the individuals diagnosed with schizophrenia and cocaine dependence performed significantly worse on tests of memory and executive functioning and significantly better on stimulus perception tests. Another study, comparing individuals with comorbid schizophrenia and cocaine abuse to those with schizophrenia only, found no significant cognitive differences (73). Unfortunately, the studies to date have not matched the groups on factors that could negatively impact cognition, such as quantity, frequency and time since last use, age, education, and symptom severity. It is interesting to note that patients with co-occurring substance use disorders and schizophrenia may present as more disorganized than schizophrenics without co-occurring substance use disorders, although they are seen as more socially skilled (74).

The Perceived Positive Effects of Substance Use

Despite the negative consequences associated with substance abuse, some individuals report that using substances helps them cope with symptoms of schizophrenia (75). They report using substances for pleasure, to alleviate boredom, to relieve feelings of anxiety, sadness, or distress, and to share the excitement of "getting high" with friends who are also using. In one study, the most common reason reported by the patients for using substances was "something to do with friends" (76). Some individuals report that substance use reduces their social inhibitions. The self-medication theory suggests that individuals may use chemicals to self-medicate the symptoms of schizophrenia; however, the research data supporting this clinical perception are mixed (56,77).

Individuals with schizophrenia may develop depressive symptoms secondary to post-psychotic depression, negative symptoms of schizophrenia, and/or antipsychotic side effects (78). Some patients report less depression and anxiety, improved sleep, and more energy when using substances (79). However, this appears to be only a temporary effect with some substances, and clinical experience suggests that patients develop increased depression, anxiety, and insomnia during the acute and protracted abstinence periods. One study found that individuals with a psychotic disorder who abused alcohol had higher rates of depression than those who did not abuse alcohol (80). Some patients with chronic auditory hallucinations report using alcohol excessively, even to the point of drinking until they pass out, as a temporary escape from the voices (57).

As with alcohol, some patients report that cocaine or amphetamine use initially improves their mood and decreases their hallucinations and negative symptoms (81–84). However, clinical observations and other research studies suggest that stimulants exacerbate psychotic symptoms, increase mood lability, and interfere with sleep in individuals with schizophrenia (85–87). Serper et al. (84) compared symptom severity among individuals with schizophrenia and cocaine dependence versus those without cocaine dependence who presented to a psychiatric emergency room. They found that the patients with schizophrenia and cocaine dependence had more positive symptoms, including delusions and hallucinations. Cannabis is another drug that can increase delusions, hallucinations, anxiety, and depression (86). From clinical experience, increased negative symptoms during the acute and protracted withdrawal period may explain some of the continued use despite consequences.

Some studies have shown that the dually diagnosed substance abusers have lower levels of negative symptoms and more anxiety and depressive symptoms than non-substance abusers (81,83,87). However, others report no difference in the negative or positive symptoms (88).

Ziedonis et al. (4) found that current smokers had significantly higher levels of positive symptoms than nonsmokers, and that heavy smokers had the highest rate of positive symptoms. Smokers also experience greater medication side effects such as tremor (89), rigidity (4), and possibly tardive dyskinesia (90–92). In contrast, heavy smokers had significantly fewer negative symptoms than nonsmokers or light smokers. Others found that individuals with schizophrenia who smoke have higher levels of both positive and negative symptoms than nonsmokers, and no differences in levels of depression (93). Hamera et al. (94) found that individuals with schizophrenia who decreased their nicotine use reported significantly more prodromal psychotic symptoms.

Recent studies suggest that individuals with schizophrenia may smoke to help improve their attention and concentration (95). One research group found that smoking may transiently normalize deficits in auditory physiology (P50 gating) that are found in individuals with schizophrenia (95,96). These deficits may be caused by a genetic defect in the nicotinic cholinergic receptors in some individuals (95,96). Evidence suggests that this deficit of P50 gating among patients with schizophrenia is related to a desensitization of the α7-nicotinic receptor (97). One study found that individuals with schizophrenia who smoked a cigarette less than 10 minutes before being evaluated for sensory gating abilities had significantly greater sensory gating normalization than nonsmokers or individuals with schizophrenia who smoked more than 10 minutes before the experiment (98). Since almost all of the studies on the positive and negative consequences of substance use are cross-sectional studies, longitudinal studies are needed to understand the complex relationships between various substances and symptoms of schizophrenia.

Medications to Treat Comorbid Substance Abuse and Schizophrenia

In the medication management of patients with comorbid substance abuse and schizophrenia, one must first consider the best means for treating the schizophrenia, followed by a consideration of the potential interactions between the abused substances and the medication options. In general, clinicians should avoid prescribing medications that cause sedation when treating patients who abuse sedating substances. In addition, clinicians should generally avoid prescribing medications with abuse liability (e.g., benzodiazepines, stimulants).

The initial goals of pharmacotherapy for this dual-diagnosis subtype are to reduce and stabilize the positive and negative symptoms so that the individual can better engage in psychosocial interventions and function in the community. The traditional antipsychotic medications (haloperidol, fluphenazine, etc.) only treat the positive symptoms of schizophrenia, while the newer atypical antipsychotic medications (risperidone, clozapine, olanzapine, etc.) can be very effective in reducing both the positive and negative symptoms of schizophrenia.

Patients presenting to an emergency room or inpatient unit may require detoxification as well as the initiation or reinitiation of an antipsychotic medication. The treatment goals

of detoxification are to reduce the symptoms of withdrawal and to prevent serious withdrawal complications such as the development of seizures or delirium tremens. New patients who present a diagnostic dilemma might first be detoxified and further assessed prior to the initiation of antipsychotic medications. Individuals known to have schizophrenia usually require the simultaneous administration of both antipsychotic medication and detoxification medication.

Patients presenting with active substance abuse, psychotic symptoms, and noncompliance can be difficult to manage in an outpatient setting. Medication compliance in outpatients may be enhanced through reducing positive and negative symptoms, providing psychoeducation and social skills training on medication management, using motivational enhancement techniques to improve compliance, and switching the route of administration of the medication from oral to long-acting injected medication.

A first-choice medication treatment option for this dual-diagnosis subtype is the use of newer atypical antipsychotic medications (e.g., clozapine, risperidone, olanzapine, quetiapine, ziprasidone). Compared to the traditional antipsychotics, the atypical antipsychotics have improved efficacy for the treatment of negative symptoms, cause fewer movement disorder side effects, and offer a different receptor-binding profile (99). The atypicals have an affinity for the serotonin receptors that may be important in the neurobiology of cocaine and alcohol dependence.

The atypical antipsychotics help in the treatment of the low-motivation dually diagnosed patients by stabilizing their schizophrenia and reducing their negative symptoms. Negative symptoms may have an important role in the etiology and/or maintenance of substance abuse among individuals with schizophrenia. Some patients may attempt to self-medicate their negative symptoms through the use of substances. Clinical observations indicate that many patients demonstrate increased negative symptoms during the acute withdrawal and protracted abstinence period.

There is an emerging literature suggesting that atypical antipsychotics, including clozapine, risperidone, olanzapine, and quetiapine, may be especially useful in treating individuals with co-occurring schizophrenia and addiction. These medications appear to help in the management of schizophrenia, but have secondary effects on the treatment of the substance use disorder. Unfortunately, many of the studies of addiction treatment in this population have used retrospective or open-label designs and include individuals with schizophrenia and polysubstance dependence. Zimmet et al. (100) did a retrospective survey of substance use in patients with schizophrenia or schizoaffective disorder and found that the initiation of clozapine was associated with reduced alcohol and polysubstance use. A retrospective data analysis from the New York Office of Health database of 21 hospitals also showed that clozapine was associated with improved psychiatric symptoms and psychosocial functioning in dual-diagnosis patients (101). Buckley et al. (102), in an open-label study, found substantial reductions in substance abuse at 6-month follow-up in the dually diagnosed patients switched from a traditional antipsychotic to the atypical clozapine. Additionally, clozapine may diminish the subjective pleasurable response to cocaine in patients with schizophrenia (103). Several other naturalistic studies that have also included case management suggest that individuals who received clozapine had greater substance use disorder remission than

those treated with other medications (104–106). In addition, in a recent 12-month open-label trial, olanzapine showed some benefit in the treatment of individuals with schizophrenia and a substance use disorder (107). Although more double-blind, randomized, controlled studies are needed, the existing data suggest that clozapine and olanzapine are useful for treating both the symptoms of schizophrenia and the comorbid substance use disorder.

There have also been several focused and reasonably well-controlled studies that have examined the use of atypical antipsychotics as anticraving agents among individuals with schizophrenia who primarily abuse cocaine. These studies have targeted the craving state early in recovery because the acute use of cocaine results in a significant increase in dopamine neurotransmission, which can last for several weeks after last use (108–110). Furthermore, individuals with schizophrenia and cocaine dependence have a heightened craving state that persists early in recovery (10,111) and may be due to the increased dopamine neurotransmission as a result of schizophrenia and the acute use of cocaine. In the pharmacological studies examining the use of patients taking typical antipsychotics, those patients receiving risperidone showed a significant reduction in cue-elicited cocaine craving, substance abuse relapses, and symptom severity (111). In this study, risperidone was dosed at 3–6 mg daily at the discretion of the study physician. More recently, a double-blind, randomized trial of olanzapine vs. haloperidol was conducted with 31 cocaine-dependent patients with schizophrenia. Upon completion of the study, patients treated with olanzapine showed significantly less cue-elicited craving on two out of four craving dimensions and fewer substance abuse relapses than those treated with haloperidol (112).

On the basis of our clinical experience, the atypicals are first-choice agents for individuals with co-occurring schizophrenia and addiction. Their additional advantage is lower risk for extrapyramidal side effects at therapeutic dosages. However, there are some risks associated with the prescription of atypical antipsychotics to dual-diagnosis patients. Patients who continue to use alcohol or other sedating drugs could have a synergistic reaction, with increased somnolence and orthostatic hypotension. In addition, some substance-abusing patients prefer to choose when they are sedated and are often less compliant with sedating medications. Patients receiving clozapine are at higher risk of a seizure than patients receiving other atypical antipsychotics. Finally, smoking cigarettes substantially lowers blood levels of clozapine and olanzapine by increasing hepatic metabolism, a moderate effect that may necessitate an increase of medication dosage. The metabolism of both sertindole and risperidone is not significantly affected by changes in smoking status (36).

Another important medication option is the use of long-acting injectable medications. This is an underutilized intervention that has an important role in improving medication compliance, especially for those with lower motivation to quit using substances. Injectable medication guarantees medication compliance when administered. The injectable standard antipsychotics (e.g., haloperidol and fluphenzine) helped reduce positive symptoms, rates of psychotic relapse, and rehospitalization when compared to oral traditional antipsychotics (113). Risperidone as a depot formulation is expected to be approved in the United States soon.

Medications Targeting the Substance Use Disorder

All patients with schizophrenia and substance abuse require stabilization of their schizophrenia before medications are used to manage additional psychiatric problems such as comorbid depression or comorbid substance abuse. Medications that target specific substance use disorders are used for detoxification, craving reduction, relief of protracted abstinence symptoms, and as agonist maintenance agents. These medications vary according to the specific substance use disorder(s) (e.g., alcohol, cocaine, opiates, nicotine). Some of these medications may also help to reduce and stabilize the negative symptoms of schizophrenia. Unfortunately, there has been limited research on pharmacotherapy for comorbid substance abuse and schizophrenia. There is, however, a growing clinical experience with medications for this indication, which shows that they can be used safely and effectively.

Adjunctive medications that are approved by the FDA for use in the treatment of alcohol dependence include disulfiram (Antabuse) and naltrexone (ReVia). Clinical experience with Antabuse is mixed in this population, but randomized control trials are lacking. Because of the potential alcohol-Antabuse reaction, the patient must be able to fully understand the risks of the medication and have the judgment to not drink because of the risk. At high doses of Antabuse (1000mg/day), some clinicians have reported psychotic symptoms in alcoholics without comorbid disorders. At the lower dose of 125–250 mg, the medication is well tolerated among individuals with or without a dual-diagnosis.

In nonpsychiatric patients with alcohol dependence, the use of naltrexone has been found to be an effective agent in some studies (114,115) and ineffective in others (116,117). Clinical experience, however, suggests that naltrexone may help to treat patients with schizophrenia and alcohol dependence, especially in patients for whom the use of Antabuse is a concern (118,119). Researchers have speculated that the adjunctive use of an opioid antagonist may help reduce the negative symptoms of schizophrenia. Research findings, however, have yielded mixed results. Naloxone did not improve symptoms in one sample of medicated patients with schizophrenia (120), but another study found that naloxone significantly decreased psychiatric symptoms—specifically, tension—on the BPRS rating scale (121). Opioid antagonists may have a role in improving psychiatric symptoms, and these data suggest that such medications are well tolerated by this population and do not increase psychiatric symptoms.

Studies to date have not shown any serious negative interactions of naltrexone with other psychiatric medications (including antipsychotics, lithium, and antidepressants). One case report described two patients with schizophrenia who were treated with thioridazine; the addition of naltrexone resulted in increased lethargy and somnolence (122). No drug interaction was noted between naltrexone and several antidepressants in a study with over 500 subjects (123). Randomized control trials are needed among individuals with comorbid schizophrenia and alcohol dependence.

Until pharmacotherapy strategies are better evaluated in patients with comorbid schizophrenia and substance use disorders, empirically supported strategies for the non-dually-diagnosed must be considered. Pharmacotherapy strategies for non-dually-diagnosed cocaine addicts have focused on medications with specific dopaminergic

activity that might reverse or compensate for the neurophysiological changes that result from chronic cocaine administration. Cocaine is a potent dopamine reuptake blocker with an acute effect of increasing activity in dopamine pathways, including endogenous reward systems. Chronic cocaine administration results in a supersensitization of pre-synaptic dopamine autoreceptors, which increases the threshold for activation of (and hence down-regulates) the dopaminergic system (124,125).

Numerous studies have evaluated dopamine reuptake blockers and dopamine agonists among cocaine addicts without comorbid psychiatric disorders, and most of these studies failed to find clinically significant improvements in outcomes (126). Of note, several studies suggest that the depressed cocaine addict may benefit from antidepressants (127,128).

Treatment guidelines for nicotine dependence have only recently been developed (129,130). The recommended treatments include multicomponent behavioral therapy and adjunctive use of transdermal nicotine patch, nicotine gum, nicotine spray, bupropion SR, or clonidine. More recently, the U.S. Food and Drug Administration approved a nicotine lozenge for tobacco dependence treatment. This nicotine preparation is not mentioned in the guidelines since it was not FDA approved at the time of the publications, but a well-controlled trial has supported its use (131). Unfortunately, nicotine dependence is often ignored in clinical settings and researchers are only beginning to study tobacco dependence treatments for smokers with schizophrenia.

Ziedonis and George (132) tested the effectiveness of a smoking cessation program in a pilot study of 24 patients with schizophrenia. The treatment program included group therapy, individual Motivational Enhancement Therapy, and nicotine replacement therapy (transdermal nicotine patch and/or nicotine gum). Despite the fact that approximately 75% of patients attending the program described themselves as not ready to quit within the next 6 months (precontemplation stage of change), 40% reduced the number of baseline cigarettes smoked by half and 13% remained abstinent for at least 6 months. In a follow-up study, the transdermal nicotine patch combined with a specialized smoking cessation group therapy program that was modified for patients with schizophrenia was found to show significantly higher rates of continuous smoking abstinence in the last 4 weeks of a 12-week trial than attendance at a standard American Lung Association group (133). Point prevalence abstinence rates did not differ between groups at the end-point. It is important to note, however, that patients taking atypical antipsychotics enjoyed significantly higher abstinence rates than those taking older, typical antipsychotics.

Addington et al. (134) examined the effectiveness of the American Lung Association's group treatment modified for smokers with schizophrenia (in combination with transdermal nicotine patch therapy) and found that 42% of patients were able to stop smoking by the end of treatment and 12% remained abstinent at 6 months. Although the study was limited by the lack of a control group and cessation rates were lower in the study than for the general population of smokers, the study by Addington et al. (134) represents a promising beginning and indicates the need for further research with this population.

The three most recent interventions for smokers with schizophrenia that were reported in the literature (135–137) examined bupropion SR combined with varying degrees of

psychosocial interventions. Evins et al. (136) examined 19 smokers with schizophrenia who participated in a 12-week, double-blind, placebo-controlled trial of bupropion SR (150mg daily) while attending a cognitive-behavioral group therapy for tobacco dependence. Seven participants reduced their baseline cigarette consumption by at least 50% (six of nine receiving bupropion SR and one of nine receiving placebo) and one (receiving bupropion SR) was abstinent at 6 months as verified by self-report and low carbon monoxide breath concentrations. The modest results may be related, in part, to the lower-than-recommended dose of bupropion SR.

In a double-blind, placebo-controlled trial, the recommended dose of bupropion SR, 150mg twice daily, was administered to smokers with schizophrenia. Treatment also included three weeks of Motivational Enhancement Therapy followed by six weeks of psychoeducation, social skills training, and relapse prevention (137). A higher proportion of patients receiving bupropion SR achieved four weeks of continuous abstinence at the end of the trial than those receiving placebo (50% vs. 12.5%). These findings were not maintained at a 6-month follow-up, perhaps due to the discontinuation of medication and group therapy after only 10 weeks. As in previous research (133), antipsychotic medications had an effect on treatment outcome in this study (137). Patients receiving bupropion SR and taking an atypical antipsychotic medication experienced a significantly greater quit rate than those in either group taking typical antipsychotic medications.

An additional open-label trial of bupropion SR with adjunctive supportive group therapy was conducted with eight smokers with schizophrenia (135). Although none of the patients were able to achieve abstinence from cigarettes, mean expired carbon monoxide readings decreased throughout the treatment phase of the study from 39ppm at baseline to 12 ppm at the end of the trial (135).

Besides the finding that smokers with schizophrenia are, indeed, capable of quitting smoking, these studies also dispel the common misconception that smoking cessation among patients with schizophrenia worsens psychiatric symptoms. Additionally, a randomized, double-blind study of placebo vs. nicotine transdermal patch was designed to determine the effects of acute nicotine withdrawal on psychiatric symptoms in smokers with schizophrenia. Over a 3-day period of abstinence, neither antipsychotic-induced parkinsonian symptoms nor the total score on the Brief Psychiatric Rating Scale (BPRS) was significantly changed as a function of patch status (138).

A third conclusion from this line of research is that atypical antipsychotic medications are associated with a better chance of quitting smoking than typical antipsychotic medications (133,137). Two studies found significant reductions in nicotine use among smokers with schizophrenia who were switched from a traditional antipsychotic to clozapine (39,139). The mechanism explaining this reduction in nicotine use is unknown. One possible explanation is that smokers had been selfmedicating negative symptoms through the use of nicotine, effects that are mediated through the nicotine receptors on dopamine tracts connecting to the frontal lobe. The switch to an atypical antipsychotic may have provided better management of negative symptoms than the traditional antipsychotic by targeting the same tracts to the frontal lobe of the brain. These findings might also be attributed, with equal plausibility, to a pharmacokinetic interaction of nicotine and the antipsychotic medication, with the atypical being less susceptible to nicotine-induced reductions in plasma concentration than the typical antipsychotic.

Medications have an important role in treating the positive and negative symptoms of schizophrenia and can be helpful during detoxification and early protracted abstinence from substances. Further pharmacotherapy research is needed in this population, especially to evaluate the relative effectiveness of specific antipsychotics. Medications are not magic bullets, and psychosocial treatments offer practical strategies to help engage with the patient, manage crises, and develop skills needed to manage the triggers that can lead to substance use relapse and psychotic relapse. Psychosocial treatment can help the patient develop a map of recovery and stay on that path.

PSYCHOSOCIAL TREATMENTS

General Considerations

Psychosocial approaches are an integral part of treatment for individuals with substance abuse and schizophrenia. A broad range of psychosocial interventions has been developed for integrated dual-diagnosis programs, including case management, self-help groups, family involvement, vocational and recreational interventions, Relapse Prevention, 12-step recovery, motivational enhancement interventions, and, more recently, the Community Reinforcement Approach (CRA). Dixon and Rebori (140) provide a comprehensive review of these interventions.

The implementation of psychosocial interventions has varied among dual-diagnosis programs, with the emphasis ranging from assertive case management to motivational enhancement interventions (26,141–147). The substance abuse psychosocial treatments that appear to be fundamental to dual-diagnosis treatment are Motivational Enhancement Therapy (148), Relapse Prevention (149), and 12-step facilitation. These three interventions are described in therapy manuals developed by the NIAAA's Project MATCH, and these manuals are available free of charge from the National Clearinghouse on Alcohol and Drug Information (NCADI, 1–800–729–6686). However, clinical experience suggests that these three treatment approaches need modification for use in the treatment of patients with schizophrenia, due to the vulnerabilities associated with that disorder.

Modification of the Primary Substance Abuse Psychosocial Interventions

The biological, cognitive, affective, and interpersonal vulnerabilities inherent to schizophrenia underlie the need to modify traditional psychosocial treatments for substance use disorders. Five factors form the basis for modification of the traditional treatments: the therapeutic alliance, low motivation, cognitive limitations, low self-efficacy, and maladaptive interpersonal skills.

Establishing a Therapeutic Alliance

The basic principles that guide the relationship between the patient and the clinician remain intact in dual-diagnosis treatment. As with all psychosocial and psychotherapy

interventions, an underlying assumption is that a strong alliance is necessary but not sufficient for treatment to work. In fact, the alliance is considered an active ingredient of treatment and is fundamental to a positive treatment outcome (150). Luborsky (151) reports that the therapeutic alliance is a reliable predictor of outcome. For a review of the therapeutic alliance and psychotherapy, see the *Handbook of Psychotherapy Research and Behavior Change* (152).

It has been well documented that individuals with schizophrenia can be difficult to engage in psychosocial treatment. Although many may accept medication from their clinicians and assist in the monitoring of side effects, their engagement in the face of additional demands, such as regular attendance in group and day hospital activities, is often erratic and inconsistent. In addition, individuals with both schizophrenia and substance abuse are more distant in relation to the therapist than non-substance-abusing individuals with schizophrenia. Many dually diagnosed individuals are less amenable to psychological and pharmacological interventions and avoid contact with mental health treatment staff. Furthermore, some literature suggests that many individuals who abuse substances demonstrate antisocial traits. Combining these observations, it may be concluded that the dually diagnosed are less likely to develop a positive therapeutic alliance than either non-substance-abusing patients with schizophrenia or nonpsychiatric patients with a substance use disorder. In spite of this, there is agreement that a positive therapeutic alliance is central to the success of psychosocial interventions with patients with schizophrenia.

Recent reports highlight the distinctive needs of the individual with schizophrenia; unlike other diagnostic subtypes, the individual with schizophrenia will best respond to a positive alliance, one based on support, consistency, nurturance, and a nonjudgmental attitude on the part of the therapist (153–158). Siris and Docherty (153) maintain that this same alliance must be developed with the substance-abusing individual with schizophrenia. A relationship based on fear, anger, or rejection may result in early termination and psychiatric deterioration. In a similar vein, Shein describes the ideal therapeutic alliance with the patient with schizophrenia as “a lever to motivate the acquisition of requisite interpersonal skills and the full utilization of available reality supports” (159, page 95). Patients seem to recognize the importance of the therapeutic alliance. This is evidenced by a focus group organized by Maisto and colleagues (160) where patients with schizophrenia spectrum disorders reported that relationships with their individual therapist were an important part of their recovery.

The therapeutic alliance is not the sole responsibility of the therapist. In providing a stable, consistent frame that communicates warmth, empathy, and acceptance, the therapist takes the first step toward a positive relationship. However, the patient has to come to treatment with some potential to form a trusting relationship. Recent studies in psychoanalysis revealed unsettling conclusions (161,162). It was found that individuals with schizophrenia had profound deficits in their ability to form and maintain relationships. Instead, their relationships were characterized by an absence of basic trust and an even more profound absence of belief that relationships can be gratifying. Not surprisingly, their social relationships were often superficial, lacking any sense of connectedness. Anger and hostile withdrawal were common, and empathy for others was quite limited. This configuration of interpersonal style suggests that developing a

therapeutic alliance can be difficult, so that working with the dually diagnosed patient requires a primary focus on the therapeutic alliance. Explicit interventions are needed to address the alliance with this patient group. Specifically, a nonconfrontational, supportive frame is needed. There is evidence that a long engagement phase of six months to several years may be required (162).

Low Motivation

Motivation has been identified as an important variable in addiction treatment, and Motivational Enhancement Therapy (MET) was developed to increase the patient's motivation for entering treatment and stopping substance use. However, MET was developed to help individuals without a serious mental illness, most of whom have relatively functional lives in which the main complication is an alcohol problem. In contrast, most of the chronic dual-diagnosis patients seen in psychiatric settings present with a more complicated picture. Their chief characteristics are a very low level of motivation and an impoverished lifestyle. The MET approach is useful for treatment of these individuals, but must be modified and elaborated to fit this picture.

Traditional MET techniques are described in *Motivational Interviewing* and the NIAAA Project MATCH *Motivational Enhancement Therapy Manual* (148,163,164). MET is based on the recognition that substance-abusing individuals vary in their readiness for change, and it attempts to build motivation for change and strengthen the commitment to change through "empathic exploration." MET is based on the transtheoretical model articulated by Prochaska and DiClemente (165), which organizes a motivational conceptualization of the processes underlying change. The model emphasizes the fundamental role of ambivalence in change processes and the role of vacillation between levels of readiness. The concept of relapse is an integral part of a continuous change process. MET combines Motivational Interviewing and personalized feedback tools.

Traditional MET must be modified for the dual-diagnosis population in several ways. First, the dually diagnosed require an active clinician who provides concrete and tangible solutions to day-to-day survival issues, rather than assuming that individuals will uncover their inner resources on their own, outside of the session. Second, MET is an ongoing part of treatment rather than a four-session treatment, as originally developed for nonschizophrenic substance users. Third, the task of using the decisional balance intervention, a major tool for MET, requires that the clinician explore the subjective experience of using drugs and having a second, more pervasive problem: schizophrenia. Lastly, individuals with a dual-diagnosis may fluctuate in their acceptance of the diagnosis of schizophrenia and their motivation to adhere to the schizophrenia medication regimen over time. The clinician's efforts at increasing motivation to address the substance use disorder must not deny or minimize the problems associated with schizophrenia and the need for medications to manage them.

MET is especially helpful for the less motivated dually diagnosed patients who do not perceive their substance use as a problem. These individuals do not perceive a need for change, nor do they seek treatment. The low-motivation patient minimizes the physical risks or complications of substance use on mood or its impact on thought processes, or

even its impact on significant others. The therapist attempts to engage the patient in a discussion about his or her substance use in an open and nonjudgmental approach, using "empathic exploration." The therapist attempts to elicit "change talk" from the patient regarding issues or problems related to substance use. A useful MET technique is to ask patients to discuss or write a "decisional balance" of the pros and cons of their continued substance use and of stopping their substance use. Although traditionally used among patients without comorbid psychiatric disorders, and in individual sessions, this strategy was found to be feasible among patients with schizophrenia spectrum disorders when delivered in a group setting (166).

Motivational Interviewing has been associated with greater initial outpatient treatment attendance (167) and treatment engagement (132) in psychiatric populations. Modifications may be necessary for the dually diagnosed, and have recently been described for patients with comorbid psychotic and substance use disorders (168). In addition, data indicate that smokers with schizophrenia who have low motivation to quit are more likely to seek treatment for tobacco dependence after a session of Motivational Interviewing than after either a session of psychoeducation about smoking or a minimal contact control intervention (169).

The low-motivation patient is likely to discuss reasons for continued use and the perceived benefits of use. Some may disclose their sense of hopelessness or their fears of quitting use of the substance. General discussions about their lives, goals, and hopes may lead them to take a different look at their substance use and their feelings of ambivalence about substance use. In MET, patient resistance is seen not only as an indication of the patient's ambivalence towards change, but as an important indicator of movement along the change continuum. Ultimately, the patient may reconsider the need to reduce or eliminate substance use. Often, the most difficult part of MET for the clinician is to refrain from providing advice, agreement or disagreement, interpretation, lecturing, or judgment.

Unlike many nonpsychiatric addicts, individuals with schizophrenia and a substance use disorder have fewer opportunities and advantages in their lives that might be threatened by using substances. In fact, most of these dually diagnosed patients demonstrate the following qualities. 1) They have limited interpersonal relationships—often the context of using substances provides a pseudo-social exchange in which the individual perceives co-substance users as "friends." 2) They may have uninvolved or rejecting family members, which for many addicts without schizophrenia is a primary source of motivation that can easily be generated in a MET session. 3) They may struggle with unstable living arrangements, including homelessness. Therefore, the loss of property due to substance use is not a threat as it can be for addicts without schizophrenia. 4) They have limited resources for recreation. Essentially, they appear to have less to lose by using substances and, therefore, less incentive to change. As a result, MET for dual-diagnosis must be modified to include ongoing contacts in which MET tools are utilized; intensive case management to facilitate alternatives that may improve the immediate quality of life for patients, especially those who live in shelters and transient housing; active participation by the clinician in making direct suggestions to help reduce substance use; and the reinforcement of other positive behaviors in patients' lives, i.e., taking medications as prescribed, exercising, eating tasty and healthful foods.

Cognitive Limitations

Wallace et al. identified cognitive skills as Receiving-Processing-Sending (RPS) skills (170). The psychosocial interventions used in addiction treatment assume that an individual can receive, process, and respond to information in an organized, meaningful way. Unfortunately, individuals with schizophrenia have problems with RPS skills, and these skills are necessary for individuals to fully engage in substance abuse interventions such as Relapse Prevention therapy. Relapse Prevention therapy is based on a cognitive-behavioral perspective, and change is believed to occur when the therapist helps the patient to unlearn "bad habits." It is based on the principles of classical and operant conditioning and social learning theory (which posits that people learn through interactions with their environment) (171). It assumes that within a teacher-student model of treatment, using cognitive learning strategies, individuals can identify high-risk situations and develop alternative behaviors to either avoid or escape situations which induce craving or which have been associated with using.

Applying this RPS system to relapse prevention skills, receiving (R) skills identify the existence of a high-risk situation, processing (P) skills organize the information received and develop a problem-solving strategy for the high-risk factor, and sending (S) skills execute a behavioral response which avoids or escapes the problem. Cognitive treatments are based on the assumption that a person has functional RPS skills (172) such as those needed to prevent relapse. If one's psychiatric symptoms (e.g., hallucinations, delusions, poor attention and concentration, heightened anxiety, or depression) interfere with the ability to process what is being presented by a situation, cognitively based relapse prevention is likely to be ineffective. This is especially important if cues that indicate a high risk using situation are not appreciated because of the individual's psychiatric symptoms. However, it is important to note that the dysfunction may be a receiving, processing, or sending skill, and treatments need to address all three RPS skills due to the pervasive nature of maladaptive cognitive functions.

Cognitive impairment in the dually diagnosed with schizophrenia may also impede traditional addiction treatment approaches. For example, cognitive impairments and difficulties in attention, memory, and reality orientation reduce the benefits of traditional relapse prevention approaches based on a cognitive learning model (149) (see Tracy et al. (31) for a review of the neuropsychological impairments associated with schizophrenia and substance use). The traditional learning or change environment of many of the cognitive therapies is based on the assumption that individuals process and interpret information in a logical, rational manner. This may not be the case with individuals with schizophrenia. Therefore, the goal of an integrated mental health and addiction treatment is to modify addiction models to accommodate the difficulties associated with schizophrenia. The cognitive-behavioral therapy of relapse prevention must be made more behaviorally centered in dual-diagnosis treatment, compared with the cognitive centering in substance abuse treatment.

Self-Efficacy

The underlying prerequisites of psychosocial interventions for preventing relapse are that individuals must be motivated to change, and must believe they have the ability to learn what to do to change. When clinicians use MET with patients who do not have schizophrenia, they assume that patients have a number of higher functional areas in their lives that promote a sense of self-esteem and self-efficacy (173). The degree of self-efficacy plays a fundamental role in the change processes involved in maintenance and relapse (149,174–176). As individuals approach the stage of motivation where they are preparing to change, MET assumes that they have a sense of self-efficacy, i.e., a belief that they have the ability to change. Traditional relapse prevention interventions were designed to facilitate and heighten the sense of self-efficacy by building skills which help reduce the probability of using substances (149).

Dual-diagnosis treatment incorporates relapse prevention as an important component of treatment. However, modifications are needed because of the pervasive vulnerabilities associated with schizophrenia. In addition to very low motivation, individuals with schizophrenia show extremely low self-efficacy and self-esteem (177,178). Bandura's research has shown that, when attempting a difficult task, individuals with high self-efficacy persevere until they succeed (179). In contrast, low-self-efficacy individuals often give up after early failures. These data have significant relevance for the change processes for substance use problems. Individuals are expected to have intermittent failures, i.e., relapses, before achieving maintenance. This suggests that the dually diagnosed individual with very low self-efficacy is more likely to disengage from Relapse Prevention treatment.

Based on the fundamental role of self-efficacy in change processes for substance use disorders, traditional relapse prevention is difficult for individuals with schizophrenia and substance use disorders to maintain. Relapse Prevention modification includes integration of behavioral tasks which are simple and easily attainable. For the dually diagnosed individual, realistic goals might include taking psychotropic mediations on schedule, keeping appointments, or keeping track of cravings. Building self-efficacy in everyday life activities is a fundamental modification of Relapse Prevention. Initially, many theorists assumed that since schizophrenia is seen as a cognitive dysfunction, cognitive therapy would be the most appropriate approach for change. However, recent clinical research has not confirmed this hypothesis (180). Liberman et al. suggested that a more active behavioral approach to learning was needed (181). The cognitive vulnerabilities that characterize schizophrenia are the primary reason why cognitively based Relapse Prevention, by itself, may be limited in effectiveness in the individual with both schizophrenia and substance abuse.

Interpersonal Skills

Relapse Prevention and 12-step recovery interventions have been successful in reducing or eliminating substance use among motivated people. Both Relapse Prevention and 12-step treatment revolve around social skills, such as communicating with others and solving problems. These general interpersonal skills are assumed to be reasonably developed in people who are treated in addiction treatment settings. However, in mental health settings, individuals with schizophrenia have demonstrated severe maladaptive

interpersonal skills. A variety of social-skills-based rehabilitation programs has been developed for individuals with schizophrenia (177). Skill-based interventions are offered as conjunctive interventions in dualdiagnosis programs (183). A recent review of psychosocial treatments for schizophrenia found that social skills interventions improved specific interpersonal behaviors but were less effective in reducing schizophrenia symptoms (32). Whether social skills interventions for the dually diagnosed will have an effect on preventing psychiatric and substance use relapse remains an empirical question.

Some individuals with comorbid schizophrenia and substance use avoid groups, including relapse prevention and 12-step peer support. Integrating social skills development with relapse prevention is another modification that clinicians should consider when planning treatment. Relapse prevention needs to be simultaneously integrated into a strategy for building social skills. Dually diagnosed patients often feel more accepted in 12-step groups modified to accommodate them. One advantage is that the appropriate use of medications is not criticized by peers in these groups.

In summary, given the issues and pervasive difficulties associated with schizophrenia, the psychosocial interventions that are typically used to treat substance abuse need some degree of modification in order for individuals with schizophrenia to be able to engage, participate, and change in treatment. Motivational Enhancement Therapy, Relapse Prevention, and 12-step treatment have been identified as the primary psychosocial interventions needed for dual-diagnosis treatment. However, the degree to which these will be successful in engaging patients and facilitating long-term stability in their lives depends on the extent to which these interventions are modified to meet the special needs of those with schizophrenia.

Solutions to These Problems

Integrating Perspectives: An Overarching Framework

The integration of addiction and mental health treatment approaches is a complex task. Although these approaches converge on a number of common goals regarding facilitation of behavioral change, they also diverge on a number of important factors underlying treatment philosophy and formulation of treatment interventions and strategies for change of addictive behavior. Some of the explicit factors that are at odds include the following: immediate goals of treatment (reduction in substance use vs. abstinence); the role of the therapist/counselor (supportive, flexible, empathic vs. confrontational, rigid, demanding); and the nature of the treatment or working alliance (maintaining an empathic therapeutic alliance vs. shifting between confrontation and empathy). In part, these differences have emerged out of the mental health field as a response to the difficulties encountered when treating the dually diagnosed individual with schizophrenia within the traditional addictions paradigm (144,184–186).

The treatment of the individual with co-occurring schizophrenia and substance abuse is probably best done in mental health treatment settings. Mental health staff must develop their own clinical tool box to include the substance abuse treatment approaches and modify them to address the unique and specific difficulties characteristic of schizophrenia. The chapter will conclude by reviewing clinical approaches that systems

use as guidelines or models to treat the dually diagnosed patient. In addition, the mental health system and staff have the opportunity to develop substance abuse prevention strategies to prevent substance use disorders and to identify them early in the course of the illness.

Substance Abuse Prevention

Given that individuals with schizophrenia are at high risk for developing a substance use disorder, primary and secondary substance abuse prevention efforts should be developed. Primary prevention attempts to prevent the development of substance abuse, whereas secondary prevention is the early detection and implementation of an intervention to stop the progression from use to abuse. Prevention efforts can be extended into the community support services of residential services, vocational programs, and social clubs. The use of audio-visual materials, peer support programs, healthy coping skills development, and drug resistance skill training can promote healthy relationships and nonchemical ways to improve a patient's wellbeing. Efforts to support healthy living activities (including exercise, nutrition, relaxation techniques, etc.) can be integrated into health promotion activities. Helping patients manage anger, depression, and boredom in ways that are healthier than using substances may reduce the incidence of substance use disorders in this population. These prevention programs can reinforce the cultural shift of addressing substance abuse problems within a mental health setting (33).

Approaches to Co-occurring Disorder Treatment

From clinical experience, several approaches have evolved to guide the dual-diagnosis treatment of individuals with schizophrenia. Treatment of this dual-diagnosis subtype requires that both schizophrenia and substance abuse be addressed in an integrated, coordinated, and comprehensive manner. Outcomes appear to improve when psychosocial and pharmacological treatments for each problem are included in the treatment plan. In addition, the treatment of this chronically mentally ill population requires a system of care that addresses needs related to housing, entitlements, rehabilitation, and community service. The task of integrating specific components of addiction treatment with mental health treatment means that staff training and education are critical.

A first step toward integrating substance abuse and mental health treatment is to develop treatment values and principles that reflect an integrated approach and orientation to care. Clinicians who are optimistic, empathic, and hopeful help the recovery and treatment process. The recommended approach to dual-diagnosis treatment addresses both problems simultaneously, conducts active outreach and case management efforts, attempts to increase patient motivation for abstinence or harm reduction in a realistic manner, integrates mental health and substance abuse approaches, provides broad-based and comprehensive services, and remains flexible to individual needs (26,142,144,145,185–190). Building on these clinical values, new models have developed within the mental health treatment system to better organize treatment for this population, including Assertive Community Treatment teams (142,172,191), the

integrated model (144,192,193), the stages of dual-diagnosis treatment (190), the Motivation-Based Dual Diagnosis Treatment model (26), and Dual Recovery Therapy (194). Most programs conceptualize dual-diagnosis treatment as a phase-specific and comprehensive treatment. The addiction recovery process within dual-diagnosis has been generally partitioned into three phases: 1) an initial engagement phase, 2) an action/changing behaviors phase, and 3) maintenance—a long-term life-style/paradigm shift phase. Specific psychosocial interventions are most effective during specific phases in the treatment process (26,140,188,190,195,196).

Case management approaches such as assertive community treatment have been developed as wraparound services to help with initial treatment engagement and to facilitate community integration. The ultimate goal of these interventions is to empower the individual to live independently and take responsibility for managing his or her daily living, including the addiction and psychiatric problems. A variety of case management approaches has been developed over the years that differ in the role of the case manager. The Broker was designed for the severely mentally ill. In this model, the case manager plans, monitors, advocates, and connects the patient to services, but does not act as a clinician. The clinical case management model is an outgrowth of the Broker model, in which the case manager provides weekly individual psychotherapy and psychoeducational skills training. The Program for Assertive Community Treatment (PACT) or Assertive Community Treatment (ACT) was designed to be more comprehensive for people with severe mental illness who are heavy utilizers of hospital services. The ACT model was designed to include a multidisciplinary team (psychiatrist, nurse, two case managers), a low patient-to-staff ratio, services carried out in the community as opposed to the office, shared caseloads, 24-hour coverage, services carried out by the ACT team rather than referring patients to other professionals, and unlimited service use. Intensive Case Management (ICM), also developed for high service users, is much like ACT, except that caseloads are not shared.

The authors of this chapter have developed a time-limited, 6-week transitional case management service that incorporates the Assertive Community Treatment model to help move individuals with comorbid substance abuse and major psychiatric disorder from the hospital to their outpatient treatment provider. This approach has the primary goals of establishing a therapeutic alliance and engaging the patient in an outpatient treatment program. However, this treatment also offers integrated substance abuse and psychiatric services with a modified version of Dual Recovery Therapy (194). An unpublished naturalistic study evaluated the effectiveness of an intervention on follow-up and engagement in outpatient appointments. In this study, 31 patients receiving six weeks of ICM were compared to 29 control patients. Results showed that ICM was superior to treatment as usual with respect to attendance at first (84% vs. 42%) and second (72% vs. 29%) outpatient appointments, and it reduced the rate of rehospitalization following the six weeks of treatment. Furthermore, upon 6-month follow-up, those individuals who received the transitional intervention showed significant reductions in rehospitalization days, Global Assessment of Functioning scores, craving, and substance use.

In a long-term and more traditional case management approach, Drake and colleagues have successfully improved coordination of substance abuse services for the dually diagnosed by developing the Assertive Community Treatment Team Model (189). This

approach relies on multidisciplinary teams that serve as the primary clinician for a relatively small number of patients and are involved in a patient's treatment in all settings. The teams are outpatient oriented and execute intensive case management within the patient's natural environment. The treatment model is a stage-wise, cognitive-behavioral substance abuse treatment, and provides comprehensive community mental health services that include outreach, case management, and medications. The stage-wise treatment phases are based on Osher and Kofoed's five stages of dual-diagnosis treatment, i.e., engagement, persuasion, coercion, Relapse Prevention, and action (190). Knoedler (197) has developed a similar program of ACT teams that provide clinical outreach services and coordinate treatment. Pepper et al. (198) have developed a community patient protection system to improve access to a comprehensive continuum of care and services.

Research indicates that treatment programs adhering to the structure and community treatment components of ACT are associated with better treatment outcomes than those programs showing poorer fidelity to those components (191). In addition, although patients in both groups improved, ACT shows consistent benefits over standard case management (190).

Minkoff has proposed an integrated treatment model based on the parallels between the disorders of schizophrenia and substance abuse (144,188). Both disorders are conceptualized as chronic relapsing conditions with a biological underpinning and a social stigma. Individuals affected with schizophrenia or a substance abuse problem often deny or minimize the presence or impact of the disorder. This approach emphasizes case management in which both problems are addressed simultaneously, and the patient is educated about the parallels between the two disorders. See Drake and colleagues for a review of integrated treatment models for patients with severe mental illness and co-occurring substance use disorders (192). This model has also been found to be more effective in homeless patients than standard treatment (193).

Although more research is needed, we believe that the integration of intensive case management with atypical antipsychotics—which have better efficacy in treating negative symptoms and a better side-effect profile—will become the state-of-the-art for this population. Noordsy et al. (199) recently reported on 6-month outcomes for patients in an open-label naturalistic design who stayed on a typical antipsychotic or were switched to an atypical antipsychotic; both groups also received intensive case management services. The individuals treated with the atypical antipsychotic showed greater improvement in symptom severity. In a similar study, Drake et al. (192) randomly assigned people to assertive community case management treatment or standard case management treatment; 36 of them also received clozapine treatment. The individuals who received clozapine made more progress in treatment and had fewer days of use. These two studies suggest that case management may work synergistically with atypical antipsychotics to improve both the psychiatric and substance use disorders concurrently.

Motivation-Based Dual Diagnosis Treatment (MBDDT) Approach

The Motivation-Based Dual Diagnosis Treatment (MBDDT) approach (26) was developed to integrate mental health and addiction treatment while addressing the key

issues and difficulties related to dual-diagnosis treatment for schizophrenic substance users. MBDDT is based on the values underpinning the other models and articulates specific goals and treatment approaches for patients on the basis of their motivation to address the addiction problem, the type of substance(s) abused, and the severity of both disorders. MBDDT takes into consideration issues related to motivation, self-efficacy, cognitive and interpersonal limitations, and the establishment of the therapeutic alliance, as discussed above. MBDDT is a comprehensive treatment model for dually diagnosed individuals with schizophrenia, with an application to other psychiatric comorbidities. It incorporates the primary substance abuse psychosocial interventions with the necessary modifications needed for substance abusers with schizophrenia. It is sensitive to the key therapeutic issues: self-efficacy, cognitive limitations, interpersonal skills, the importance of the therapeutic alliance, and motivational stage of change.

In MBDDT, the five motivational stages of Prochaska and DiClemente (precontemplation, contemplation, preparation, action, and maintenance) are incorporated into the assessment of all patients (27). Each motivational stage is matched with specific treatment approaches. The transtheoretical model articulated by Prochaska and colleagues organizes a conceptualization of process underlying change, acknowledging that individuals vary in their readiness for change. Treatment approaches and treatment goals (abstinence or reduction, attendance, medication compliance, etc.) should be matched with the patient's level of motivation. Motivation to change may vary within an individual for different substances of abuse and different psychiatric symptoms (28).

In MBDDT, the clinician is encouraged to develop realistic and appropriate treatment goals. While the overall approach is eclectic, specific treatment approaches are suggested during the different motivational stages. Clinicians should have skills and knowledge in integrating different therapy approaches: Motivational Enhancement Therapy, psychoeducation, Relapse Prevention, 12-step, pharmacotherapies (for both psychiatric and substance use disorders, including detoxification and maintenance), behavioral contracting, ongoing assessments including urine and breath toxicology monitoring, social skills training, peer support counseling, vocational/ educational counseling, and family/network therapies.

Specific goals and techniques are matched to each motivational phase. The primary counselor for each patient is the person primarily responsible for providing the substance abuse treatment and the overall management of a dual-diagnosis treatment plan. Treatment plans reflect the motivational level of the patient, but the primary treatment goal for all patients is to advance to the next motivational stage. Most patients enter the program at a low level of motivation for substance use treatment, but are often motivated to stabilize and decrease psychiatric symptomatology (28). This situation lends itself to the initiation of MET techniques around the engagement of psychiatric issues, eventually branching out to possible concerns and issues related to substance use. Treatment of the less motivated patients can be a lengthy process. The addition of multiple supports, external motivators, and monitors can help quicken the process through the stages of treatment. The Community Reinforcement Approach (CRA) offers a way to develop external motivation for a dually diagnosed population with few external motivators (120). CRA uses behavioral therapy principles of contingencies, rewards, and consequences. Disability income, probation, and family can provide external motivation to engage in

treatment and progress to abstinence. As the patient's motivation for substance use treatment unfolds, the second phase of MBDDT begins with the integration of Relapse Prevention and 12-step interventions.

Dual Recovery Therapy (DRT) Approach

Dual Recovery Therapy (DRT) (194) integrates substance abuse relapse prevention, psychiatric social skills training, MET, and the "recovery language" of 12-step programs in linked group and individual treatment sessions (26,194). Self-efficacy, cognitive, and interpersonal limitations are the basis for integrating social skills development (traditional psychiatric intervention for schizophrenia) with Relapse Prevention skills building (traditional addiction approach to substance use). Social skills development is based on the active, behavioral components of role play exercises, in addition to modeling and coaching techniques introduced by the therapists and, at times, by other members of the group. The role play techniques are used to develop problem-solving skills and communication skills. It can be introduced in both group and individual therapy. Both Relapse Prevention and social skills training share a common theoretical grounding in cognitive-behavioral theory. The social skills training format's use of behavioral therapy addresses the cognitive and social skills deficits common in patients with schizophrenia. The understanding and management of their substance use problems are improved through an emphasis on coping strategies such as how to organize one's time. The therapist gives ongoing consideration to both substance abuse and psychiatric problems, monitors their interactions, and adjusts the treatment emphasis accordingly. Substance abuse relapse prevention therapy focuses on the problem of relapsing to substance use and teaches skills that help the individual identify and cope with early warning signs or triggers. Patients are taught how to develop both general coping strategies and specific skills which may help prevent relapses and improve the patient's functioning in everyday life. Traditional Relapse Prevention therapy needs to be modified to treat patients with schizophrenia who may have deficits in attention span, abstraction, reading, and social skills. Specific relapse prevention techniques include assessing internal and external triggers, defining slips vs. relapses, analyzing a relapse, developing coping and relaxation skills, practicing drug refusal exercises, structuring time and activities, managing a "slip," and understanding the abstinence violation effect (201).

MET and 12-step recovery language were added to address the low levels of motivation for change that are often present in this patient population and to take advantage of the common lexicon of the 12-step programs with which many patients were already familiar. The resulting treatment is designed to enhance intrinsic motivation for change, bolster patients' sense of self-efficacy, improve their social skills, and give them tools for coping with high-risk situations. A patient's motivation to address the symptoms of schizophrenia may not be the same as his or her motivation to address substance use, and treatment is best tailored to the individual's motivation for each problem area.

The first month of DRT involves twice-weekly individual sessions. Motivation is assessed and enhanced in these early individual sessions while the therapist works on building a strong therapeutic alliance. A plan for change is discussed, and basic skills that

will be necessary for later group sessions are introduced. Later, individual sessions focus on reinforcing material discussed during group therapy sessions. After the first month, once a therapeutic alliance has been established and the patient has been prepared for group therapy, the structure shifts from two individual sessions per week to one individual and one group session weekly. These sessions are linked in that individual sessions are used to reinforce the material discussed during the group sessions. Group sessions follow a standard format whereby they begin with a relaxation exercise followed by an update by each patient. Group structure is also provided by focusing on a specific topic each week (for example, Relapse Prevention, mood management, symptom management, increasing pleasurable activities, communication skills, asking for help, and medication compliance). As skill building plays a central role in DRT, behavioral rehearsal and role-playing are used regularly.

Clinical experience in referring individuals with schizophrenia to 12-step programs has been mixed. The DRT therapist should therefore be thoughtful about encouraging attendance at 12-step meetings. The individual with schizophrenia may need to be encouraged to find the 12-step meeting in which he or she is most comfortable. Many areas have 12-step meetings designed for the chronically mentally ill. In a group setting, peers provide information about their own recovery, including experiences at 12-step meetings (202–204).

Further on in the recovery process, the patient develops extended periods of abstinence and is in the maintenance stage within the Stages of Change model (27). The transition from action to maintenance can be difficult. During the maintenance phase, the goal shifts from an exclusive focus on abstinence to improving core areas of one's life. For the substance abuser without schizophrenia, this stage has been labeled Stage II recovery (205). The focus is on reducing dysfunctional relationships and increasing healthy relationships. Patients are attempting to pursue alternative highs, including employment, better relationships with significant others, and other social outlets with nonusers. This stage in treatment can be difficult for the individual with schizophrenia.

Encouraging involvement in self-help at this time may be very appropriate, particularly 12-step meetings which target the dually diagnosed, such as those at mental health facilities. The 12 steps can provide a guide through this stage of recovery. Sustaining change can be difficult, and positive patterns may need to be learned and relearned until they are fully integrated into patients' lives. Serving as peer counselors can help reinforce their motivation to make fundamental changes.

Individuals may cycle through the motivational levels at various times in their lives. Both the patient and the clinician must remember that the change process is ongoing, not finite. Relapse is always a possibility. Old patterns may reemerge, and new stressors may bring on cravings and ineffective coping strategies.

SUMMARY

Co-occurrence of schizophrenia and addiction is very common in mental health treatment settings, and the substance abuse profoundly impacts the symptomatology and course of illness and treatment. Undetected substance abuse continues to be a major problem in

mental health settings, and there is a need for staff training on co-occurring addiction and mental illness. Treatment must be realistic and appropriate to the severity of both disorders, the type of substance(s) abused, and the motivation of the patient to address either problem. Psychosocial and pharmacological treatments must be integrated and modified to address the unique vulnerabilities of individuals with schizophrenia. The Motivation-Based Dual Diagnosis Treatment model provides a framework to match specific treatments with varying motivational levels. Future research efforts must help us to better understand and address the interacting relationships between underlying neurobiology, psychopathology, social correlates, treatment strategies, and health care systems associated with the two individual disorders.

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13
Comorbidity of Substance Use and Gambling Disorders

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INTRODUCTION

Pathological gambling is an impulse control disorder characterized by lack of control over gambling, tolerance to amounts wagered, and forgoing other activities to gamble (1). The lifetime prevalence rate of this disorder is about 1.6%, and the past year prevalence rate is about 1.1% (2). The terms "problem gambling," "transitional gambling," and "at-risk gambling" are used to describe a pattern of gambling that causes some harm to the individual, but not enough to diagnose the person with pathological gambling. For the purposes of this chapter, we will refer to sub-threshold gambling as "problem gambling," and the term "disordered gambling" will be used to refer to samples that contain both problem and pathological gamblers. The lifetime prevalence rate of problem gambling is about 3.9%, and the past-year rate is about 2.8% (2). Thus, slightly over 5% of the population experiences disordered gambling at some point in their lives.

A sophisticated understanding of psychiatric comorbidities in the field of disordered gambling is lacking. In part, this is because few large-scale, random sample population surveys are available that evaluate the prevalence rates of disordered gambling in conjunction with other psychiatric disorders. Nevertheless, some data are published on the prevalence rates of disordered gambling with substance use disorders. In this chapter, we first review general population surveys that assessed both gambling and substance use disorders. These types of surveys represent the most accurate account of comorbidity, but few general population surveys have been conducted, and only two have done so on a national basis. Second, we review studies of the prevalence of substance use disorders in treatment-seeking pathological gamblers. Third, we describe rates of pathological gambling among individuals seeking treatment for substance abuse. The focus of these two latter methods on treatment-seeking populations may overestimate rates of comorbidities because individuals with the most severe problems, such as dual disorders, may be more likely to present for treatment than individuals with one disorder.

Studies in treatment-seeking populations, nevertheless, allow for a detailed examination of the relationship between gambling and substance use disorders. The second half of the chapter addresses issues in comorbid patients, such as increased drug abuse and other psychosocial difficulties. Methods for identifying disordered gambling in substance abusers are reviewed, along with recommendations for treatment.

GENERAL POPULATION SURVEYS

Any Substance Use Disorder

Results from general population surveys that evaluated the relationship between gambling and substance use disorders are summarized in Table 1. The National Opinion Research Center (3) undertook a telephone survey of 2417 US adults. The survey found that lifetime pathological gamblers constituted 1.2% of the population, and that an additional 1.5% were lifetime problem gamblers. Individuals identified with problem or pathological gambling were more likely than nongamblers to have a lifetime diagnosis of drug or alcohol dependence, with 9.9% of pathological and 12.4% of problem gamblers meeting criteria for a lifetime substance use diagnosis, compared with 1.1% of nongamblers and 1.3% of recreational gamblers.

Bland et al. (4) conducted face-to-face interviews of 7214 randomly selected adult residents in Edmonton, Canada. Four questions regarding gambling were included in the interview, and a very low 0.4% of the sample (n=30) was classified as lifetime pathological gamblers. Over half of the pathological gamblers had a substance use disorder, compared with less than 20% of nongamblers. The rate of pathological gambling was strikingly lower in this study than in other surveys (e.g., Ref. 2), most likely because an instrument with limited psychometric properties and strict skip-out criteria was used. Nevertheless, the trends of comorbidity found in this study, which probably identified only the most severe pathological gamblers, were

Table 1 Lifetime Prevalence Rates of Substance Use Disorders in General Population Surveys

Disorder	*N* of sample	Percentage of disordered gamblers with substance use diagnosis	Percentage of nongamblers with substance use diagnosis
General or any substance use disorder (16.7%)[a]			
Bland et al., 1993 (4)	7214	63.3[b]	19.0
Feigelman et al., 1998 (5)	6308	26.0[b]	6.5[c]
National Opinion Research Center, 1999 (3)	2417	9.9[b,d]	1.1[d]
Alcohol abuse or dependence (13.5%)[a]			
Bland et al., 1993 (4)	7214	63.3[b]	16.5

Cunningham-Williams et al., 1998 (8)	1704	44.1[b]	7.5
Smart and Ferris, 1996 (9)	2016	8.5[d]	4.4[d]
Welte et al., 2001 (7)	2638	25.0[b,d,e]	1.4[d,e,f]
Drug abuse or dependence (6.1%)[a]			
Bland et al., 1993 (4)	7214	23.3[b]	6.3
Cunningham-Williams et al., 1998 (8)	1704	15.5	3.5
Nicotine dependence (25%)[g]			
Cunningham-Williams et al., 1998 (8)	1704	54.7[b]	27.2
Smart and Ferris, 1996 (9)	2016	40.6[b]	21.3

[a]Lifetime general population rate (6); *N*=20,291. [b]Disordered gamblers differ from nongamblers in same study, $p<0.05$. Percentage of *non-problem* gamblers. [d]Dependence only. [e]Current prevalence rate. [f]Percentage of *non-pathological* gamblers. [g]Estimated current general population rate (1).

similar to those noted in other general population surveys in that a strong association was noted between substance use and gambling disorders.

In a telephone survey of 6308 adults from Texas, Feigelman et al. (5) found that among all the respondents identified with a lifetime gambling problem (*n*=265), 26% also had a substance use disorder. This rate of substance use disorders is clearly higher than the 16.7% prevalence rate found in other general population surveys (e.g., Ref. 6), and it was also significantly higher than the overall rate of substance use disorders noted in this same study—6.5%. Feigelman et al. (5) also explored the converse relationship and found that among respondents with a current substanee use disorder (*n*=412), 16.7% also had a lifetime gambling problem. This rate of gambling problems was substantially higher than the 4.2% overall rate of disordered gambling noted in the full sample. Thus, this general population study provides evidence for a bi-directional association between gambling and substance use disorders, broadly defined. In the next sections, the relationships between disordered gambling and specific substance use problems are reviewed.

Alcohol Use Disorders

In examining specific types of substance use disorders, the most recent national survey of disordered gambling (7) evaluated the co-occurrence of alcohol use disorders and pathological gambling in 2638 US adults. Among current pathological gamblers

identified in this survey, 25% were currently alcohol dependent, compared with 1.4% of nonpathological gamblers. The odds ratio of current alcohol dependence with current pathological gambling was extraordinarily high: 23.1.

Several general population surveys from specific geographical locations corroborate these findings. In the early 1980s, the Epidemiological Catchment Area survey from the St Louis, MO, area included four questions on gambling along with the Diagnostic Interview Schedule (DIS) for other mental health disorders. Cunningham-Williams et al. (8) analyzed these data and found that disordered gamblers were more likely to suffer from alcohol abuse or dependence than nongamblers. Lifetime rates of alcohol abuse or dependence exceeded 40% in individuals identified with problem or pathological gambling vs. less than 10% in nongamblers, with intermediate rates of about 20% in recreational gamblers. In Canada, Bland et al. (4) found that lifetime alcohol abuse or dependence was 3.8 times more prevalent in pathological gamblers than in nongamblers. However, Smart and Ferris (9) found only a modest and nonsignificant elevation of alcohol dependence among heavy gamblers in a telephone survey of 2016 adults in Canada.

Illicit Drug Abuse or Dependence

Several studies have examined comorbidity of gambling and drug use disorders. Illicit drug abuse and dependence also show trends of increased prevalence among individuals identified with disordered gambling in general population surveys.

In the NORC study (3), formal drug use diagnoses were not made, but 8.1% of lifetime pathological gamblers and 16.8% of lifetime problem gamblers reported illicit drug use in the past year, compared with 4.2% of social gamblers and 2.0% of nongamblers. Of the problem and pathological gamblers identified in the study by Cunningham-Williams et al. (8), 15.5% had illicit drug problems, compared to 7.8% and 3.5% of non-problem/recreational gamblers and nongamblers, respectively. The survey by Bland et al. (4) of Canadian residents also found that the prevalence of illicit drug abuse or dependence was about four times higher in pathological gamblers than in nongamblers.

Nicotine Dependence

Some studies also examined rates of smoking or nicotine dependence and comorbidity with disordered gambling. Cunningham-Williams et al. (8) noted that rates of nicotine dependence were about twice as high in problem or pathological gamblers as in nongamblers, and intermediate rates of smoking (43.7%) were noted among recreational gamblers. Similarly, Smart and Ferris (9) found that problem gamblers were more likely to be current smokers than were non-problem gamblers, with rates of 41.6% in “heavy” gamblers compared to 30.1% in recreational gamblers and 21.3% in infrequent or nongamblers. Heavy gamblers were also more likely to smoke 25 or more cigarettes per day, with rates of 30.0% in heavy gamblers, 16.9% in recreational gamblers, and 12.9% in nongamblers. This study, along with the findings of Cunningham-Williams et al. (8), provides evidence for an association of nicotine use with gambling disorders.

In summary, these general population surveys from national samples in the United

States and Canada, as well as some specific regional studies, suggest a strong relationship between disordered gambling and virtually all substance use disorders. Because these large sample surveys focused primarily on issues related to diagnosis, details about the onset and patterns of the symptoms or disorders were rarely available. Research in treatment-seeking samples tends to corroborate these patterns of comorbidity between substance use and gambling disorders, and some of these studies provide added information about comorbidity, severity, and onset of disorders, as is described below.

SUBSTANCE USE DISORDER COMORBIDITY IN TREATMENT-SEEKING PATHOLOGICAL GAMBLERS

Prevalence Rates of Substance Use Diagnoses

Compared to the general population, treatment-seeking pathological gamblers are more likely to have alcohol and other drug diagnoses, with rates across studies ranging from about one-quarter to over two-thirds, as shown in Table 2. For example, Ramirez et al. (10) assessed substance use disorders in 51 successive admissions to the Cleveland Veterans Administration Gambling Treatment Program, and found that 39% of gamblers met DSM criteria for past-year drug or alcohol use disorders, and 47% met lifetime criteria for an alcohol or drug use disorder other than nicotine. In a study of 25 male Gamblers Anonymous (GA) members, Linden et al. (11) found a 48% prevalence rate of alcohol dependence, and Lesieur and Blume (12) reported rates of alcohol abuse of 26% among 50 female GA attendees. McCormick et al. (13) found that 32% of 50 pathological gamblers seeking inpatient gambling treatment suffered from alcohol use disorders, and 4% from other drug use disorders. In a small study of 30 respondents to advertisements for pathological gamblers (who were not necessarily seeking treatment), Black and Moyer (14) found rates of lifetime alcohol abuse or dependence to be 63%, while rates of other substance use disorders were 27%. More recently, Ibanez et al. (15) found that in a sample of 69 treatment-seeking pathological gamblers in Madrid, Spain, 23% were currently abusing or dependent on alcohol, and 35% had lifetime diagnoses of alcohol abuse or dependence.

Specker et al. (16) interviewed 40 outpatients from a gambling treatment program in Minnesota, and found that 60% met lifetime criteria for a substance use disorder, with 50% meeting criteria for alcohol abuse or dependence, 23% for cannabis, 8% for stimulants, 5% each for cocaine and sedatives, and 3% for hallucinogens. Maccallum and Blaszczynski (17) interviewed 75 poker-machine players seeking gambling treatment in Australia. Using a semi-structured interview schedule and the Composite International Diagnostic Interview, which assessed mental disorders during the past year, 16% met criteria for alcohol abuse, 8% for alcohol dependence, 37% for nicotine dependence, 5% for cannabis abuse, 5% for cannabis dependence, and 1 % each for amphetamine and inhalant abuse.

In the gambling treatment outcomes monitoring project from Minnesota, Stinchfield and Winters (18) found that 33% of the 944 admissions over a three-year period reported a prior history of treatment for substance use disorders. In a gambling treatment outcomes

monitoring project for the State of Connecticut, we similarly found that 31% of 335 admissions reported a history of one or more substance abuse treatment

Table 2 Lifetime Prevalence Rates of Substance Use Disorders in Treatment-Seeking Pathological Gamblers

Disorder/Ref.	*N*	Percentage with substance use disorder
General or any substance use disorder (16.7%)[a]		
Petry, 2001 (19)	335 outpatients	31[b]
Ramirez et al., 1983 (10)	51 inpatients	47
Specker et al., 1996 (16)	40 outpatients	60
Stinchfield and Winters, 1996 (18)	994 outpatients	33
Alcohol abuse or dependence (13.5%)[a]		
Black and Moyer, 1998 (14)	30 ad respondents	63
Ibanez et al., 2001 (15)	69 outpatients	35
Lesieur and Blume, 1991 (12)	50 GA members, all-female)	26
Linden et al., 1986(11)	25 GA members, all-male)	48
Maccallum and Blaszczynski, 2002 (17)	75 outpatients	24[c]
McCormick et al., 1984 (13)	50 inpatients	32
Petry, 2001 (19)	335 outpatients	21[b]
Specker et al., 1996 (16)	40 outpatients	50
Any illicit drug abuse or dependence (6.1%)[a]		
Black and Moyer, 1998 (14)	30 ad respondents	27
McCormick et al., 1984 (13)	50 inpatients	4
Cocaine abuse or dependence (0.2%)[a]		
Petry, 2001 (19)	335 outpatients	8[b]
Specker et al., 1996 (16)	40 outpatients	5
Heroin abuse or dependence (0.7%)[a]		
Petry, 2001 (19)	335 outpatients	1[b]

Cannabis abuse or dependence (4.3 %)[a]		
Maccallum and Blaszczynski, 2002 (17)	75 outpatients	11[c]
Specker et al., 1996 (16)	40 outpatients	23
Nicotine dependence (25%)[d]		
Maccallum and Blaszczynski, 2002 (17)	75 outpatients	37[c]
Petry and Oncken, 2002 (20)	345 outpatients	62[c]
Stinchfield and Winters, 1996 (18)	944 outpatients	69[c]

[a]Lifetime general population rate (6); *N*=20,291. [b]Past history of treatment. [c]Current prevalence rate. [d]Estimated general population rate (1).

episodes (19,20). Of the gamblers who underwent substance abuse treatment, treatment for alcohol was the most common, followed by cocaine and others drugs (primarily marijuana), while only a few had received treatment for opioid dependence.

Cigarette smoking is common in treatment-seeking pathological gamblers, but little research has been published on this topic. Although Maccallum and Blaszczynski (17) reported rates of nicotine dependence only slightly higher than in the general population, Petry and Oncken (20) found that 62% of 345 consecutive admissions to gambling treatment programs in Connecticut were current smokers. Similarly, in a group of 944 treatment-seeking pathological gamblers, Stinchfield and Winters (18) found that 69% were current daily cigarette smokers. In summary, substantial evidence, and no contradictory data, indicate that substance use disorders are prevalent in treatment-seeking pathological gamblers.

Psychosocial Problems in Dually Diagnosed Pathological Gamblers

The above studies all demonstrate that individuals seeking treatment for pathological gambling have high rates of substance use disorders. However, in most cases, the bulk of the substance use diagnoses were past, not current. In our studies of patients seeking outpatient treatment for pathological gambling in the State of Connecticut, only about 10% of patients report current use of illicit drugs or regular, heavy use of alcohol, and similarly low rates of current substance abuse are noted among pathological gamblers seeking outpatient treatment in the State of Minnesota programs.

Despite the fact that most of the substance use diagnoses are not current, some differences emerge rather consistently in reports comparing pathological gamblers with and without past substance use diagnoses. Treatment-seeking pathological gamblers with a history of substance use disorders tend to have more severe gambling problems, psychiatric symptoms, and other psychosocial difficulties than pathological gamblers with no prior substance abuse problems. In a sample of 341 consecutive admissions to outpatient gambling treatment programs, Ladd and Petry (21) compared the 31% of

patients with substance abuse histories to the 69% without such histories. The substance abusers had more years of gambling problems, more frequent gambling activity, and more gambling problems in the month prior to initiating gambling treatment. They were also more likely to be concurrently receiving treatment for mental health problems and reported greater lifetime psychiatric distress than gamblers without substance abuse problems.

Another analysis (20) of the same sample of treatment-seeking gamblers evaluated the association of cigarette smoking with severity of gambling and psychosocial problems. The smokers in this sample were more likely to have a history of treatment for a substance use disorder than the nonsmokers. After controlling for substance abuse treatment histories, gender, and age, the smokers demonstrated more severe gambling, family/ social, and psychiatric problems. Compared with nonsmokers, the smokers gambled on more days and spent more money gambling; they also "craved" gambling more and had lower perceived control over their gambling. The smokers were more likely to be taking psychiatric medications, and they experienced psychiatric symptoms, especially anxiety symptoms, on a greater number of days than non-daily smokers. Thus, results from this study suggest that smoking status is associated with more severe gambling and psychiatric symptoms.

The results of the above studies call for further investigation of the role of substance use (both past and current) in the development and course of pathological gambling and whether substance abuse status affects the course of treatment or outcomes among gamblers. To date, no studies have systematically investigated the effects of substance use disorders on treatment outcomes in pathological gamblers. One report suggests that pathological gamblers with a past history of a substance use disorder were *less likely* to relapse to gambling than those without other addictive disorders (22). Perhaps having overcome another addictive disorder may assist the gambler in ceasing gambling. Clearly, more research on the relationship between substance use and outcomes in the treatment of pathological gamblers is needed.

GAMBLING PROBLEMS AMONG PATIENTS SEEKING TREATMENT FOR SUBSTANCE USE DISORDERS

Not only are substance use problems common in treatment-seeking pathological gamblers, but gambling problems also frequently occur in individuals seeking treatment for substance abuse. As shown in Table 3, rates of disordered gambling are approximately two to six times higher in treatment-seeking substance abusers, compared to rates found in general population surveys. In the next sections, we review rates of disordered gambling in patients seeking treatment for substance use disorders in general outpatient clinics, and then in specific populations of substance abusers, including alcoholics, cocaine-dependent patients, methadone-maintained patients, and marijuana abusers.

General Substance Abuse Patients

First, in terms of general substance abuse patients (not differentiated by substance use diagnoses), Lesieur et al. (23) found that 9% of 458 patients

Table 3 Gambling Problems Among Individuals Seeking Treatment for Substance Use Disorders

Substance use disorder/Ref.	*N*	Percentage identified with problem gambling	Percentage identified with pathological gambling
General substance use			
Castellani et al., 1996 (24)	154	n.s.	14
Cunningham-Williams et al., 2000 (29)	512	22	10
Daghestani et al., 1996 (26)	276	n.s	33
Langenbucher et al., 2001 (28)	372	n.s.	13
Lesieur et al., 1986 (23)	458	10	9
McCormick, 1993 (27)	2171	n.s.	13
Rupcich et al., 1997 (25)	328	11	14
Alcohol			
Cho et al., 2002 (32)	5176	n.s.	4[a]
Elia and Jacobs, 1993 (31)	85	n.s.	13
Lejoyeux et al., 1999 (30)	79	n.s.	9
Lesieur et al., 1986 (23)	243	10	5
McCormick, 1993 (27)	581	n.s.	10
Toneatto and Brennan, 2002 (33)	n.s.	4	12
Cocaine			
Hall et al., 2000 (35)	313[b]	n.s.	8
Lesieur et al., 1986 (23)	113	16	14
Steinberg et al., 1992 (34)	298	n.s.	15
Toneatto and Brennan, 2002 (33)	n.s.	4	12
Opioids			

Feigelman et al., 1995 (36)	220	3	7
Ledgerwood and Downey, 2002 (38)	62	11	18
Lesieur et al., 1986 (23)	34	15	18
Spunt et al., 1995 (37)	117	15	16
Toneatto and Brennan, 2002 (33)	n.s.	2	5
Cannabis			
Tonneatto and Brennan, 2002 (33)	n.s.	14	24

n.s.=not stated. [a]Percentage includes only men; number of men in original sample not reported. [b]200 patients also opioid-dependent.

were pathological gamblers and an additional 10% were problem gamblers. Castellani et al. (24) found that 14% of 154 homeless veterans who were hospitalized for substance misuse had a significant gambling problem. In a substance abuse treatment facility in Windsor, Ontario, Rupcich et al. (25) found that 14% of 328 patients were pathological gamblers, with an additional 11 % classified as problem gamblers. Daghestani et al. (26) found an extremely high rate of pathological gambling (33%) in 276 hospitalized substance-abusing veterans. Finally, in groups of 2171 and 372 substance abusers, respectively, McCormick (27) and Langenbucher et al. (28) each found that 13% were pathological gamblers.

Cunningham-Williams et al. (29) recently evaluated prevalence rates of disordered gambling in a sample of 990 substance users, recruited from either treatment programs (*N*=512) or the community (*N*=478) as part of an HIV prevention project. Over 10% of the sample met criteria for pathological gambling, with an additional 22% classified as problem gamblers, regardless of recruitment site. Thus, across all these studies of individuals seeking treatment for substance use disorders in which patients were not differentiated by their primary drug of abuse, rates of disordered gambling were substantially higher than the 1–5% rates obtained from general population surveys (2).

Alcohol Dependence

In examining rates of disordered gambling among specific populations of substance abusers, fewer studies are available. In a study of 458 substance-abusing outpatients, Lesieur et al. (23) differentiated patients by substance use diagnosis. They found that, of the 395 alcohol-abusing patients, 8% were pathological gamblers and 10% problem gamblers. Similarly, McCormick (27) reported on rates of disordered gambling among patients with only alcohol dependence (*n*=581) in his sample of over 2000 substance abusers, and found that 10% were pathological gamblers. Another study conducted by Lejoyeux and colleagues (30) found that 9% of 79 patients receiving inpatient

detoxification for alcohol dependence were pathological gamblers. Elia and Jacobs (31) evaluated gambling problems among 85 alcohol-dependent patients, with a large representation of Native Americans (38%), and found that 22% of the Native Americans were pathological gamblers, compared to 7% of the Caucasians.

More recently, Cho et al. (32) found that in a group of 5160 Korean adults seeking treatment for alcohol abuse or dependence, only a small percentage of men met criteria for pathological gambling, but a significant association between alcohol use disorders and pathological gambling was noted relative to general population norms. Finally, Toneatto and Brennan (33) examined rates of problem and pathological gambling in a sample of 581 individuals seeking residential substance abuse treatment. They investigated rates of disordered gambling based on primary substance use diagnosis, and found that 6% of the alcohol-dependent group were problem gamblers, with an additional 9% who were pathological gamblers.

Cocaine Abuse

In examining rates of disordered gambling in cocaine abusers, Lesieur et al. (23) reported that 14% of 113 cocaine abusers were pathological gamblers and an additional 16% were problem gamblers. Steinberg et al. (34) found that 15% of 298 treatment-seeking cocaine abusers were pathological gamblers. Hall et al. (35) obtained lifetime rates of 8% for pathological gambling, and current rates of about 4%, in a sample of 313 cocaine-dependent outpatients, of whom 200 were also opioid-dependent. Toneatto and Brennan (33) found that among patients seeking residential treatment for cocaine, 12% were pathological gamblers and an additional 4% were problem gamblers.

Heroin Dependence

A few studies evaluating rates of disordered gambling have also been conducted in opioid-abusing or methadone maintenance patients. Toneatto and Brennan (33) found that among patients seeking residential treatment for opioids, 5% were pathological gamblers and 2% were problem gamblers. Lesieur et al. (23) found that 18% of the 34 opioid-abusing patients seeking inpatient substance abuse treatment were pathological gamblers, and 15% were problem gamblers. In studies of methadone-maintained opioid-dependent outpatients in New York City, Feigelman et al. (36) found that 7% of 220 individuals were pathological gamblers and an additional 3% were problem gamblers. Spunt et al. (37) found even higher rates in a sample of 117 methadone patients, also from the New York City area; 16% were pathological gamblers and 15% were problem gamblers, for a combined lifetime prevalence rate of 31%. Finally, Ledgerwood and Downey (38) reported that among 62 patients enrolled in an inner-city methadone maintenance program in Detroit, 18% met criteria for pathological gambling, while 11 % were problem gamblers.

Cannabis Abuse

Only one known study (33) has evaluated rates of gambling disorders in patients seeking

treatment for cannabis problems. This study found very high rates of gambling disorders in marijuana abusers, with 14% identified as problem gamblers and 24% as pathological gamblers. Substance-abusing patients with marijuana use disorders were more likely to suffer from gambling problems than patients with any other drug use disorder in that study, but the number of patients within each substance abuse category was not stated. Therefore, these results may be biased by small samples in some of the drug use categories and require replication in other samples of treatment-seeking marijuana users.

In conclusion, these findings indicate that gambling is an important comorbid condition that should be routinely evaluated in addiction treatment settings. In the next sections, we describe problems associated with dual diagnosis, and then we suggest methods to screen for gambling disorders among substance abusers, and possible treatment interventions.

ONSET AND SEVERITY OF PROBLEMS IN DUALLY DIAGNOSED PATIENTS

In studies evaluating the prevalence of gambling disorders in treatment-seeking substance abusers, most find that individuals with dual addictive disorders have more severe problems than individuals with a substance use diagnosis alone. These problems include psychosocial and legal difficulties, more psychiatric symptoms, and more severe drug use problems.

In terms of psychosocial problems, several studies have found that disordered gamblers identified among treatment-seeking substance abusers have more severe employment, legal, and family difficulties. For example, Hall et al. (35) found that cocaine-dependent patients with pathological gambling were more likely to be unemployed, to have recently engaged in illegal activities for profit, and to have served time in prison than cocainedependent patients without pathological gambling. In another sample of cocaine abusers, Steinberg et al. (34) reported that those identified with pathological gambling had more arrests, were convicted on more occasions, and spent more time in prisons than those without gambling problems. Langenbucher et al. (28) did not assess illegal activities, but they found that substance abusers with pathological gambling scored higher on indices of social impairment than substance abusers who were not pathological gamblers. Petry (39) found that severity of gambling problems in substance abusers was significantly and independently predictive of high-risk sexual activities that spread HIV and other infectious diseases.

Psychiatric disorders and symptoms also appear to be more severe in substance abusers identified with gambling problems. Both Hall et al. (35) and Langenbucher et al. (28) reported increased rates of conduct disorder, attention deficit disorder, and antisocial personality disorder among substance abusers with gambling problems than among those without. Steinberg et al. (34) noted increased rates of attention deficit disorder among cocaine abusers with gambling problems. McCormick (27) found that substance abusers with gambling problems scored higher on measures of impulsivity, aggression/hostility, and negative affect. Petry (40) found they had increased symptoms of somatization, obsessive-compulsive behavior, interpersonal sensitivity, hostility, and paranoia than

substance abusers without gambling problems.

Finally, severity and number of drug use problems appear to be increased in substance abusers with gambling problems relative to those without. Hall et al. (35) found that cocaine patients identified with patho logical gambling had higher rates of tobacco dependence than cocaine abusers without pathological gambling. In a general sample of substance abusers, Langenbucher et al. (28) noted higher nicotine dependence scores, more frequent use of alcohol, more alcohol dependence symptoms, and more other drug dependence symptoms in pathological than in nonpathological gamblers. Steinberg et al. (34) reported increased prevalence of alcohol dependence in cocaine abusers with pathological gambling compared to cocaine abusers without pathological gambling. They also had more drug abuse treatment attempts, a greater number of overdoses, and more frequent recent drug use than nonpathological gamblers. McCormick (27) found that substance abusers with gambling problems abused a greater number of substances than nongamblers. Daghestani et al. (26) found that substance-abusing veterans who had a gambling problem began drug and alcohol use at an earlier age and reported more frequent current alcohol use than their counterparts without a gambling problem.

While the evidence is quite strong that gambling problems among substance abusers are associated with increased problems along a number of dimensions, very little research has addressed issues related to onset and patterning of the disorders. Cho et al. (32) found that alcohol problems more often preceded gambling problems in the majority of their sample of alcoholic men with problem gambling in Korea. Hall et al. (35) similarly found that onset of gambling preceded onset of cocaine dependence in 72% of their cocaine-dependent sample from the Baltimore, Maryland, area. Cunningham-Williams et al. (29) found that most pathological gamblers began smoking cigarettes, drinking alcohol, and smoking marijuana prior to developing gambling problems, but pathological gambling often preceded dependence on other drugs, especially stimulants.

Regardless of which comes first, once pathological gambling and substance abuse become manifest, the two disorders may perpetuate one another. Spunt et al. (37) found that substances are often used in conjunction with gambling. Methadone patients in that study reported that they combined gambling and drug use to make money to buy drugs, to increase their high from drugs, and that they used drugs to celebrate after winning at gambling. In laboratory models with healthy subjects, Baron and Dickerson (41) found that ingestion of alcohol reduced resistance to begin and resistance to end a gambling session, and Kyngdon and Dickerson (42) demonstrated that alcohol prolonged the duration and intensity of gambling. Thus, the use of substances immediately prior to or during gambling may impair judgement and lead to increased problems in one or both areas.

In terms of the relationship of disordered gambling with outcomes of substance abuse treatment, only a couple of studies have been published. Ledgerwood and Downey (38) found that methadone-maintained patients identified with pathological gambling were more likely to use cocaine during treatment, and were more likely to drop out of the clinic within a 6-month follow-up period than their counterparts without pathological gambling. In contrast, Hall et al. (35) did not find that pathological gambling status was associated with increased cocaine or opioid use or treatment retention in samples of drug-free, cocaine-dependent and methadone-maintained, cocaine-dependent outpatients.

Thus, more research needs to be conducted to ascertain whether gambling status influences the outcomes of substance abuse patients.

SCREENING AND TREATMENT OF GAMBLING PROBLEMS AMONG SUBSTANCE ABUSERS

Given the high rates of comorbidity and the increased problems among the dually diagnosed, all substance abusers initiating treatment should be screened for gambling problems. The most common instrument for assessing gambling problems is the South Oaks Gambling Screen (SOGS) (43). This is a 20-item scale, and individuals endorsing five or more items are identified as "probable" pathological gamblers. More than two endorsed items is usually indicative of problem gambling. The SOGS was based on DSM-III-R criteria and demonstrates good reliability and validity in clinical samples (43). It is widely used in epidemiological studies, but data regarding psychometric properties in general populations are lacking (44). Despite its widespread use, some criticisms of the SOGS are noted. Because it is a lifetime measure, it is not sensitive to changes in gambling over time. It also has been criticized as having a high false-positive rate (45,46), but it still may be useful for identifying substance abusers at risk for gambling problems.

The NORC study (3) used a DSM-IV-based questionnaire called the NODS. Affirmative responses to five or more of the ten criteria classify individuals as pathological gamblers, with greater than two positive responses indicating problem gambling. Both lifetime and past-year versions are available. Limited data regarding its reliability and validity are available, but the NODS generally identifies lower prevalence rates than the SOGS (e.g., Ref. 7).

TREATMENTS FOR PATHOLOGICAL GAMBLING

Once problem or pathological gambling is identified, clinicians are left with an additional condition to treat. However, few randomized controlled trials of treatments for pathological gambling have been conducted (47), and no known studies have been published that have specifically examined interventions for gambling disorders in samples of patients who are seeking substance abuse treatment. The lack of data on efficacy or effectiveness of treatments for disordered gambling substance abusers makes treatment recommendations speculative. Below, we briefly review the most common interventions for individuals seeking treatment specifically for pathological gambling, and we provide suggestions for the possible roles of these treatments for substance abusers with gambling disorders.

Gamblers Anonymous

Gamblers Anonymous (GA) is the most popular intervention for pathological gamblers, with over 1000 chapters existing in the United States. GA is a self-help fellowship

modeled after Alcoholics Anonymous (AA). The philosophy and structure of GA are similar to those of AA. GA proposes that pathological gambling is a disease that can never be cured, but only arrested by complete abstinence from gambling. As in AA, 12 principles or steps are followed, and members "work the steps." These steps include accepting their problem and powerlessness over gambling and surrendering to a Higher Power. Many of the slogans and philosophies used in AA have been adapted by GA, including "taking one day at a time," and the Serenity Prayer.

Referring substance-abusing patients identified with a gambling problem to GA may be a reasonable approach to treat their gambling problems. The modality and philosophies of GA would appear to be familiar to most substance abusers. However, despite the popularity of GA, little published literature exists on the efficacy of this intervention for reducing gambling. One study (48) found that less than 10% of 232 consecutive attendees at GA meetings became actively engaged in this fellowship and were abstinent a year later.

In a recent study of 345 consecutive admissions to outpatient gambling treatment programs in Connecticut, Petry (49) found that patients with a substance use disorder were less likely to have involvement with GA than patients without substance use problems. The relative lack of involvement of substance abusers in GA may be reflective of demographic differences or perceived severity of problems. Given the emphasis on complete abstinence and concepts of "rock bottom," substance abusers with less severe gambling problems may not respond well to GA. Individuals who are seeking treatment for drug use problems, by definition, would be likely to have less severe gambling problems than substance abuse problems. They may be reluctant to endorse a complete abstinence goal for gambling, and may be less likely to relate to other members of GA. Therefore, referral to GA may be a useful option only among a relatively small number of treatment-seeking substance abusers with severe gambling problems.

Effectiveness appears to be enhanced when professionally delivered counseling is provided in conjunction with GA. Lesieur and Blume (12), Russo et al. (50), and Taber et al. (51) conducted follow-up evaluations of patients with gambling problems who were treated in inpatient programs that combined GA and professional therapy. Often, treatments for substance abuse and gambling problems were combined in these settings. Across these studies, gambling abstinence rates 6–14 months after treatment ranged from about 25% to over 50%, and attendance at GA, as well as engagement in professional treatment, was positively associated with outcomes. However, in the above studies, the professional treatment was not standardized or well described, and random assignment procedures were not used.

Cognitive-Behavioral Therapy

Cognitive-behavioral therapy is a relatively widely used treatment for pathological gambling. In three studies (52–54), this type of therapy was shown to be more efficacious in treatment-seeking pathological gamblers than a wait-list, or no further treatment, control condition. Cognitive-behavioral treatments for pathological gambling tend to vary in their emphasis across site and treatment programs. Some are oriented toward relapse prevention and based on traditional models of cognitive-behavioral therapy for substance

use disorders, while others focus on irrational cognitions associated with gambling. Much more study of this area is needed. Through an NIH-funded grant, we are currently evaluating the efficacy of cognitive-behavioral treatment.

Our treatment provides an overall framework for restructuring the environment to increase reinforcement from nongambling behaviors. Gamblers are taught to identify triggers of gambling, which in the case of substance abusers may include use of drugs or alcohol. They are taught to conduct functional analyses of their gambling. The functional analysis consists of breaking gambling episodes into their precipitants (or triggers), and evaluating both the positive and negative consequences of the gambling. In another session, gamblers are provided with a "leisure checklist" that contains lists of activities and hobbies and are asked to check those they once liked to do, or those they might consider trying in the upcoming weeks. In other sessions, gamblers are taught to brainstorm about new ways of managing both expected and unexpected triggers, in order to help them handle cravings and urges to gamble. Because interpersonal conflicts commonly trigger gambling, skills training and role-playing for handling interpersonal conflict are included. Each session concludes with a weekly tracking form to record triggers, cravings, or interpersonal difficulties, as well as the response strategies the client used to cope with such situations.

One session is devoted to addressing cognitive biases associated with gambling, such as selectively remembering wins while not giving equal weight to the multitudes of losses experienced (the availability heuristic), overestimating the odds, and superstitious behaviors. Finally, the "gambler's fallacy" is reviewed; this refers to belief that a future win or loss is related to past payoffs when, in fact, gambling episodes are discrete entities.

Many of the exercises used in such an approach can incorporate issues relevant to both substance use and gambling. For example, if drinking is a trigger for gambling, then scheduling alternative activities that do not involve either drinking or gambling would be important. Cognitive-behavioral treatment may be particularly useful for patients with both substance abuse and gambling problems. The work of Castellani et al. (24) supports this idea. They reported that coping responses were poorer in substance abusers who also have a gambling problem than in patients with only a substance use diagnosis. Further research is necessary, however, to confirm these findings and to assess the short- and long-term efficacy of cognitive-behavioral therapy in samples of treatment-seeking pathological gamblers as well as among substance abusers with concurrent gambling problems.

Motivational Approaches

Another promising approach to treating addictive behaviors is motivational enhancement therapy (e.g., Ref. 55). This treatment is based on the conceptualization that behavior change occurs through identifiable stages (e.g., precontemplation, contemplation, action, and maintenance), and that motivation represents a state of readiness to change that can be influenced by use of stage-specific interventions (56,57). The therapist elicits the individual's understanding of the consequences of his or her substance use or gambling and strengthens commitment to change. Motivational enhancement techniques have been

shown to be efficacious in reducing alcohol use among heavy alcohol users (as reviewed in Ref. 55). Reports describe the rationale behind and use of motivational techniques to treat gamblers as well (e.g., Refs. 58,59).

Dickerson et al. (58) demonstrated the efficacy of a brief intervention that combined coping skills training and motivational techniques to treat pathological gamblers. They randomly assigned 21 gamblers to one of two brief interventions: a self-help manual alone, or the manual plus a motivational interview. Gambling behaviors were assessed prior to distribution of the manual and 3 and 6 months later. Compared to pretreatment levels, both groups showed reductions in days gambled, average amount spent per gambling episode, and mean dollars per week spent on gambling. The only difference noted between the groups was that those assigned to the manual plus interview intervention showed a more marked reduction in gambling at the 3-month evaluation, but this group also had more problems with gambling prior to the intervention. Whether the interview provided benefit above and beyond the manual cannot be determined. Nevertheless, this study suggests that brief motivational/skills-training interventions may be effective in reducing gambling.

Hodgins et al. (59) conducted a much larger study of the efficacy of motivational enhancement therapy in treating gamblers. One hundred and five individuals were randomly assigned to one of three conditions: a 1-month wait-list, a cognitive-behavioral skills training workbook, or the same workbook plus a one-session telephone intervention with a therapist using motivational enhancement techniques. The workbook plus motivational intervention resulted in a significantly greater reduction of gambling than the wait-list control condition. In the follow-up periods, the patients assigned to the motivational intervention tended to maintain their gains better than those who received only the workbook.

These results demonstrate the possible efficacy of motivational techniques in reducing gambling. Due to their brief duration and nonconfrontational approach, motivational enhancement treatments may be suitable for substance abusers who are identified as having a gambling problem during the course of substance abuse treatment. Integrated treatments, combining motivational enhancement techniques either alone or in conjunction with cognitive-behavioral skills training for both substance use and gambling problems, may be particularly useful for this population.

SUMMARY

In summary, substantial evidence suggests that disordered gambling and substance use are common comorbid conditions. General population surveys as well as studies in treatment-seeking populations point to a high prevalence of comorbidity between these disorders. Individuals with both gambling and substance use problems tend to have more severe problems along a number of dimensions than individuals with either disorder alone. These results underscore the need to develop and test treatments for patients with comorbid conditions. To date, little systematic research has evaluated treatments for substance-abusing pathological gamblers, but integrated treatment, focusing on both the substance use and gambling problems, may assist in reducing problems associated with

one or both disorders.

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14
The Neuropsychology of Alcoholism

Effects of Premorbid and Comorbid Disorders

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INTRODUCTION

Given the extensive literature on alcohol's effects on brain function, this chapter will review only that literature, rather than attempt to cover the neuropsychological effects of a wider range of drugs of abuse. The reader is referred elsewhere to published reviews of the neuropsychological effects of cocaine (1–3) and opioids (4,5).

Neuropsychological studies of alcohol-related brain dysfunction have quantified what has been known for hundreds of years, namely that chronic alcohol use can have a deleterious effect on human cognition and personality. The sensitivity of neuropsychological testing has proved to be important in demonstrating the scope and range of the problem. This includes elucidating the nature and prevalence of impairment among problem drinkers, the role of impairment as a limitation in treatment, and the potential for recovery among chronic alcoholics who can maintain sobriety. Neuropsychological testing in children exposed to alcohol during gestation has been instrumental in defining the fetal alcohol syndrome and fetal alcohol effects that are often overlooked at birth. Prospective studies of non-affected family members of alcoholics have helped to identify neuropsychological variables that may be risk factors for problem drinking.

Excessive alcohol use and alcohol-related cognitive dysfunction rarely occur in isolation. Concomitant developmental learning disabilities, personality disorders, polysubstance abuse, poor nutrition, physical ailments, and head trauma are a few of the many comorbid conditions reported to occur in patients with alcohol abuse and dependence. Moreover, each condition is known to have a potential negative impact on normal cognitive functioning that is independent of alcohol abuse. Like many brain diseases that can result in cognitive dysfunction, the aging process also increases an alcoholic's vulnerability to more severe and permanent cognitive dysfunction.

Despite the frequency of premorbid and comorbid diagnoses among alcoholics, most investigations attempt to isolate the effect of one variable, such as alcohol use, on cognitive change. However, given the theme of this book, this review of the literature will emphasize the synergy between common premorbid and comorbid conditions and excessive alcohol use in shaping neuropsychological function. Premorbid conditions to be discussed include the effects of prenatal exposure to alcohol and their relationship to

developmental disorders such as attention deficit disorder, conduct disorder, and antisocial behavior—all known risk factors for subsequent alcohol abuse. The review will also examine the potential role of excessive alcohol use in degenerative brain disorders that occur towards the end of life, including Alzheimer's disease. Finally, an attempt will be made to explain at least some of the variability in severity and neuropsychological outcomes related to alcohol misuse and alcoholism, using the model of brain reserve capacity or threshold theory (6). Brain reserve capacity is a hypothetical construct proposed to explain differences in threshold for the onset of clinical syndromes and severity of impairment in neuropsychological functioning.

NEUROPSYCHOLOGICAL CONSEQUENCES OF ALCOHOL

The most severe forms of alcohol-related cognitive dysfunction are Korsakoff's syndrome and alcohol dementia. Korsakoff's syndrome is characterized by profound memory loss and impaired executive functioning, with relatively normal IQ scores (7). Alcoholics who meet the usual DSM-IV (8) criteria for dementia, including profound amnesia without preserved intelligence, are often given the diagnosis of alcohol dementia, although some consider alcohol dementia to be the result of multiple etiologies (9). Relative to the number of alcoholics in the United States, which is estimated to be about 10% of the population (7), the number of patients with alcohol Korsakoff 's syndrome or alcohol dementia is relatively low (9). However, large-scale studies of alcoholics in treatment have reported that as many as half of recovering alcoholics have measurable brain abnormalities and cognitive deficits during the intermediate abstinence period (10), which begins after detoxification and extends through the first two months of abstinence (11). Other reviews have estimated that as high as two-thirds of patients have significant neurocognitive impairment, depending on subject selection and treatment setting (11).

The use of refined neuroradiological, neurophysiological and neuropsychological techniques has demonstrated clear evidence of neuropathology during the intermediate-stage abstinence period. Computer tomography (CT) scans of the brain have shown cortical atrophy, enlarged ventricles, widened cerebral fissures and sulci, and enlarged cerebellar cisterns and sulci (12–14). Magnetic resonance imaging (MRI) studies have confirmed and clarified the nature of structural abnormalities in abstinent alcoholics. Enlarged ventricles and sulcal spaces are associated with reduced volumes of adjacent subcortical and cortical gray matter (15). Whereas younger alcoholics (26–44 years old) show reductions in cortical gray matter but not white matter, relative to controls, older alcoholics show reductions in both gray and white matter, particularly prefrontal gray matter (16). This pattern is consistent with functional neuroimaging studies, positron emission tomography (PET), and single photon emission computed tomography (SPECT), which have demonstrated diffuse hypometabolism, primarily in the frontal lobes of such patients (17). Studies of resting EEG show that alcoholics in treatment have decreased activity in the normally dominant alpha range and increased low-frequency activity (18,19), and decreased P300 amplitudes in the evoked response potential (ERP) to novel or infrequent stimuli (20). A multicenter study of ERPs in 393 alcohol-

dependent adults and 170 controls confirmed decreased P300 responses to a rare visual target, but only from anterior brain sites (21). Reviews of neuropsychological studies consistently show defects in learning, memory, problem solving, and perceptual motor skills (7). Although overall intelligence and language skills appear mostly unaffected, at least mild deficits in executive functioning are frequently reported (22). Mild generalized brain dysfunction with variable patterns of impairment have been postulated as the most parsimonious explanation, given the wide range of alcohol-related deficits (7). However, others (23) argue that the frontal lobes are particularly vulnerable to the effects of alcohol, and that impaired executive functioning constitutes the core cognitive disorder.

There is abundant evidence to indicate that the severity of alcohol-related changes in the brain and cognition are more pronounced in the older alcoholic. Although some studies described changes in alcoholics younger than 40 years old (24), others do not (25). It has been argued that residual neuropsychological deficits occur only after 10 or more years of problem drinking (26). However, a recent study demonstrated that groups of alcoholics with 4–9 years of problem drinking or 10 or more years of problem drinking both performed more poorly than controls on tests of word knowledge, verbal abstractions, and psychomotor performance (24). The two alcohol groups did not differ on any measure.

Abnormal brain morphology is significantly greater in older alcoholics than in younger ones (14,27). Moreover, alcohol-induced brain abnormalities are more related to age than to years of problem drinking (27–29). Memory loss is also greater in older than younger alcoholics (30). In these studies, younger alcoholics performed similarly to older controls, suggesting that excessive alcohol use may cause premature aging. Thus, there appears to be sufficient evidence to conclude that the aging brain is more susceptible to the effects of alcohol than are the brains of younger alcohol abusers, although the mechanism of this effect has not yet been determined.

Although the literature shows a consistent relationship between age and impairment in recovering alcoholics, younger alcoholics are not immune from alcohol-related cognitive impairment. A recent study of teenage alcoholics, aged 15–16, reported verbal and nonverbal retrieval defects and impaired visuospatial functioning compared to adolescents without alcohol problems (31). Because children with certain developmental disorders appear to be at risk of becoming alcoholic at a young age and developing a severe form of the disorder, some researchers have postulated that some cognitive deficits may predate the onset of drinking (32,33) or that they at least make some problem drinkers more susceptible to alcohol-related brain damage (34).

DEVELOPMENTAL DISORDERS, ALCOHOL, AND THE BRAIN

The role of alcohol's effects on the developing brain will be reviewed from two perspectives: effects resulting from exposure to alcohol in utero and developmental disorders that have been linked to the development of alcoholism. Brain damage resulting from prenatal alcohol exposure has been labeled fetal alcohol syndrome (FAS) or fetal alcohol effects (FAE), depending on facial morphology. Exposure to alcohol in utero has been linked to high rates of cognitive deficits and psychopathology, including high rates

of substance abuse. Attention deficit hyperactivity disorder (ADHD), conduct disorder (CD), and antisocial personality (ASP), in particular, have been thought to involve developmental deficits in neuropsychological functioning that may increase the risk of substance abuse. Much of the research focusing on these developmental disorders has used family history to designate high- and low-risk groups. In the following paragraphs, I will review this literature and attempt to build a model of additive risk based on ideas proposed in the brain reserve hypothesis (6).

Fetal Alcohol Syndrome and Fetal Alcohol Effects

Fetal alcohol syndrome (FAS), first described by Jones and Smith (35), is one of the leading known causes of mental retardation in the U.S. (36), affecting as many as 4.8 per thousand children (37). The diagnosis of FAS requires evidence of growth deficiency, a compromised central nervous system (CNS), facial dysmorphology, and the presence of maternal alcohol abuse (38). The related diagnosis of fetal alcohol effects (FAE) has been applied to patients with CNS compromise and a history of prenatal exposure without all of the physical findings. The population prevalence of FAE for children born in Seattle in 1975 was estimated to be higher, about 6:1000 (37). However, without the physical abnormalities, individuals with FAE are often not recognized as having alcohol-related deficits (see Mattson et al. (39) for a comprehensive review).

Children with FAS/FAE show a broad range of cognitive deficits, including impaired overall intellectual functioning, attentional disorders, reduced short-term memory, and deficits in executive functioning. Although FAS/FAE children have been consistently described as having below-average IQ scores (40,41), there is considerable variability in their IQ. In a sample of 178 individuals with FAS, the average IQ was 79, with a range of 29 to 120 (42). In a sample of 295 individuals with FAE (42), the average IQ was 90, with a range of 42 to 142. Thus, a large number of FAS/FAE individuals have IQ scores in the normal range. However, the frequency and severity of cognitive deficits in non-retarded FAS/FAE children are typically disproportional to what would be predicted on the basis of IQ alone (43).

A variety of other deficits have also been associated with exposure to alcohol in utero (44,45). Conry (46) showed significant deficits in FAS children, as compared to controls, in intellectual abilities, motor development, development of visual/perceptual abilities, attention, and receptive and expressive language skills. A psycholinguistic assessment on a small group of FAS children (47) identified deficits in the production and comprehension of grammar, semantic comprehension, short-term memory, and articulation. Relative to controls, children with FAS and FAE are impaired on tests of language skills, verbal learning and memory, academic skills, fine motor speed, and visual motor integration (39). Moreover, this consistent pattern of deficits may be independent of the physical features associated with FAS.

Nanson and Hiscock (48) compared attentional skills in children diagnosed with ADHD to children with FAS, and to normal controls. Four aspects of attention were investigated: 1) the investment, organization, and maintenance of attention and effort; 2) the inhibition of impulsive responding; 3) the modulation of arousal level to meet situational demands; and 4) the inclination to seek immediate reinforcement. FAS and

FAE subjects were generally slower and showed greater benefit from practice than did controls or subjects with ADD. The FAS/FAE subjects were also unable to modulate arousal to meet task demands. However, the FAS/FAE subjects were similar to the ADD subjects in that both groups exhibited difficulties with the inhibition of impulsive responding and the investment, organization, and maintenance of attention over time. Some investigators have attempted to link FAS/FAE to ADD on clinical grounds (49). However, the differences in patterns of attention deficits (50) and the differences in the brain regions affected in each disorder make any attempt at linkage questionable.

Children exposed to alcohol prenatally often show impairment in fine and gross motor movement (51). The alcohol-exposed children were slower on the grooved pegboard task, took longer to correct errors, and had poorer balance on all gross motor tasks. Conry (46) also found that tasks of motor function distinguished children with FAS and FAE from controls.

Although facial anomalies may become less notable by adulthood, the neurological and neuropsychological deficits of FAS persist (52). Academic functioning in adults with FAS was at the early grade school level. Particular difficulties were noted in abstraction ability, attention, judgment, communication, and socialization skills. FAS/FAE adolescents and adults also have particular difficulty performing calculations and in cognitive estimation (53). The greatest impairment was found in cognitive estimation, which is sensitive to frontal lobe lesions. More recent work has identified specific impairment on many standard neuropsychological measures of executive functioning (54), which are also localized to frontal brain regions.

Limited data suggest that adolescent and adult FAS/FAE individuals have a high frequency of personality disorders and other psychopathology, particularly substance abuse. Specific problems include impulsivity, failure to consider consequences of one's action, lack of appropriate initiative, stubbornness or sullenness, social withdrawal, crying or laughing too easily, and periods of high anxiety (52). Twenty-five subjects, 18 or older, who met the criteria for FAS/FAE and who had an IQ of at least 70 were given a structured clinical interview (55). Eighteen (72%) had received inpatient psychiatric treatment. The most common DSM Axis I disorders were alcohol and drug dependence (60%), depression (44%), and psychotic disorders (40%). In a 14-year follow-up of a study of pregnant women with self-reported alcohol use, there was a high incidence of adolescent alcohol use among their adolescent children (56). Fetal alcohol exposure was a more powerful predictor of adolescent alcohol use than a family history of alcoholism.

The neuroanatomical abnormalities contributing to this diverse set of deficits in FAS/FAE are still being elucidated. Neuropathological case studies of FAS children revealed that cerebellar dysgenesis was the most frequent brain abnormality at autopsy (57). This finding is particularly interesting in light of the fact that only half of the subjects examined postmortem exhibited sufficient external characteristics to warrant a diagnosis of FAS. Thus, even in the absence of the gross physical anomalies typically associated with FAS, prenatal alcohol exposure can affect the structural integrity of the brain. Neurological abnormalities reflecting cerebellar dysfunction were described in each of five case studies of children diagnosed with FAS (58), including kinetic tremors, axial ataxia, and dysdiadochokinesis. More recent work using magnetic resonance imaging (MRI) to compare neuroanatomical differences between FAS/FAE and normal

individuals revealed marked differences in the shape of the corpus callosum and the relationship between the diencephalon and the brain stem. There were no differences in these features between FAE and FAS subjects (59). FAS/FAE adults also have much greater variability in callosal shape than normal subjects (60). A relatively thick callosum was associated with a pattern of executive functioning deficits, whereas a relatively thin callosum was associated with deficits in motor function. Neither variation was related to full-scale IQ or a distinction between FAS and FAE. However, these data are consistent with studies that show a variety of deficits in FAS adolescents with normal or low-average IQ scores.

Developmental Risk Factors for Adult Alcoholism

Attention Deficit Disorder

Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder that affects an estimated 3–5% of children. Childhood ADHD, previously referred to as hyperkinesis (HK) and minimal brain dysfunction (MBD), has long been considered as a possible risk factor in the development of alcoholism (32). The term MBD lost favor in the late 1960s because of the lack of objective evidence of structural brain damage (61). Although there are theoretical and clinical distinctions between the MBD syndrome and the currently used DSM-IV diagnosis of ADHD, there is considerable symptom overlap. Because much of the early research refers to MBD, that term will be used when reviewing those studies. The presence of MBD was typically assessed retrospectively using a behavior checklist (62), whereas ADHD is defined by actual behavioral criteria. The DSM-IV (8) criteria list the symptoms of inattention separately from those of hyperactivity and impulsivity, so that the diagnosis for each subtype can be made independently.

Theories about the core nature of ADHD have evolved from the belief that the central deficit was hyperactivity to a shift in focus on inattention. Currently, the focus is on deficits in cognitive control mechanisms that mediate attention and executive functions (63). Barkley (61) has proposed that behavioral disinhibition is the central cognitive deficit in ADHD. Behavioral disinhibition is defined as the failure to inhibit a prepotent response, to stop an ongoing response, or to maintain a response in the presence of distraction or interference. This core deficit sets the stage for other disrupted cognitive abilities. However, this theory primarily applies to the hyperactive-impulsive form of ADHD. To explain the full range of deficits seen in ADHD, including deficits in initiating and sustaining executive functions, others (64,65) have postulated that behavioral disinhibition alone is inadequate. They have proposed deficits in effort, arousal and activation, or in various executive functions. There is a continuing debate as to whether ADHD is a unitary disorder, or a collection of apparently similar disorders with different neurobiological substrates (66).

Although the pathophysiology of ADHD remains unknown, several lines of evidence point to anomalies in frontal lobe function. Measurements of brain regions based on MRI have shown anatomical differences between brain structures among patients with ADHD compared to nonaffected controls. In ADHD, the prefrontal cortex is reduced in size, particularly in the right hemisphere (67,68). Most studies find that ADHD individuals

have smaller caudate head and globus pallidus volumes than normal controls, but the results vary as to which hemisphere is most affected (67–70). White matter tract volumes have also been found to be reduced in right anterior brain regions (68) and in the corpus callosum (71–73). PET studies show reduced metabolism in anterior brain areas during the performance of an executive function in ADHD adults (74), but not in adolescents (75). To date, there have been only a few studies examining brain activity in ADHD using functional magnetic resonance imaging (fMRI). fMRI produces detailed measurement of brain activity through the use of blood-oxygen level changes that occur naturally in the brain following neural activity. Those studies show reduced activation in the right prefrontal cortex and left caudate nucleus (76) and anterior cingulate (77) in ADHD subjects compared to normal controls, on a variety of attention tasks.

ADHD is a developmental disorder that was once thought to affect only children until Wender and his colleagues (62) described cases in which symptoms persisted into adulthood. There is now a growing body of evidence to suggest that some ADHD symptoms continue into adulthood in some individuals (78). Estimates suggest that some form of the disorder persists in as many as 30–70% of those having the disorder in childhood, or 1–2% of the adult population (78,79).

Because core features of MBD include problems with attention span, concentration, perceptual cognitive functioning, distractibility, and poor organization, in addition to hyperactivity, Parsons and Leber (33) and others (32) speculated that neuropsychological deficits associated with alcoholism may, in part, represent residual deficits associated with childhood MBD. Tarter (32) compared two groups of alcoholics on the basis of their psychosocial drinking patterns. In this schema, primary alcoholics were those who could not identify any precipitating or specific cause for their excessive drinking. Additional criteria for primary alcoholism included beginning drinking at an earlier age, becoming addicted at a younger age, and having experienced more serious consequences related to drinking. Secondary alcoholics were alcoholics who did not meet these criteria. On a questionnaire of childhood HK/MBD symptoms, the primary alcoholics endorsed significantly more items than secondary alcoholics, suggesting that some aspects of development are related to severity of alcoholism. Because the symptoms of HK/MBD can persist into adulthood, the next question was whether primary alcoholics would show greater deficits on neuropsychological testing than secondary alcoholics. Tarter (32) compared primary and secondary alcoholics on a battery of cognitive tests requiring psychomotor control, speed of processing, and perceptual organization. Although the groups again differed on the number of self-reported HK/MBD symptoms in childhood, there were no differences in their neuropsychological test performances. However, Parsons (80) reported that, in addition to reporting more childhood symptoms of MBD, primary alcoholics were more impaired on verbal and abstract problem solving, complex attention, learning, and memory. Taken together, these data suggest that while MBD symptoms may be indicative of more severe forms of alcoholism, these symptoms alone do not always predict greater cognitive dysfunction. Also, these data do not negate the potential role of impaired premorbid neuropsychological functioning in contributing to alcohol-related cognitive dysfunction, but suggest that the relationship is more complex and may involve multiple variables and risk factors associated with the development of alcoholism.

Another way of examining cognitive impairment as a possible risk factor for the development of alcoholism is to study individuals who are at higher risk for the disorder because of a family history of alcoholism. It is well documented that an individual with at least one biological alcoholic parent will be at greater risk of also becoming an alcoholic (81). Alcoholics with a family history of alcoholism (FH+) are more likely to meet the criteria for primary alcoholism (82). An obvious advantage to studying the nonaffected offspring of alcoholics is that neuropsychological test performance will not be confounded by the effects of chronic alcohol use. Among nonalcoholic FH+ subjects, poorer neuropsychological performance on measures of executive functioning was a significant predictor of increased alcohol consumption in a three-year follow-up study (83). However, the attempt to find differences in neuropsychological test performance between nonalcoholic FH+ and individuals without a family history of alcoholism (FH−) has yielded mixed results.

Parsons (82) compared alcoholics and controls with or without a family history of alcoholism on a battery of neuropsychological tests. Alcoholics clearly performed worse than controls on measures of learning and memory, abstract problem solving, and a general impairment index. However, when the groups were compared by family history, there was only a modest decrement in performance for the FH+ group and only on the general impairment index. There were no interactive effects of alcohol dependence and family history of alcoholism, which led Parsons to suggest that these two variables are independent with regard to neuropsychological functioning. Tarter (32) compared the sons of alcoholics to the sons of normal or depressed fathers, using a comprehensive battery that included measures of intelligence, perceptual efficiency, language memory, psychomotor skill, attention, and abstract reasoning. The FH+ group performed more poorly than the other two groups in several cognitive domains including tests requiring planning ability, psychomotor efficiency, and inhibitory control. However, other studies have failed to find differences in performance using similar tests. Hesselbrock et al. (84) assessed childhood HK/MBD symptoms and neuropsychological test performance in FH+ and FH− nonalcoholic men and women. There were no differences in the number of self-reported childhood symptoms between groups, although more symptoms were indicative of an earlier onset of regular drinking. Each subject was also administered the Wechsler Intelligence Scale—Revised (WAIS-R) and the Halstead Reitan Neuropsychological Test Battery. Although the FH+ sample performed slightly lower on several measures, there were no statistically significant differences between groups, and all groups performed within the normal range. Workman-Daniels and Hesselbrock (85) were also unable to establish a relationship between HK/MBD symptoms and a family history of alcoholism, but did find that higher HK/MBD symptom scores correlated with poorer performance on selected measures of attention and memory.

Gillen and Hesselbrock (86) studied young, nonalcoholic FH+ and FH− men, differentiated by the presence or absence of antisocial personality disorder (ASP). They used a comprehensive battery of intelligence and neuropsychological tests, including the Wechsler Adult Intelligence Scale (WAIS-R) and multiple measures of executive function visual perception, learning, and memory. These investigators found no group differences or interactive effects on most of the WAIS-R or neuropsychological tests. The ASP group performed more poorly than the non-ASP group on measures of fine motor

coordination and verbal reasoning, but there were no family history effects. It is noteworthy that even when investigators found that FH+ and FH− groups differed statistically, the mean scores for all groups were within the normal range. For most neuropsychological tests, probable impairment and clinical significance are interpreted only when a score falls at least two standard deviations below the normative mean. In summary, when mean differences were found between nonalcoholic FH+ and FH− groups, these differences tended to be subtle and not clinically significant.

Although the evidence for differences in cognitive functioning between groups of nonalcoholic offspring of alcoholic fathers and controls is equivocal, differences in neurophysiology, including resting EEG activity and the event-related potential (ERP), appear to be more reliable indicators of family history. FH+ men, particularly those with ASP, show higher frontal high frequency β (18.6–27.6 Hz) activity than their FH− counterparts (87). ERPs are time-locked to the stimulus and represent the brain's response to the stimulus as well as cognitive processes engaged by the stimulus that are defined by the context of the task. The P300 component of an ERP is a wave of electrical activity that occurs about 300 milli-seconds after the presentation of a novel or rare stimulus. The P300 component is postulated to represent an electrophysiological indicator of attention to new or different information, similar to the orienting response. A recent localization study, using ERP together with f MRI and dipole modeling techniques, suggested that the P300 response recorded from the scalp originates from neural generators in the frontal (anterior cingulate) and posterior temporal regions (supramarginal gyrus) of the brain (88).

Studies comparing individuals differentiated by a family history of alcoholism have repeatedly demonstrated smaller P300 responses for those who are FH+ (20,81). It is important to emphasize that no direct link or mechanism has been established between low-amplitude P300 waveforms and the development of subsequent excessive alcohol use, other than that both family history and attenuated P300 responses appear to be risk factors for developing alcoholism. Moreover, reduced P300 responses are not unique to offspring of alcoholic fathers. P300 decrements have also been reported with other psychopathology (89), alcohol dependence (20,21), ASP (90,21), conduct disorder (91), ADHD (92,93), and toxic encephalopathy (94).

Conduct Dlsorder/Antisocial Personality Disorder

Child conduct disorder (CD) and its continuation into adulthood as adult antisocial personality disorder (ASP) is a major risk factor for the development of substance abuse as well as other health and social problems. CD often exists with ADHD in younger children, but CD has been shown to exist without comorbid psychiatric disorders in adolescents, with the prevalence of comorbidity depending upon whether subjects are recruited from treatment centers or non-treatment sources (91). ADHD children, particularly those with CD, are more likely to develop ASP traits during adulthood. CD, together with ADHD, is a known risk factor for the development of alcoholism (95). ASP has also been linked to earlier onset and severity of alcoholism (84). It is estimated that 25–33 percent of children with CD will display antisocial behaviors as adults (96,97). Approximately one-third of subjects with CD will meet the DSM threshold for antisocial

personality disorder (97).

ASP adults can be three to four times more likely to develop substance abuse than non-ASP adults (84). Moreover, among alcoholic males in treatment, ASP is among the most common comorbid disorders, with prevalence rates ranging between 16 and 49%. Female alcoholics are found to have lower but elevated rates of ASP, at approximately 20% (98). Stevens et al. (99) studied a large group of patients in treatment for substance abuse, with 1–5 months of abstinence from alcohol and other drugs of abuse. The primary determinant of residual cognitive impairment in these abstinent substance abuse patients was not years of substance abuse or months of abstinence, but a diagnosis of ASP with a history of conduct disorder. These cognitive deficits in ASP adults likely represent impaired premorbid functioning or a heightened vulnerability to the effects of alcohol and drugs of abuse. In contrast, children with CD who do not meet the criteria for ASP as adults appear to outgrow their deficits and are similar to controls when tested as adults (99). Other studies have also shown a link between ASP and symptoms of CD in nonalcoholic males and performance on neuropsychological tests that are sensitive to frontal lobe functioning, such as motor tests from the Luria Nebraska and Porteous Maze Test (100). Decrements in P300 amplitude over frontal, but not other, electrode sites have also been shown in comparisons of ASP with non-ASP, nonalcoholic men, further suggesting the presence of subtle frontal brain dysfunction (90). It has been proposed that ASP reflects a developmental delay in brain maturation in frontal brain regions (101).

In a large multicenter study, Bauer and Hesselbrock (91) studied the P300 component of the ERP as a function of CD, family history of substance abuse, and age. Whereas teenagers with more conduct disorder problems had significantly lower P300 amplitudes, a family history of alcohol or drug dependence had no appreciable effect on P300 amplitude. There was also decreased P300 attenuation from posterior brain regions among older adolescents, suggesting that these anomalies begin to disappear after age 16. However, there was an emergence in frontal P300 decrements in this older teenage group. Since normal brain development occurs from posterior to anterior regions, and the frontal lobes are not fully developed until late adolescence, this finding was interpreted to reflect delayed development in a subset of CD teenagers. The authors further speculated that these observations may represent the subset of CD adolescents who go on to develop ASP. Additional support for the delayed brain hypothesis comes from a study of 94 teenagers, aged 14–19, who varied in the type and number of conduct disorder problems. Among the four subtypes of conduct disorder problems—aggression, rules violation, deceitfulness, and destructiveness—boys with a history of rules violations failed to show the normal increase in P300 found in boys without a history of rules violations (101).

The etiological relationships between developmental disorders, family history of alcoholism, brain maturation, and frontal lobe functioning have only been partially disentangled. Nonetheless, there appears to be converging evidence for the presence of functional frontal lobe anomalies and subtle deficits in frontal lobe mediated behaviors that increase the risk of alcoholism. In the sections that follow, the role of alcohol-related cognitive impairment will be explored with respect to the maintenance of abstinence and the risk of relapse and the onset of dementia.

ABSTINENCE AND RECOVERY

Literature reviews of studies of neuropsychological recovery in sober alcoholics provide a consistent theme. There is a measurable recovery beginning about 2 weeks after detoxification (102), and cognitive recovery can continue in alcoholics who remain abstinent for several years (82). However, there is considerable variability among patient populations depending on the age, health, and presence of comorbid psychopathology. In addition, there is often recovery in one but not all cognitive domains. The most dramatic improvement occurs during the first 4 to 6 weeks following detoxification. Verbal abilities, such as verbal paired associate learning, recover relatively early during the abstinence period, whereas visual spatial abilities, abstraction and problem solving, and short-term memory show more persistent impairment. Goldman (102) reviewed the effects of practice in two studies of early recovery. Practice was assessed using a multiple testing paradigm. In both studies, tests of verbal learning, word meaning, and paired associate learning were administered to three groups of recently detoxified alcoholics after admission to a treatment program. The first group was tested on days 5, 15, and 25 following detoxification. The second was tested twice on days 15 and 25, and the third group only once on day 25. The patients tested on day 5 performed most poorly on every test. By day 15, performance was normal on all the verbal measures, with no additional improvement on day 25. However, a decrement in performance continued on the visual spatial paired-associate learning test on day 25 for those alcoholics with 12 or more years of heavy drinking. Thus, time rather than practice appears critical to recovery, at least in the short term.

In a large cross-sectional study, Brandt and colleagues (103) studied cognitive recovery in short-term abstinence (1–2 months), long-term abstinence (1–3 years), and prolonged abstinence (5+years) in 134 sober alcoholics. Subjects were compared to matched controls on measures of verbal short-term memory, non-verbal paired associate learning, non-verbal short-term memory, psychomotor speed, and visual perceptual pattern recognition. As with short-term recovery, the recovery of cognitive skills was a function of both time and task. Short-term memory for words and designs and psychomotor performance improved with abstinence, and those abstinent for at least 5 years did not differ from controls. However, deficits persisted on a paired associate learning task, in which numbers were matched with two-dimensional line drawings, or complex pattern recognition, and the three groups did not differ on these tasks.

Taken together, there appears to be a biphasic recovery of function, with rapid change early in sobriety (4–6 weeks) and a slower rate change occurring over many years. Verbal abilities, including new verbal learning, recover more quickly, and appear more resilient to the effects of alcohol-related brain changes than performance on tests requiring complex attention, visual perception, abstraction, and problem solving (102). Lastly, variables other than abstinence, such as comorbid psychopathology, can also affect recovery.

Relapse

More than half of all alcoholics in treatment resume drinking alcohol during the first year post-treatment. Neuropsychological deficits commonly found during treatment have been shown to contribute to this high rate of relapse. However, as with most studies of alcohol-related cognitive dysfunction, the results vary among studies. Generally, patients who perform more poorly on neuropsychological testing tend to remain abstinent longer, but not all studies support this conclusion (7). In a long-term (8–20 months) study conducted in a residential treatment community, patients classified as cognitively impaired, on the basis of neuropsychological testing, were more likely to be discharged from treatment due to rules violations, leave treatment against clinical advice, relapse faster after leaving treatment, and report more psychosocial adjustment problems (104). However, other factors, including depression and childhood attention deficit disorder, were also shown to affect treatment outcome.

Bauer (105) used a novel approach to predict relapse in alcohol-dependent patients. Quantitative EEG and autonomic activity during the first three weeks post-abstinence were compared to relapse within three months of abstinence. Relapse-prone patients had more fast activity EEG (β power) and greater cardiac pulse amplitude than nonrelapsing alcoholics and controls. Bauer (106) extended these EEG findings in a relapse prediction study of recovering alcoholics and polysubstance abusers. Again, fast β power activity in the resting EEG was a good predictor of relapse at three months post-treatment for both groups. In a secondary analysis, relapse was also associated with two premorbid risk factors, CD and a family history of alcoholism.

THRESHOLD MODELS

Alcohol and Dementia

Dementia, defined by the onset of multiple cognitive deficits, including memory impairment, affects 2–4 percent of the population over age 65 (8). Dementia related to probable Alzheimer's disease (AD) represents the largest proportion of these cases. Although criteria for diagnosing AD have been established (8,107), the etiology remains obscure. Despite recent advances in the genetics of AD, most notably the discovery of the apolipoprotein E (ApoE) gene on chromosome 19, genetic factors do not account for a relatively large percentage of AD patients (108). These findings have led many investigators to conclude that the causes of AD are likely to be heterogeneous and to involve both genetic and environmental factors.

The brain reserve capacity (BRC) model (6) is an attempt to explain differential thresholds in the onset and progression of neurological syndromes and neuropsychological impairment. The BRC model may be helpful in understanding disorders like AD, Parkinson's disease, vascular dementia, and HIV-1-related dementia, in which significant neuropathology can be present before overt symptoms of the disorder become apparent. Greater BRC provides some level of protection against functional impairment, whereas decreased BRC acts as a vulnerability factor, reducing threshold to time of onset and severity. In the case of AD, some environmental factors have been shown either to increase or to decrease the risk of dementia. For example, higher levels of

education and occupational achievement have been linked to a reduced incidence of AD (109). A sample of 593 nondemented adults between the ages of 60 and 99 were administered a brief neuropsychological test battery twice over a 4-year period. At follow-up, 106 met the DSM-III-R criteria for dementia. All but nine individuals met the criteria for possible or probable AD. The risk of dementia was significantly higher in the low education and low occupation groups and highest in the subgroup with both low education and low occupation. Why a higher premorbid level of cognitive functioning raises the threshold for developing probable AD is unclear. One possible explanation is that higher premorbid functioning makes AD more difficult to detect. Alternatively, higher levels of education and employment may reflect greater cognitive reserve, thereby providing a reserve against the early manifestations of disease. This protective phenomenon is not unique to AD. Higher levels of education and occupational achievement have been shown to produce a similar protective effect on the onset of neuropsychological impairment in HIV-1 dementia (110). In contrast, head injury early in life can exacerbate neuropsychological impairment in later years (111).

To our knowledge, the BRC model has not been applied to alcohol-related brain dysfunction. However, it follows that years of excessive alcohol use might reduce BRC and increase the vulnerability to dementia. In a review of three studies comprising over 300 patients (112), it was found that between 21 and 24 percent had a history of heavy alcohol use. On the basis of these data, it has been argued that significant numbers of patients diagnosed with AD or vascular dementia actually have alcohol dementia. Because there is a lack of clear diagnostic criteria for alcohol dementia, the diagnosis is often missed (see Smith and Atkinson (9) for a comprehensive review). However, rather than argue that alcohol dementia is underdiagnosed, I would propose that the brain damage sustained from excessive alcohol use may lower the threshold for degenerative diseases of aging, such as AD, by lowering BRC. As noted above, many abstinent alcoholics continue to have some measurable cognitive impairment, albeit mild in many cases, years after achieving sobriety. Thus, even in abstinent alcoholics whose cognitive functioning appears recovered, there may be increased vulnerability to dementia in later life because of subclinical neuropathology. Moreover, fast β power activity in the resting EEG and attenuated P300 amplitude in sober alcoholics may be markers of such pathology. By analogy, this is similar to the early stages of neuropathology in diseases like Parkinson's disease, AD, and HIV-1. In these disorders the pathology in early disease is not sufficient to reach a threshold for overt behavioral change.

Risk Factors for Alcoholism as Another Case of Reduced Threshold for Neuropsychological Impairment

Neural networks of the anterior brain comprise the primary substrates for mediation of attention and executive functions (113). The prefrontal cortex is believed to be specifically involved in the integration, execution, and regulation of planned behaviors. Damage to this region has long been recognized to result in a syndrome of impulsive and disinhibited behavior (114). Giancola and Moss (22) reviewed this literature and concluded that deficits in executive functioning characterize individuals with a variety of disinhibitory disorders, including alcoholism and ASP. However, many studies have not

shown strong evidence of impaired cognitive functioning in these high-risk groups (85,86,115). EEG studies (90,106) and ERP studies (21,81) have consistently shown abnormalities associated with anterior brain functioning, compared to controls. It has been hypothesized that these brain anomalies represent developmental delays in brain maturation, which together with other risk factors predispose affected individuals to later substance use disorders (116). However, these neurophysiological markers of increased vulnerability rarely correspond to differences in ERP task performance (91) or the presence of neuropsychological deficits (84). It is therefore possible that these anomalies are only markers with no functional significance. Alternatively, these brain anomalies, while not affecting neuropsychological test performance, may represent altered thresholds that make affected individuals more (or less) susceptible to specific behaviors, such as problem drinking, under certain conditions. Silent premorbid conditions are known to lower the thresholds for neuropsychological deficits in other clinical syndromes such as mild head injury (117) and dementia (118). Thus the threshold model appears useful for explaining how physiological anomalies, such as attenuated P300 components of the ERP, while subclinical, may alone or in concert with other risk factors contribute to increased vulnerability to alcoholism. Moreover, this model lends itself to empirical evaluation.

FUTURE DIRECTIONS

Future research in the neuropsychology of alcoholism should address individual risk factors. Neuropsychological testing has been shown to be a powerful method for evaluating developmental disorders and changes in cognition and other behaviors secondary to alcohol use.

However, the traditional approach to measuring changes in cognition that follow treatment is to compare group differences using inferential statistics. In these models, significant mean differences on group scores can provide evidence of the efficacy of treatment. Although useful for assessing the overall effect on high-risk groups or abstinent alcoholics, this may not be useful in evaluating endpoints that predict behavioral change for the individual patient. With the impetus coming from the use of neuropsychological methods to assess drug efficacy and the search for methodologies whose validity is based on evidence, this has been a new challenge for the field of neuropsychology. To this end, several methods have been developed (119) to assess change in neuropsychological variables in individual patients. In order to assess individual risk it will be necessary to adapt these methods to the neuropsychology of alcoholism.

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15
HIV Infection

From Dual to Triple Diagnosis

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INTRODUCTION

Since first reported in 1981, human immunodeficiency virus type 1 (HIV) infection and its late manifestation, the acquired immune deficiency syndrome (AIDS), have become epidemic in the United States and other parts of the world. Worldwide, some 40 million people are living with HIV/ AIDS (1). In the United States, it is estimated that more than 800,000 people have been diagnosed with AIDS (2). Men who have sex with men and injection drug users (IDUs) have been the predominant HIV risk groups. Of men living with AIDS in 2001, 32% were IDUs or men who have sex with men and who were also IDUs (2). Women, ethnic minority groups, and children have been particularly hard-hit by injection drug-related and heterosexual transmission of HIV. Since the epidemic began, 57% of AIDS cases among women have been attributed to injection drug use or sex with partners who inject drugs. Of new AIDS cases reported in 2000, AIDS associated with IDU accounted for 26% of cases among African American and 31% among Hispanic adults and adolescents, compared with 19% of all cases among Caucasians (2).

Use of non-injection drugs such as crack cocaine is also a risk factor for HIV infection when users engage in unsafe sexual behaviors. Non-injection substance use and psychiatric disorders are common risk factors for HIV infection. This risk occurs among IDUs who come for HIV testing and counseling (3), among clinical samples of HIV-positive individuals seen in specialty medical clinics (4,5), among research cohorts of HIV-positive individuals assessed with standardized diagnostic instruments (6–8), and among seronegative men who have sex with men in an HIV vaccine preparedness study (9). Non-injection substance use and psychiatric disorders also increase risk among individuals who are not members of these high-risk groups. It is likely that the co-occurrence of drug use and other psychiatric disorders may have an additive effect on the risk for acquiring HIV by increasing the likelihood of risky sexual and drug use behaviors (10–12).

Practitioners in HIV treatment settings routinely face the clinical problems associated with substance use disorders. Substance use complicates the psychiatric diagnosis and treatment of patients with HIV (13,14), while HIV itself can produce psychopathology through direct effects on the central nervous system (15). The treatment of individuals with the "triple diagnosis" of HIV, substance abuse, and psychiatric disorders has multiple levels of complexity from ongoing substance use, increased psychological distress, and potentially poor adherence to medical treatment regimens (16,17). It is conceivable that these co-occurring disorders may be associated with greater morbidity and mortality (18,19). These concerns have led to the development of integrated HIV, drug abuse, and psychiatric treatment services (4,20–23).

In this chapter, we begin by reviewing the potential association between substance use, psychiatric disorders, and HIV risk behaviors. We then discuss the prevalence of psychiatric and substance use disorders among HIV infected individuals in various treatment settings and in research cohorts. Next, we discuss the medical, psychiatric, and substance abuse treatment of individuals with a triple diagnosis of psychiatric disorder, substance use, and HIV infection. Finally, we consider HIV risk reduction, issues related to the practitioner and the triple diagnosis patient, and then conclude with directions for future research.

In this chapter, we focus mainly on injection drug users, since they are most affected by HIV; however, we address non-injection drug and alcohol users where relevant. We will use a broad definition of dual (or triple) diagnosis to reflect the heterogeneity of this population. We therefore include individuals with severe mental illnesses such as schizophrenia, bipolar or schizoaffective disorders, in addition to those with depressive, anxiety, and personality disorders, since these disorders are prevalent among drug and alcohol users in general and among individuals in HIV treatment settings.

Substance Use, Psychiatric Disorders and HIV: Scope of the Problem

Evidence for a connection among psychiatric disorders, substance use, and HIV can be derived from four sources: 1) data concerning HIV risk behaviors of individuals with psychiatric and/or substance use disorders; 2) HIV seroprevalence studies in psychiatric and substance abuse treatment settings; 3) clinical samples of HIV patients in various treatment settings; and 4) cohort studies of psychopathology among homosexual/bisexual men and IDUs with HIV infection.

HIV Risk Behaviors of Individuals with Psychiatric and Substance Use Disorders

High levels of HIV risk behaviors are found both in groups of individuals with substance use disorders and in groups with psychiatric disorders. Injection and non-injection drug use and alcohol use are associated with HIV risk behaviors (24). Psychiatric disorders also appear to confer risk that is higher than that in the general population. Studies among psychiatric patients have revealed high rates of HIV risk behaviors (25) among both inpatients (26–29) and outpatients (10,12). For example, Cournos and colleagues (29) found that 44% of inpatients with schizophrenia were sexually active in the prior six

months and more than half had multiple sexual partners. Among the sexually active group, consistent condom use was infrequent, nearly half of individuals used alcohol or drugs during sex, and half had exchanged sex for money or drugs.

To date, evidence that having a dual diagnosis confers higher risk for HIV than having a substance use or a psychiatric disorder alone is largely indirect. A link between dual diagnosis and HIV risk can be inferred from the knowledge that psychiatric and substance use disorders frequently co-occur (30,31), that injection and non-injection drug use are known risk factors for HIV infection (32), and that psychiatric symptoms may magnify HIV risk (11,33) by producing impaired knowledge, judgment, and interpersonal skills regarding sexual and drug use behavior.

HIV Seroprevalence in Psychiatric and Substance Abuse Treatment Settings

Among drug users entering treatment, the prevalence of HIV varies greatly by geographical region and ranges from 0 to 35% (34). Among psychiatric patients, studies in the United States—mostly from the New York City area—using discarded blood samples revealed rates of HIV infection between 4.0% and 22.9% among inpatients (25,35). Factors associated with HIV-positive serostatus in studies of psychiatric inpatients have included younger age, ethnic minority status, poor reality testing, hypersexuality, childhood and adult sexual victimization, and homelessness, but the most prevalent risk factors have consistently been homosexual/bisexual activity among men, and history of IDU (25). Males and females in these studies have generally had equal HIV infection rates. Information on specific psychiatric and substance use disorders, and their combinations, has been limited in these studies. One study showed organic mental disorders (generally among individuals with known HIV serostatus), non-intravenous substance use, and bipolar, unipolar depressive, and schizophrenic disorders to be present in HIV seropositive psychiatric inpatients (36). Two other studies have shown schizophrenia with comorbid substance use (83% comorbidity in one study) to be the most common psychiatric diagnosis (37,38). In addition to the high rates of HIV risk behaviors and seroprevalence in these studies, it is noteworthy that HIV risk was often undocumented in patient records, those with documented HIV risk factors were infrequently tested by their treating clinicians, and up to 80% of those with unknown HIV status on admission whose discarded blood later tested HIV antibody positive were discharged without knowledge of their HIV-positive status (36,39,40).

Psychopathology and Substance Abuse in Clinical Samples of Patients with HIV

The triple diagnosis of HIV infection and psychiatric and substance use disorders is commonly described in studies of HIV-positive patients seen in integrated methadone maintenance treatment (MMT) programs and in HIV medical clinics. Clinical samples of IDUs with HIV infection entering methadone maintenance treatment (MMT) reveal high rates of prior psychiatric morbidity, current distress, and suicidal ideation (16). Further, while in MMT, up to 80% of these patients require psychiatric consultation for the

treatment of depression, psychotic symptoms, anxiety, insomnia, cognitive impairment, and behavioral disinhibition, often with concurrent substance (cocaine, amphetamine, alcohol, and/or sedative-hypnotics) abuse (41). Psychiatric symptoms in these patients are often attributable to multiple factors, including concurrent drug abuse, antiretroviral or other medications for HIV disease, or HIV infection in the central nervous system (15).

Reports describing HIV-positive patients seen in specialized HIV medical clinics document the frequent occurrence of psychiatric and substance use disorders, which complicate the manifestations and treatment of HIV infection (4,5,13,42,43). Clinical samples have tended to be heterogeneous, reflecting the demographics of the HIV epidemic in general, and provide information on HIV-positive individuals with differing HIV risk factors, gender, and ethnic backgrounds. Some clinical investigators have documented increased prevalence of prior suicide attempts (4,42–44) and psychiatric disorders (44) among HIV-positive substance users compared to individuals who do not use substances. Lyketsos and colleagues (4) found that more than 50% of individuals in their HIV clinic had a psychiatric diagnosis, mostly concurrent psychiatric and substance use disorders, and those with a triple diagnosis had higher mean scores on the Beck Depression Inventory (BDI) and the General Health Questionnaire than individuals with no diagnosis or a psychiatric or substance use disorder alone. Although one group did not find increased rates of psychiatric disorders in HIV-positive individuals with substance use disorders (5), the collective data from clinical studies underscore the importance of psychiatric and substance abuse screening in HIV medical clinics (4).

Psychopathology and Substance Abuse in Research Cohorts with HIV

Data derived from controlled studies of mostly asymptomatic HIV-positive gay men have shown very high lifetime rates and generally much lower current rates of major depressive, drug use, and alcohol use disorders (Table 1) (3,7,45–47). Generally, data on co-occurring depression and alcohol/drug disorders are not described in these studies, though it is likely that lifetime comorbidity is common. Interestingly, one study (47) found that, during the mid-1980s, a select sample of mostly white, educated gay men, with or without HIV, significantly reduced their use of drugs and alcohol (from 59% with lifetime disorders to 10% with current disorders), and made other positive life changes (e.g., exercise, better diet). These changes were likely made in response to perceived vulnerability to AIDS. However, in recent years, there has been a resurgence of HIV risk behavior among young gay men and men of color in association with the use of methylenedeoxymethamphetamine (MDMA, “Ecstasy”) (48) as well as methamphetamine (49).

In a cross-sectional study of psychopathology among IDUs with HIV infection, Lipsitz and colleagues (8) reported relatively high rates of current depressive disorders among both men and women. The rates of current depressive disorders they found were comparable to those found in other

Table 1 Medical Problems (HIV-Related and Other) that are Common Among Injection Drug Users with HIV Infection

Severe bacterial infections
Pneumonia
Endocarditis
Sepsis
Mycobacterium tuberculosis (including multi-drug resistant)
Pulmonary
Extrapulmonary
Sexually transmitted diseases
Herpes simplex virus (genital; chronic mucocutaneous)
Human papillomavirus (oral; genital; cervical dysplasia/carcinoma in women)
Syphilis (genital; neurosyphilis)
Pelvic inflammatory disease
Others
Skin abscesses, cellulitis (from “skin popping”)
Infectious hepatitis (B,C)
Alcohol-induced hepatitis and cirrhosis
Alcohol-induced gastritis
Intoxication and withdrawal states
Other CNS complications (hepatic encephalopathy; cocaine-induced ischemia and seizures)

IDU treatment populations studied prior to the HIV epidemic (50,51), but much higher than the rates found in studies of homosexual men (3,7,45,46). Lifetime disorders were not studied because of unreliable reporting of lifetime disorders by these subjects. When these investigators compared rates of current depressive disorders among HIV-positive IDUs vs. HIV-negative IDUs, HIV-positive men (and not HIV-positive women) were more depressed than their HIV-negative counterparts. Longitudinal follow-up of this cohort over three years revealed that, when sociodemographic and other potential confounders were controlled statistically, HIV serostatus and baseline major depressive disorder (MDD) independently predicted persistent or recurrent episodes of MDD (53).

Personality disorders are another aspect of psychopathology that may be important in terms of HIV because they are, by definition, enduring traits which may be associated with substance abuse, HIV risk behavior, distress, and maladaptive coping with HIV infection. One study by Brooner and colleagues (54) found that, among 100 IDUs tested for HIV, the 36 individuals with antisocial personality disorder (ASPD) engaged in

significantly more needle sharing with more drug-using partners than the 64 IDUs without ASPD.

In a study using the Personality Disorder Examination in individuals from various risk groups presenting for HIV testing and counseling, Jacobsberg and colleagues (55) found higher rates of "dramatic cluster" (borderline, antisocial, histrionic, narcissistic) personality disorders among individuals who tested seropositive compared to those who tested seronegative. ASPD was significantly more common among individuals with IDU as their HIV risk factor. Although borderline personality disorder (BPD) was the single most common axis II disorder among the seropositives (13.6%), others were fairly common: dependent (11.1%), avoidant (9.9%), and paranoid (9.9%). Perkins and colleagues (56) also found statistically significantly higher rates of personality disorder, mainly BPD or borderline traits, in asymptomatic HIV-positive gay men when compared to a group of HIV-negative gay men. Individuals with a personality disorder, compared to those without a personality disorder, had greater levels of mood disturbance, were more likely to use denial and helpless coping with HIV infection, and were more likely to report social conflict. While Johnson and colleagues (57) did not find personality disorders to be more prevalent among HIV-positive (19%) vs. HIV-negative (19%) gay men, they found that being HIV-positive with a personality disorder interactively increased the likelihood of current distress and axis I disorders.

Cognitive dysfunction is an important aspect of psychopathology in HIV infection. Studies on neuropsychological performance in HIV-positive drug and alcohol users have mainly focused on IDUs with asymptomatic HIV (58–60). In comparing asymptomatic HIV-positive IDUs with HIV-negative IDUs, investigators have found that drug use is a more important factor in producing neuropsychological impairment than HIV itself. Furthermore, increasing evidence suggests that individuals with HIV and comorbid methamphetamine, cocaine, heroin, and alcohol abuse may deteriorate more rapidly in their cognitive functioning than individuals without such comorbidity (61). This may be due to the propensity for HIV and these substances to induce neuropathological changes in striatal and other dopaminergic systems.

MEDICAL ASPECTS OF HIV INFECTION IN SUBSTANCE USERS

Pathophysiology and Course of HIV Infection

The pathophysiology of HIV infection and AIDS is discussed in detail elsewhere (62). We provide a brief overview here, with particular emphasis on the medical problems most commonly seen among substance users with HIV and AIDS.

HIV-1 is a human retrovirus, now known to cause a decline in cellmediated immune function (principally by reducing T-cells and macrophages) and the eventual development of AIDS. HIV causes immune cell dysfunction and destruction by invading the host cell genome and causing the cell to reproduce HIV rather than normal cellular proteins. HIV is most commonly transmitted through unprotected insertive intercourse or various blood-borne routes (including drug injection with shared injecting equipment). Antibodies to HIV develop in 95% of individuals within 6 months. The HIV serum

antibody test, available since 1985, has been, and will likely continue to be, the primary diagnostic screening tool for HIV. Since 1995, the polymerase chain reaction (PCR) method has been employed to directly test clinically for HIV DNA or RNA ("viral load") (63). This test is now used widely, along with CD4 lymphocyte count, to track the clinical progression of HIV illness, to guide antiretroviral treatment decisions, to detect HIV infection in individuals immediately after known or suspected exposure to HIV and prior to the development of HIV antibody, and for infants born to HIV-positive mothers who continue to have maternal HIV antibody for several months after birth.

The mainstay of HIV treatment is antiretroviral medications (64). There are now 16 antiretrovirals approved by the U.S. Food and Drug Administration to treat HIV, with many more candidates under development. These drugs are classified as nucleoside analog reverse transcriptase inhibitors (NRTIs, e.g., zidovudine or AZT), non-nucleoside analog reverse transcriptase inhibitors (NNRTIs, e.g., efavirenz), and protease inhibitors (PIs, e.g., indinavir), depending on the drug's primary target in the HIV replication cycle. For optimal potency and to reduce the development of medication resistance, three or more of these drugs are used in combination (commonly referred to as highly active antiretroviral therapy, or HAART). The goal of treatment is to suppress HIV replication to undetectable levels, as measured by viral load testing. This requires adherence to >95% of doses of these sometimes complex HAART regimens, which is difficult under the best of circumstances. If viral replication progresses in the presence of medications, drug resistance will develop, viral load will increase, CD4 lymphocyte count will fall, and HIV illness will progress. Medication resistance testing is now used clinically to guide therapy when one or more HAART regimens have failed to adequately suppress HIV replication.

Various systems have been used to characterize the stages of HIV illness. The CDC criteria, most commonly used in the United States (65), are based on two parameters: measure of immune function (CD4 lymphocyte number and/or percentage) and degree of medical symptoms (asymptomatic, symptomatic, opportunistic infection(s) and/or malignancies). The typical course of HIV infection is as follows. After initial infection, there is an acute rise in HIV present in serum (and central nervous system), followed by a fall to a lower level, which persists for an average of 7–10 years. Antibody to HIV appears within the first 6 months, and remains present throughout the course of infection. The CD4 lymphocyte number remains normal for roughly 7–10 years, then begins to decline as HIV replication accelerates. Generally, individuals are at increased risk for AIDS-defining opportunistic infections and malignancies when T cells drop below 200 cells/mm^3. When to initiate antiretroviral therapy remains controversial and depends on an array of factors ranging from degree of HIV illness progression to individual "readiness" to adhere to therapy (64).

Common HIV-Associated and Other Medical Problems Seen in Substance Users

The course and complications of HIV disease may be different for substance users than for individuals in other HIV risk groups. IDUs and women infected through heterosexual contact (often with IDUs) are more likely than gay men to be diagnosed with AIDS late

in the course of illness, delaying medical and substance abuse treatment and risk reduction efforts (18,66). The course of HIV may be accelerated in IDUs and other drug users compared to individuals in other risk categories, likely reflecting differences in access and adherence to care (19,67). Even when HAART is freely available, active drug users outside of drug treatment have a reduced likelihood of receiving antiretroviral treatment (68).

Once substance users enter medical treatment, the secondary complications of continued drug and alcohol use (e.g., decreased self-care, pneumonia, skin abscesses, sexually transmitted diseases) and behavioral disturbances secondary to psychiatric distress or disorders may complicate the course and treatment of HIV infection. For those who continue to use drugs, there may be the danger that heroin (69), cocaine (70), alcohol (71), or drugs and alcohol in combination (72) can suppress various aspects of humoral and cellular immune function. However, drug-immune relationships are complex, and there is conflicting data as to whether or not alcohol or illicit drugs themselves accelerate the progression of HIV infection (73–75). Another complicating factor is that active drug and alcohol users are often unreliable in keeping follow-up medical appointments, and are prone to using expensive emergency medical services rather than routine outpatient medical care (76), implying that they tend to seek care when illness is more acute.

Table 1 lists some of the more commonly seen medical complications of HIV in drug users, in addition to other medical problems that are not directly attributable to HIV. Severe bacterial infections, including pneumonia, endocarditis, and sepsis, are common in IDUs, and may be mistaken for other complications of HIV disease (e.g., bacterial pneumonia may be presumed to be secondary to PCP). In addition, *Mycobacterium tuberculosis* (TB), including drug-resistant strains, may be seen in drug users with HIV and homeless individuals living in shelters. However, the incidence of TB has declined in epicenter cities in the United States, likely due to better HIV treatment and TB control strategies (77). Primary sexually transmitted diseases are common among IDUs with HIV infection, as many HIV-infected drug users continue to practice unsafe sex in spite of having adopted safer drug use practices (78). In addition, reactivation of old infections, such as development of neurosyphilis, may occur in drug users with advanced immunosuppression. These may be difficult to diagnose because of the broad differential diagnosis for encephalopathy (79), nonspecific cerebrospinal fluid (CSF) abnormalities, and negative CSF VDRL due to lack of immune response (80).

Hepatitis C virus (HCV) infection is increasingly recognized as a significant comorbid condition that affects the clinical outcome of patients with substance use disorders and HIV disease (81). Coinfection is common as both HIV and HCV share routes of transmission, notably injection (34). HIV is a risk factor for accelerating the course of HCV, and HCV conversely can worsen the outcome of HIV disease. HCV treatment involves the use of interferon alpha, which is associated with numerous neuropsychiatric adverse effects, most notably the onset or exacerbation of depression and other dysphoric symptoms (82). These psychiatric adverse effects can be successfully treated with antidepressant medications such as the selective serotonin reuptake inhibitors (83,84). Alcohol use is a highly significant cofactor in further increasing the morbidity and mortality associated with HCV infection, making abstinence from alcohol an important treatment goal in the individual with HCV infection (85).

Medical Treatment of Substance Users with HIV Infection

Because of the aforementioned medical complications and barriers to medical care for HIV-infected substance users with and without psychiatric morbidity, innovative models of care delivery are needed. Primary medical care provided on site may be an especially relevant model for opioid-dependent IDUs in MMT, because it may allow for easier access to treatment. Some investigators have shown that such on-site medical care, when compared to off-site referral, can improve the utilization of health care by HIV-infected drug users (86,87). Some MMT programs with on-site medical care may dispense antiretroviral or antitubercular medications daily to drug users with HIV as a means of increasing compliance (17).

For HIV-infected drug users not in MMT, some urban HIV medical clinics provide on-site psychiatric and drug abuse treatment which assists individuals to adhere to medical care (4). However, these comprehensive services are not always available, especially in smaller, non-epicenter cities. In settings where medical, substance abuse, and psychiatric treatment may be split, intensive case management services delivered by individuals with some substance abuse and/or psychiatric training may help to coordinate care and increase the likelihood that individuals will adhere to their medical treatment.

Adherence to antiretroviral treatment is adversely affected by both substance use and psychiatric disorders (88–90). Interventions that appear to increase the likelihood of adherence among substance users with HIV disease include peer-driven support systems, on-site dispensing of HIV medications in substance abuse treatment programs, and individual medication management (91).

The treatment of pain is also an important issue for the substance user with HIV infection and AIDS. Clinicians in substance abuse treatment programs and medical doctors are often concerned about opioid-seeking behavior among drug users, and may be hesitant to prescribe opioids for pain complaints. Breitbart and Dipiase (92) did not find an increased number or intensity of pain complaints, or opioid analgesic use, among HIV-positive substance users compared to individuals in other HIV risk groups. They point out that it is the actively using drug user who is most problematic to treat, while individuals with extended sobriety or on MMT are often treated without difficulty. Generally, if opioids are necessary, long-acting agents (e.g., sustained-release morphine) are helpful in providing stable opioid analgesic levels without the sensation of intoxication produced by shorter acting agents. Methadone-maintained patients should receive appropriate opioid analgesia over and above their usual methadone dose, as methadone alone does not provide appropriate analgesia for these patients. It is also important to keep in mind that substance users with AIDS may require chronic opioid analgesics in the late stages of illness for complications such as peripheral neuropathy. When possible, the patient and medical and substance abuse treatment clinicians should collaborate in pain management, as this may optimize pain control and ease concerns about opioid abuse.

PSYCHIATRIC TREATMENT OF SUBSTANCE USERS WITH HIV INFECTION

Psychiatric treatment of individuals with a triple diagnosis may be complicated by the same factors that affect access to medical care. Some investigators have found that when drug users discover their HIV-positive status, they may react with higher and more sustained levels of distress than individuals in other risk groups (93), and their continued or heightened drug use in combination with depression may increase ongoing high-risk sexual activity (94). Other investigators have found that testing drug users for HIV when they are in or out of treatment is not associated with major acute or ongoing distress or behavioral deterioration (95,96), though, over the long term, HIV-infected IDUs may be more prone to suicide than IDUs without HIV (97). Those IDUs who test HIV-negative while in MMT may experience immediate relief and maintain risk reduction behaviors (95). The above findings support the provision of HIV testing and counseling of drug users in treatment centers or where referral to substance abuse treatment and ongoing counseling is readily available, so that distress, risk reduction, and relapse issues can be addressed.

The diagnosis and psychiatric treatment of HIV-infected drug users may be complicated by multiple factors that can produce neuropsychiatric disturbance in these patients. These include long-term and acute effects of alcohol and drugs of abuse, methadone, and past history of head trauma (41,98). HIV-associated opportunistic infections of the CNS may cause neuropsychiatric disturbances (15). Finally, HIV itself may be associated with cognitive, motor, and behavioral abnormalities both early and late in the course of HIV infection, progressing from HIV-associated minor cognitive-motor disorder to HIV-associated dementia (HAD) (15,99). Early cognitive/motor deficits are subtle, with impaired attention, concentration, and short-term memory, and reduced psychomotor speed. Only later, with severe immunosuppression and AIDS, does a frank dementia develop, with global cognitive impairment, apathy, other behavioral disturbances (including psychosis and mania), and movement disorders. Neuropathologically, HAD has been associated with abnormalities of periventricular white matter, subcortical gray matter, thalamus and basal ganglia, consistent with the neuropsychiatric manifestations of the disorder. Clinical neuropsychiatric evaluation, neuropsychological assessment, and brain imaging should be available to drug users with HIV in order to characterize the nature of cognitive deficits and help distinguish the multiple factors that may be responsible for these deficits. Serial assessments are helpful, especially in differentiating the acute effects of drugs and alcohol from other sources of cognitive dysfunction (98). Fortunately, combination antiretroviral treatment may significantly benefit neuropsychological function (15,100).

Both psychotherapeutic and psychopharmacological treatments may be necessary for drug users with HIV. Professional-led support groups can help reduce social isolation, supporting sustained risk reduction behaviors and educating about the basics of health care for HIV. Attendance at self-help groups can also be quite helpful, though patients should be steered toward meetings where discussion of HIV, psychiatric symptoms, methadone, and other psychotropic medications will be accepted. These may be difficult to find, and patients should be encouraged to try a number of meetings in order to find a “good fit”. In drug abuse treatment programs, counselors can provide supportive psychotherapy, though patients with severe psychiatric disorders, including HIV- and drug-associated neuropsychiatric disturbances, may require psychiatric consultation and

treatment.

There are relatively little specific data on the safety or efficacy of psychopharmacological treatment of psychiatric disorders in drug users with HIV infection, as drug users have generally been excluded from psychotropic medication trials (23). For most treatments, available recommendations are based on studies that have involved HIV-infected patients who were not drug users (101). In general, psychopharmacological treatment of drug users with HIV infection is guided by three main issues: safety, abuse liability, and compliance. A stepwise approach to the pharmacological treatment of psychiatric disorders in drug users with HIV has been proposed to reduce risks associated with these medications (23).

For treatment of depression, the selective serotonin-reuptake inhibitors are preferred because of their lack of anticholinergic and antiadrenergic side effects and lethality on overdose (101). One placebo-controlled study of the antidepressant fluoxetine in HIV-infected cocaine-dependent MMT patients found that the medication, in doses up to 40mg/day, was well tolerated and associated with improvements in ratings of both depression and cocaine use (102). While tertiary amine tricyclic antidepressants (e.g., imipramine) may be helpful for HIV-associated depression, anxiety, and insomnia, and as adjuvant analgesics in lower doses, long-term treatment is hampered by adverse effects of these medications (101), and many clinicians choose less-sedating secondary amines, such as desipramine. The psychostimulants (dextroamphetamine, methylphenidate, and pemoline) are generally safe and rapidly effective for the treatment of apathy, fatigue, and cognitive impairment (103–105) in the late stages of HIV infection and AIDS, although these medications may carry considerable abuse liability if used to treat drug users in earlier stages of HIV disease.

The treatment of anxiety and insomnia in the HIV-infected drug and alcohol user is particularly problematic because of the abuse liability associated with benzodiazepines and other sedative-hypnotics (101,106). It is best to initiate pharmacotherapy for anxiety disorders with a medication that has little or no abuse liability, such as the serotonin reuptake inhibitors or buspirone. An open trial of buspirone in doses of 30–40 mg per day in HIV-infected drug users found that the majority of patients showed improvements in anxiety levels, with few adverse effects (107). Other medications with low abuse liability that may be helpful in the treatment of acute anxiety and insomnia include hydroxyzine, trazodone, and atypical neuroleptic medications such as olanzapine or quetiapine, although few data are available to clinicians regarding the utility of these agents.

Manic syndromes have been reported to be a manifestation of HIV infection in the central nervous system. Even so, some HIV-infected drug and alcohol users have bipolar spectrum disorders and characterologic mood instability (41). The diagnosis of mania and mood instability in drug users is complicated by the possibility of concurrent stimulant use, sedative or alcohol withdrawal, a past history suggestive of mania, and comorbidity with personality disorders. Treatment of HIV-associated mania in drug users is complicated by the toxicity of mood stabilizers, particularly lithium (neurotoxicity) (108) and carbamazepine (blood disorders and induction of antiretroviral metabolism) (101). Divalproex sodium is often chosen as a treatment for HIV-associated mania because it is the best tolerated of the mood stabilizers (108); however, there has been some concern over its use because of in vitro evidence that this drug may stimulate HIV replication

(101). More recently, the atypical neuroleptics, such as olanzapine, have been used to treat HIV-associated mania, particularly where patients are less likely to adhere to serum level monitoring of mood stabilizers.

The diagnosis and treatment of psychosis in the HIV-infected drug or alcohol user is also complicated by concurrent drug use and withdrawal, difficulty in sorting out a past history of psychosis, delirium related to acute medical illness, and the increased risk of anticholinergic, antiadrenergic, and extrapyramidal side effects (EPS), and neuroleptic malignant syndrome (NMS) in HIV-infected patients (108,109). As in the treatment of mania, atypical neuroleptic agents such as risperidone (110) and olanzapine may be useful for HIV-associated psychosis and mania because of the relatively low risk of producing extrapyramidal effects (101).

TREATMENT OF SUBSTANCE USE DISORDERS IN HIV-INFECTED PATIENTS

The treatment of substance use disorders is an important aspect of the overall care of HIV-infected substance users. It improves their quality of life and reduces the risk of their spreading HIV infection to others. As previously discussed, substance abuse treatment can also serve as a setting for the provision of primary medical and psychiatric care for the HIV-infected patient. Alcohol and drug abuse treatment settings range in intensity from outpatient to inpatient, and vary widely in their ability to manage psychiatric problems (1). Treatment has acute and non-acute phases, and includes pharmacological as well as psychosocial modalities.

The initial phase of treatment focuses on detoxification, which may require brief inpatient treatment, particularly for severe alcohol withdrawal (111). Alcohol and sedative withdrawal in the HIV-infected patient can be managed with benzodiazepines, generally at the same dosages as in non-infected patients. In the later stages of HIV illness patients may require smaller doses because of serious physical debility. Methadone is generally helpful for management of acute opioid withdrawal symptoms, on both an inpatient and outpatient basis (111).

After patients are medically stabilized and no longer require detoxification, the goals of treatment include maintenance of abstinence and rapid remission of relapses. Several weeks of abstinence provides an opportunity to evaluate psychiatric and cognitive symptoms, which, when treated, may increase substance abuse treatment retention (23). Substance abuse treatment is usually provided on an outpatient basis, although residential therapeutic communities may be indicated for HIV-infected patients with more severe, refractory, substance use disorders.

Outpatient treatments for drug abuse include drug-free programs that are most often used for those who are dependent on stimulants, alcohol, multiple drugs, and opioids (but who are not candidates for methadone treatment). Because of the high prevalence of HIV infection, outpatient programs are increasingly equipped to address HIV risk reduction and emotional sequelae of HIV infection. Participation in self-help programs, such as Alcoholics Anonymous and Narcotics Anonymous, is generally encouraged as part of outpatient treatment, and groups that openly encourage participation by those with HIV

infection are available. Adjunctive pharmacological treatments, such as aversive and anticraving agents, may be used for the HIV-infected substance user who is likely to comply with such treatment (111). These include disulfiram for alcohol dependence (112) and naltrexone for alcohol or opioid dependence (113). Naltrexone is, however, contraindicated for patients with late-stage AIDS who require opioid analgesics for pain control.

While outpatient drug-free programs are the setting for the bulk of substance abuse treatment, pharmacologic maintenance treatments play a particularly important role in the long-term management of injection opioid users with HIV infection. The pharmacologic maintenance treatment that is of greatest applicability to HIV-infected injection drug users is MMT (23). Because the majority of opioid-using patients are at risk for resuming injection drug use after methadone is discontinued, it is recommended that HIV-infected opioid-dependent patients be offered long-term MMT. Standard doses of methadone can be used—generally at least 60 mg per day and often considerably higher—and can be maintained even when the HIV or AIDS patient is acutely ill and requires additional analgesia. However, at times the dosage must be lowered because of the patient's physical debility. Dosage of methadone is affected by some important interactions with other medications used in HIV disease. For example, the antiretrovirals ritonavir and nevirapine and the antibiotic rifampin may significantly enhance the elimination of methadone and could induce opioid withdrawal symptoms (101). Thus, close monitoring of opioid withdrawal symptoms and serum methadone levels may be warranted when initiating treatment with antimicrobial medications in methadone-maintained patients. Drug interactions are complex and recognition of them is increasing as new findings are reported. Clinicians are advised to constantly update their knowledge by checking any of the several websites devoted to these and related issues, e.g., HIV InSite (http://hivinsite.ucsf.edu).

MMT is particularly effective for opioid-dependent patients with HIV infection since it affords nearly daily contact and provides a stable setting for the provision of medical and psychiatric care (20). Despite concerns about the potential of opioids (including methadone) to depress immune function (114), studies of IDUs have shown that MMT is associated with normalization of the alterations in immune function associated with intravenous heroin use (115) and with reduction in serum neopterin levels (a predictor of progression to AIDS) as long as MMT patients do not continue to use heroin (69). Furthermore, MMT is protective against the spread of HIV (116) and may have some efficacy in slowing the progression of HIV disease (117). One significant concern with MMT, however, is the high rate of cocaine use among HIV-positive methadone-maintained patients (41), although the rate is likely to be lower than that in untreated IDUs (118).

Drug abuse treatment of patients with HIV disease requires more flexibility than is customary in traditional substance abuse treatment programs (16,23,119). This flexibility is required because of medical and psychiatric comorbidity and the potential for relapse when HIV-infected substance users are out of treatment. The latter raises personal and public health concerns due to the potential for high-risk drug use and sexual behavior, and is consistent with other approaches based on the concept of harm reduction (119). Physical illness, depressed mood, hopelessness, and suicidal ideation may erode

motivation to succeed in drug abuse treatment. Consequently, depressed or medically ill patients with HIV need more assistance in reducing or stopping drug use than do individuals who are more physically and psychologically healthy.

HIV RISK REDUCTION INTERVENTIONS

Reducing the risk of transmitting HIV infection is a public health priority. It is crucial that risk reduction interventions be delivered to individuals with, or at high risk for, HIV infection. The concept of harm reduction has been advanced as a useful overarching strategy in approaching HIV prevention in drug users (119,120). The basic assumption behind harm reduction is that the harmful consequences of drug use (i.e., HIV transmission) can be reduced through various interventions. Harm reduction realistically assumes that a certain percentage of individuals will continue to use drugs, and that the vast majority will not abstain from sexual activity, and thus encourages strategies that reduce the risk of these activities. Harm reduction strategies employ multiple, sometimes simultaneous interventions, including MMT, provision of sterile syringes, syringe exchange (121), syringe cleaning education (with bleach distribution), and safer sex education (with condom distribution). Syringe exchange programs not only provide a mechanism for IDUs to obtain clean injection equipment, but also for them to receive safe sex and drug use education, to obtain condoms, and to be encouraged to seek HIV testing and counseling, and medical and drug abuse treatment.

The National Institute on Drug Abuse (122) has published a summary of research-based findings on prevention interventions. The approach recommended by NIDA stresses community-based outreach, education, and access to sterile syringes.

Individuals with severe psychiatric disorders pose special challenges in HIV risk education and have been shown to respond less well to HIV prevention efforts (123). For many reasons (including thought disorder, impaired reality testing, inattention, poor concentration, impulsivity, helplessness, impaired judgment, low motivation, and poor social skills), they may have difficulty absorbing, retaining, and implementing safe sex and drug use practices. It is necessary first to treat the underlying psychiatric and substance use disorder. Then, risky behavior can be assessed. McKinnon and colleagues (124) found that the Sexual Risk Behavior Assessment Schedule developed for IDUs and adapted for a psychiatric population had high test-retest reliability for sexually active psychiatric inpatients and did not exacerbate psychiatric symptoms. Interventions should be tailored to individuals on the basis of their level of HIV knowledge, risk, and manifestations of their psychopathology. For instance, individuals with poor social skills and depression may benefit from education plus assertiveness training, while those with impaired attention and concentration may benefit from multimedia presentations of educational material and an active “role-playing” approach to learning to manage various potentially risky situations. One pilot HIV prevention study with psychiatric inpatients, most of whom had comorbid substance use disorders, used a 7-week multifaceted group approach that relied heavily on topical discussion, role playing, and assertiveness training (125). The group was well received and well tolerated and was supplemented by individual counseling to cover topics that patients were reluctant to discuss in a group

setting. Whatever the approach, risk reduction efforts for individuals with substance use and psychiatric disorders require repetition and reinforcement, as their efforts to reduce risk may attenuate over time.

THE CLINICIAN AND THE TRIPLE DIAGNOSIS PATIENT

Clinicians treating individuals with the combination of HIV infection and psychiatric and substance use disorders experience a variety of positive and negative reactions. Therefore, they must be aware of and prepared to address a multitude of issues, often simultaneously. Attempting to integrate the many levels of problems faced by the HIV-infected substance user can evoke in the clinician feelings of being overwhelmed, out of control, helpless, and hopeless. These reactions may resonate with the feelings experienced by the patient. Grief and loss are other issues faced by the clinician working with the HIV-positive patient. It is important for clinicians to keep the perspective that they are dealing with a complex combination of disorders, all of which are prone to relapse, exacerbation, and crisis, and that even a modicum of help may be more than many of these patients have ever received. The phenomenon of staff burnout, especially in public service agencies where resources are limited and large numbers of HIV-positive substance users are seen, may result in the development of emotional problems in the clinician. It is most helpful to use a multidisciplinary team approach to help the HIV-infected substance user. In this way, team members can distribute the burden of care and support each other in the process. Many agencies have established regular multidisciplinary support groups during work hours, though it is important for the clinician to develop his or her own supports and growth-enhancing activities outside of work.

On the positive side, working with the HIV-positive substance user can be extremely rewarding. Some individuals with HIV, who have previously led chaotic, destructive lives fraught with antisocial behavior, make remarkable positive changes. The diagnosis of HIV may serve to motivate these individuals to enter treatment and significantly reduce or cease using drugs and alcohol and to engage in community activism, volunteer work or peer counseling. Ironically, it is not unusual to hear patients say that being diagnosed HIV-positive may have contributed to the success of their subsequent substance abuse recovery efforts. While these transformations are certainly not universal, witnessing them can be the impetus that keeps many clinicians working in the field.

DIRECTIONS FOR FUTURE RESEARCH

Several areas of future research are relevant to HIV infection in individuals with drug use and psychiatric disorders. The first is primary HIV disease prevention. In this area it is necessary to continue to target specific risk reduction interventions to meet the needs of an ever-broadening population that is vulnerable to HIV transmission. This includes women, individuals in ethnic minority groups, adolescents, and individuals with various psychiatric disorders. Related to this is the need to continue to develop and test harm

reduction strategies in terms of their ability to reduce HIV transmission and to make these interventions more acceptable to society at large.

The second area for future research is secondary prevention of HIV disease progression. The course of HIV disease in drug users, and in women and ethnic minorities who are infected directly or indirectly via drug use, needs to be better characterized so that medical interventions can be specifically tailored to meet the needs of these individuals. Further, innovative service delivery mechanisms need to be developed and tested, particularly those that integrate a broad array of services, including medical, psychiatric, and drug abuse treatment. A necessary feature of enhanced service delivery mechanisms consists of strategies to increase access, appropriate utilization, and adherence to medical treatment for HIV infection, since these issues are most likely to impact HIV disease progression in drug users.

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16
Medical Disorders in Substance Abuse Patients

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INTRODUCTION

Comorbid medical disorders in patients with substance use disorders are a major concern of both patients and practitioners. Before HIV disease surfaced, a great deal was written about the many medical disorders that occur as a result of substance abuse. In the health care system, it is often these disorders that bring substance abuse to the attention of caregivers. Medical disorders can result directly from the use of specific substances or as the result of the route of administration of a substance (e.g., intravenous or inhaled). In addition, certain medical disorders can be indirectly related to substance abuse, such as in the case of tuberculosis in injection drug users. This chapter reviews the major medical disorders associated with substance use (other than HIV disease, which is covered in Chapter 15) by considering four major substances of abuse: alcohol, cocaine, opioids, and cannabis, as well as the specific routes of administration commonly employed for these substances.

COMORBIDITY ASSOCIATED WITH SPECIFIC SUBSTANCES

Alcohol

Although patients may be "asymptomatic," alcohol is known to cause a variety of social and behavioral problems along with medical comorbidity that can serve as a clue to the presence of problem drinking.

Social and Behavioral Problems

Social and behavioral complications may be the earliest and most common presenting manifestations of alcoholism seen by health care providers. These behaviors can be diverse and include aspects of psychiatric disease (discussed elsewhere in this book), family dysfunction, legal and employment problems, and frequent accidents. For example, a cross-sectional survey of homeless adults in California demonstrated that they were two to four times more likely to suffer from alcoholism than were those who were non-homeless (1).

A variety of studies have shown a strong link between alcohol use and behaviors

resulting in accidents or trauma. Trauma patients seen in emergency rooms are often found to have a clear causal link between the injury or trauma and alcohol (2). While acute alcohol intoxication has been shown to lead to trauma, chronic alcohol abuse increases both the risk of trauma-related complications and mortality (3). A prospective study of 301 patients admitted to a level 1 trauma center found evidence of acute and/or chronic alcohol use in 48% of cases (4). In addition, alcohol abuse is associated with an increased risk of readmission for recurrent trauma, a finding which emphasizes the need to identify and treat all trauma patients who have alcohol abuse histories (5). There is evidence that acutely intoxicated patients, particularly those that are severely injured or incapacitated, are not always readily identified in the emergency room setting (6). Burn patients are also more likely to be alcohol dependent; in one study, alcohol dependence was found in 57% of patients admitted to a burn unit (7). The association of alcohol abuse with injuries and trauma has led to the development of efforts to prevent alcohol-related accidents (8). While these efforts require thorough evaluation, it is clear that both emergency rooms and trauma units must play a major role in establishing the potential link between alcohol and trauma and intervening to prevent recurrent problems in identified patients (9).

Medical Problems (see Table 1)

Gastrointestinal: Patients with alcohol dependence have been shown to experience frequent gastrointestinal symptoms such as heartburn, nausea, vomiting, and diarrhea (10). Chronic esophagitis, Mallory-Weiss tears, esophageal varices and malignancies have all been associated with alcohol use (11). Presenting symptoms can include difficulty swallowing, heartburn, hematemesis, and weight loss. In addition to causing mucosal abnormalities,

Table 1 Medical Comorbidity Associated with Alcohol Use

Organ system/disease	Comorbid problems[a]	Commom symptoms
Gastrointestinal	Esophageal disease	
	Esophagitis	Difficult/painful swallowing
	Mallory-Weiss tear	Pain, hematemesis
	Varices	Hematemesis
	Stomach/duodenum	
	Gastritis	Nausea, vomiting, pain
	Peptic ulcer disease	Nausea, vomiting, pain
Liver	Fatty liver	Abdominal discomfort
	Alcoholic hepatitis	Nausea, vomiting, fever, pain

	Cirrhosis	Jaundice, weight loss, edema, bleeding
Pancreas	Acute pancreatitis	Abdominal pain, nausea, vomiting, fever
	Chronic pancreatitis	Pain, weight loss, diarrhea
Nervous system	Central	
	Dementia	Cognitive dysfunction
	Withdrawal	Cognitive dysfunction, seizures
	Stroke	Fixed deficits (motor, sensory)
	Peripheral neuropathy	Paresthesias, numbness, weakness
Cardiac	Hypertension	Usually none
	Cardiomyopathy	Dizziness, syncope (due to arrhythmias), shortness of breath (due to heart failure)
Malignancies	Esophagus	Difficult/painful swallowing
	Pharynx, larynx	Pain, hoarseness
	Liver Pancreas, colon, breast?	Jaundice, weight loss
Hematopoetic system	Thrombocytopenia	Bleeding, rash (petechiae)
	Anemia	Fatigue, dizziness
	Neutropenia	Infections
Metabolic/ endocrine	Ketoacidosis	Mental status changes
	Osteoporosis	Fractures
	Menstrual dysfunction	Abnormal periods, infertility

[a]Patients may be asymptomatic or symptomatic for many of these problems.

alcohol has also been associated with abnormal primary and secondary contractions, resulting in esophageal symptoms (12).

Alcohol has also been associated with nausea, vomiting, and abdominal pain due to acute gastritis (11). Although cigarette smoking has been linked to ulcer disease, the association of peptic ulcer disease with alcohol is less clear (13). Unrelated to the type or amount ingested, alcohol facilitates the development of gastroesophageal reflux disease by reducing the pressure of the lower esophageal sphincter and esophageal motility (14). Chronic alcohol use may also lead to malnutrition, due to either poor eating habits or malabsorption. Alcohol-dependent individuals are at higher risk of inadequate intake or absorption of several vitamins (15). These nutritional deficiencies can be evident in a patient who presents with weight loss, peripheral neuropathy due to folate deficiency, and Wernicke's encephalopathy due to thiamine deficiency. However, the exact mechanism of vitamin deficiency in alcoholics is somewhat controversial. For example, alcoholic

patients receiving adequate doses of thiamine and other vitamins may still be deficient, possibly due to malabsorption or interference with vitamin metabolism (16). One study suggests that in patients in earlier stages of alcohol dependence, it is the cumulative lifetime exposure to alcohol, and not current nutritional status, that is associated with peripheral neuropathy (17).

Liver: In the United States, alcohol abuse is an important cause of morbidity and mortality from liver disease (18). Acute alcohol intake is associated with "fatty liver," which may be asymptomatic or associated with nonspecific symptoms including abdominal discomfort and anorexia. It is thought to occur in up to 90% of "heavy" drinkers (19).

Alcoholic hepatitis, which may be seen in up to 40% of "heavy" drinkers, represents more advanced acute liver disease as manifested by nausea, vomiting, fever, abdominal pain, and liver dysfunction (20). Alcoholic hepatitis may be clinically indistinguishable from viral hepatitis, and therefore the diagnosis relies on obtaining an accurate alcohol consumption history. Laboratory evaluation can also be helpful with patients with alcoholic hepatitis typically presenting with mild-to-moderate elevations in serum aminotransferases with relatively higher serum aspartate aminotransferase (AST) levels. Alcoholic hepatitis responds well to abstinence, although a significant proportion, approximately 30%, will progress to cirrhosis (21). Viral hepatitis, particularly hepatitis C, may be more prevalent among some patients with alcoholic liver disease (22). In one study of alcohol-dependent subjects, 30% of heavy drinkers were hepatitis C positive, a finding that was associated with a higher prevalence of alcoholic liver disease (23). A history of previous injection drug use, a significant risk factor for acquisition of the hepatitis C virus, may be a major contributor to this phenomenon in alcoholic patients (24).

Cirrhosis is the eighth leading cause of death in the United States, resulting in over 25,000 deaths in 1988 (25). Although often asymptomatic, patients with more advanced liver disease experience significant morbidity and may present with jaundice, weight loss, and evidence of hepatic dysfunction, such as bleeding. Interestingly, women may be more susceptible to cirrhosis than men. Clinical studies have shown that cirrhosis occurs more rapidly in women and at lower relative levels of alcohol consumption than in men (26,27). In addition to end-stage liver disease, patients with alcoholic cirrhosis face the risk of the subsequent development of hepatocellular carcinoma (28).

The association of alcoholism with life-threatening liver disease has raised the controversial issue of liver transplantation in alcoholic patients. Many would argue that alcoholism should be a contraindication to transplantation, given the high risk of relapse and the scarcity of available organs. Uniform guidelines need to be developed that include an assessment of the prognosis of individual patients, including an estimate of the likelihood of success in treating the alcohol dependence (29).

Pancreas: Among the most dramatic manifestations of alcoholism is acute pancreatitis, a condition in which patients can present with significant abdominal pain, nausea, vomiting, and fever. The diagnosis of acute pancreatitis is often based on the appropriate presenting clinical picture in the setting of a history of alcohol dependence. In addition, a history of high levels of alcohol consumption may be correlated with a more severe initial episode of acute pancreatitis (30). Laboratory evaluation may aid in the diagnosis of

alcoholic pancreatitis. One study suggests that serum lipase is more reliable than amylase (31), with the serum lipase being a more specific and sensitive index of pancreatic disease (32). In addition, the serum lipase:amylase ratio has been proposed as an effective way to differentiate alcoholic from nonalcoholic pancreatitis (33,34). Serum carbohydrate-deficient transferrin (CDT) and trypsin levels have also been identified as markers of chronic alcoholism and have been shown to have utility in differentiating alcoholic from non-alcoholic acute pancreatitis (35).

Patients with recurrent acute pancreatitis may develop chronic pancreatitis, which can manifest as chronic intractable abdominal pain and malabsorption with weight loss or diarrhea. Although chronic pancreatitis is thought to be irreversible once it develops, there are data to suggest that abstinence from alcohol is associated with decreased morbidity and mortality (36).

Nervous system: Alcohol can have acute and chronic toxic effects on both the central and the peripheral nervous systems (37). While acute central nervous system effects, such as intoxication and withdrawal, are commonly seen in emergency room settings, primary care physicians and psychiatrists may also face these issues in managing patients. Chronic alcohol use may be associated with mild-to-severe cognitive impairment, including impaired short- and long-term memory, along with deficits in functioning in activities of daily living. Later stages of alcoholic dementia may resemble Alzheimer's disease. There may be similar biological mechanisms involved in the effects of alcohol abuse and Alzheimer's disease on the brain but there is still limited evidence that alcohol increases the risk of the development of Alzheimer's disease (38–40). Both direct toxicity of alcohol and thiamine deficiency are possible etiologies for alcoholic dementia (41).

Alcohol withdrawal seizures are a well-described phenomenon, although their diagnosis and treatment can be challenging (42). Generally these are considered benign in the absence of other neurologic disease, and they respond well to abstinence (42). The relationship between alcohol consumption and the risk of stroke is controversial, with some studies showing a modest increase in the risk of stroke (43) while other studies showed no overall significant association between total alcohol intake and stroke, and in fact showed a protective effect of alcohol amongst older subjects (44). Cerebellar degeneration presenting as gait ataxia can also result from chronic heavy alcohol use.

Peripheral neuropathy is also a major comorbidity of alcoholism (45). Presenting symptoms include parasthesias, numbness, weakness, and chronic pain. Similar to dementia, there is evidence that both direct toxicity and vitamin deficiency may play a role in the development of peripheral neuropathy (45). The results of one study showed that alcohol-related neuropathy is a frequent condition and is mostly characterized by axonal degeneration of peripheral nerve fibers and earlier involvement of sensory fibers and the lower extremities. Alcoholic disease duration and total lifetime dose of ethanol could be more important than malnutrition in leading to neuropathy (46).

Cardiovascular system: Common cardiovascular manifestations of alcohol use include hypertension, acute supraventricular arrhythmias or "holiday heart," and chronic cardiomyopathy (47). Evidence suggests that moderate-to-high levels of alcohol intake are associated with hypertension and that decreased alcohol intake may lower blood pressure (48,49). In addition, hypertensive alcoholics may be more prone to left ventricular hypertrophy than hypertensive patients who are not alcoholic (50). The data

from one study suggested that there is a dose-dependence effect, with chronic alcohol consumption exceeding 29ml per day leading to the development of left ventricular hypertrophy in patients with hypertension, while lighter drinkers exhibited less end-organ damage and a risk of cardiovascular disease (51). Despite the evidence of the harmful cardiovascular effects of alcohol, other data suggest that moderate alcohol intake may have beneficial cardiac effects (52). These data have been derived from retrospective studies and any benefit to the heart may be outweighed by the risks of the other alcohol-related complications. Alcoholic cardiomyopathy presents clinically with congestive heart failure and arrhythmias. It responds to abstinence and to the usual treatments for congestive heart failure (47). Heavy alcohol intake has also been linked to sudden cardiac death. In one study, heavy drinkers (i.e., those consuming >6 drinks daily) were 1.7 times more likely to die suddenly than controls (53).

Malignancies: Alcohol has been associated with cancer of the upper digestive and respiratory tract, the liver, and, in at least one study, the prostate, pleura, and cervix (54). Alcohol-related malignancies of the mouth, oropharynx, and esophagus are thought to be in part related directly to alcohol and in part due to increased tobacco use in alcohol-dependent individuals (55,56). Other cancers that have been postulated to be associated with alcohol dependence include cancer of the pancreas, colon, and breast, although data for these have been less convincing (56–58). There is evidence that in patients with colorectal adenomas, excessive alcohol intake increases the likelihood of developing high-risk adenomas or colorectal cancer (59).

Hematopoietic system: Alcoholism may present with bleeding as a result of dysfunction of hepatic synthesis of clotting factors. Alcohol may also cause bleeding or petechiae due to thrombocytopenia. All bone marrow cell lines are susceptible to the toxic effects of alcohol. In addition, immune dysfunction has been attributed to excessive alcohol intake, potentially making alcoholics more susceptible to infections such as pneumonia and tuberculosis (60).

Metabolic and endocrinological problems: Acute metabolic ketoacidosis represents an acute and treatable manifestation of binge drinking (61). Alcohol consumption may also cause more subtle metabolic and endocrinologic abnormalities. For example, the potentially reversible disruption of bone metabolism, potentially leading to osteoporosis, has been documented in male alcohol-dependent patients (62). Alcohol-associated osteopenia appears to be both a direct effect of alcohol on bone cells and an indirect effect through mineral-regulating hormones (63). Alcohol has also been associated with disturbances in lipid metabolism (64). Endocrinologic abnormalities such as menstrual problems, anovulation, infertility, and early menopause have all been linked to alcohol abuse (65). Similarly, male gonadal function is impaired by alcohol intake. Moderate consumption of alcohol may affect semen quality, and high alcohol consumption may result in serious disorders of spermatogenesis (66). Finally, the toxic effects of alcohol on thyroid and adrenal function have also been demonstrated (67).

Other medical issues: Toxic effects of alcohol on the kidney are generally subclinical or secondary to other alcohol-related effects (68). Gout is associated with alcohol consumption and may occur in alcoholics at lower serum urate levels than in nonalcoholics (69). In addition to the dermatologic manifestations of chronic liver disease, alcohol has been related to other important skin conditions including psoriasis

and dermatologic malignancies (70,71). A high prevalence of dental and periodontal disease has also been documented in alcohol-dependent patients (72).

Cocaine

Similar to all forms of substance use, cocaine use is associated with social and behavorial problems. Cocaine use is also associated with a unique spectrum of comorbid medical problems (see Table 2).

Table 2 Medical Comorbidity Associated with Cocaine Use

Organ system	Comorbid problems[a]	Common symptoms
Nervous	Nonspecific symptoms	Headache, tremor, vertigo, dizziness, syncope, etc.
	Cerebrovascular disease	
	Hemorrhage	Headache, mental status changes, focal deficits
	Infarct	Focal deficits
	Seizures	Generalized and partial
Cardiovascular	Ischemic heart disease	
	Ischemia	Chest pain
	Infarction	Chest pain, dizziness, shortness of breath
	Arrhythmias	Palpitations, dizziness, syncope
	Cardiomyopathy	Fatigue, shortness of breath
	Aortic dissection	Chest pain
Other medical complications		
	Intestinal ischemia	Abdominal pain
	Acute renal failure	Agitation, altered mental status

[a]Patients may be asymptomatic or symptomatic for many of these problems.

Acute Intoxication

Cocaine hydrochloride is a water-soluble salt and thus easily injected or absorbed through mucus membranes. “Freebase” cocaine is an alkaloid which is insoluble in water but soluble in alcohol, acetone, oils, and ether and vaporizes at high temperatures without decomposing, thus allowing it to be smoked (73). The time course of the physiological and subjective effects of a single dose of cocaine are closely correlated with the route of

administration and blood levels achieved. Injected and smoked cocaine is absorbed immediately, while there are delayed effects with cocaine used by nasal inhalation. An intravenous infusion of lethal doses of cocaine in animals produces a predictable sequence of physiological events, which can be seen in humans as well. Such infusions cause an increase in heart rate, blood pressure, cardiac output, and body temperature. When combined with a fall in blood pH, these phenomena can cause severe metabolic acidosis (74), leading to the development of generalized seizures, cardiopulmonary collapse, and multiorgan failure.

Central nervous system stimulation may result in irritability, restlessness, emotional lability, paranoia, and, in severe cases, paranoid psychosis and violent behavior. Hyperthermia and grand mal seizures may accompany stimulant toxicity (75). A recent study of cocaine-induced hyperthermia concluded that in humans a major mechanism by which cocaine raises the body temperature is by impairing heat dissipation, affecting sweating and cutaneous vasodilation, as well as by impairing heat perception (76). Stimulation may be followed by central nervous system depression, which is characterized by paralysis of motor activity, hyperreflexia with eventual areflexia, coma, loss of vital functions, and potentially death.

In the case of cocaine intoxication, supportive measures and symptombased treatments are indicated. Agitation may respond to benzodiazepines, psychosis to haloperidol, and hyperthermia to cooling measures. Acidification of urine will hasten excretion of cocaine and seizure activity can be controlled with the use of diazepam (77). Withdrawal from cocaine may be accompanied by hypersomnia, depression, fatigue, and apathy, all of which are usually transient (78).

Nervous System

Cocaine use has been associated with neurological symptoms and diseases, including severe headaches, tremor, vertigo, nonspecific dizziness, syncope, blurred vision, ataxia, tinnitus, transient ischemic attacks with transient hemiparesis of unknown origin, choreiform movements, seizures, confusional states, cerebral hemorrhage, cerebral infarction and spinal cord ischemia, and toxic encephalopathy. In one study, Lowenstein et al. reported that the most frequent neurological complications observed at one hospital were seizures, focal neurological deficits, headaches, and transient loss of consciousness (79).

Potential mechanisms of cocaine-related neurological comorbidity have been proposed. The enhanced sympathetic activity, cerebral vasoconstriction or vasospasm, accompanied by a sudden surge of blood pressure following cocaine use, may precipitate ischemic symptoms and even spontaneous bleeding in a previously normotensive person (80). Cocaine has been shown to decrease cerebral metabolism in vivo and may thus cause a decrease in cerebral blood flow. Because serotonin is a potent vasoconstrictor, the cocaine-induced increase in serotonin levels at the synapse may contribute to the neurological effects of cocaine (81). Cocaine also leads to an enhanced response of platelets to arachidonic acid, resulting in increased thromboxane production and platelet aggregation (82,83).

Headaches from cocaine use may be related to the combination of disturbed

sympathetic, serotonergic, and platelet functions similar to dysfunctions that have been reported in patients with migraine headaches. Migraine headache or migraine-like symptoms have been associated with cocaine use (84). In acute cocaine encephalopathy, hyperpyrexia and metabolic acidosis ensue, which, along with the effect of the drug on neurotransmitters, may contribute to the development of neurological complications.

Cerebrovascular accidents: According to a retrospective review by Kaku and Lowenstein (85), cocaine use is frequently associated with cerebrovascular accidents in stroke victims aged 17 to 44. Recent studies support the findings that cocaine abuse significantly increases the risk of ischemic stroke (86). The main mechanism of cocaine-induced cerebral ischemia is vasospasm, primarily mediated by increased levels of extracellular dopamine, which also has an effect on regulation of cerebral blood flow. There is evidence that cocaine-induced hypoperfusion and the resultant cognitive deficits can persist even after six months of abstinence. The dihydropyridine class of calcium channel antagonists is being investigated as potential therapeutic agents for preventing cocaine-induced cerebral ischemia.

Klonoff et al. (87) reviewed 47 known cases of cocaine-related stroke and concluded that the incidence of stroke related to cocaine use is increasing, that stroke may occur following any route of cocaine administration, with onset occurring from within minutes to as long as a day after use, and that stroke after cocaine use is frequently associated with cerebrovascular abnormalities. In addition, they concluded that in cocaine-associated strokes the frequency of intracranial hemorrhage exceeds that of cerebral infarction. This finding is in contrast to stroke in the general population, where cerebral infarction is most common. Clinical presentations of subarachnoid and intracerebral hemorrhage related to cocaine use have been similar, with varying combinations of headache, altered mental status, lateralized deficits, and seizures. Sudden death is also a presenting feature. In addition to thrombotic and hemorrhagic cerebrovascular disease in two cases, cerebral vasculitis has been presumptively linked to cocaine use (86,88,89).

Seizures: Seizures following cocaine use are a well-recognized comorbidity. Seizures associated with smoking crack cocaine have been described in adolescents (90,91). In humans, seizures from cocaine use are generally brief, with generalized tonic-clonic features, although complex partial status epilepticus has also been reported (92–94). The interval between most recent cocaine use and the seizure may vary from minutes to 12 hours and seizures may occur in first-time users, induced after a single dose of cocaine, as well as in chronic users (95).

Cocaine-related seizures may occur in association with anatomic lesions, cerebral hypoperfusion secondary to cardiac events, and in association with metabolic derangements such as hyperpyrexia and metabolic acidosis (96). Of the traditional anticonvulsants, only diazepam and barbiturates have been found to have any preventive effect. Cocaine-induced status epilepticus may be refractory to standard anticonvulsants and may require aggressive treatment, including induction of a phenobarbital coma (96).

Cardiac Complications

Increasingly, a variety of cardiovascular problems have been recognized to be associated with cocaine use, including hypertension, tachycardia, arrhythmias, acceleration of

atherosclerosis, myocardial ischemia and infraction, cardiomyopathy, myocarditis, aortic dissection, and sudden death (97). Cardiac consequences are seen with all routes of cocaine administration, often occur in the absence of underlying heart disease, and can occur at relatively low doses of cocaine administered. Published case reports have documented myocardial infarction and ventricular fibrillation in individuals, including previously healthy young women, who received cocaine from physicians during otolaryngotic procedures (98–100).

Ischemic heart disease: Acute non-Q wave and Q wave myocardial infarctions (MIs) have been associated with cocaine abuse (101,102). Acute chest pain is the typical presenting symptom and ischemia and myocardial infarction may occur in the absence of significant underlying coronary artery disease (103–105). Affected patients may be young, without evidence of hyperlipidemia, diabetes mellitis, or hypertension, and may be stricken on initial use of cocaine (106,107). The Third National Health and Nutrition Examination Survey, which collected data from a sample of 10,085 U.S. adults aged 18 to 45 years, showed that regular cocaine use was associated with approximately one of every four nonfatal MIs in persons in the age group surveyed (108). The mechanism of cocaine-induced ischemia is controversial, but may relate to an increase in cardiac workload and coronary artery vasospasm. In one review of case reports of cocaine-related infarction, 55% of patients had abnormal cardiac catheterizations, suggesting that cocaine may uncover previously unrecognized disease (109). The Cocaine Associated Chest Pain (COCHPA) study prospectively followed a cohort of 246 patients presenting to emergency departments with cocaine-associated chest pain and found that 5.7% had myocardial infarctions and 0.8% died (110). The authors found no clinical features predictive of infarction in these patients and thus recommended that all such patients be evaluated for myocardial infarction (110).

In some cases it is postulated that thrombosis in normal or near-normal arteries may result from prolonged spasm and intimal damage (111,112). In patients with fixed coronary artery disease, cocaine causes a dose-related increase in heart rate and blood pressure secondary to the adrenergic output, and thus predictably increases myocardial oxygen demand, potentially leading to myocardial ischemia and infarction (97). “Street” cocaine may be mixed with a variety of diluents including lidocaine, procaine, antihistamines, lactose, and amphetamines, which may contribute to the cardiac dysfunction (97). The cardiovascular effect of mixed substance abuse, especially that of cocaine and alcohol, has not been well studied.

The treatment of cocaine-related acute myocardial ischemia/infarction generally includes the standard protocols for cardiac ischemia (113). With regard to newer approaches, Smith et al. found thrombolytic therapy to be successful, whereas Bush cautioned against the use of thrombolytics in intravenous drug abusers because of the risk of intracranial bleeding secondary to the increased risk of mycotic aneurysm in this population (114,115). In a report from Hollander et al., no significant complications were seen among 25 patients with cocaine-related myocardial infarction who received thrombolytic therapy (116).

Cardiac arrhythmias: Cocaine-associated cardiac arrhythmias may occur alone or in the setting of ischemia and may include sinus tachycardia, supraventricular and ventricular tachycardias, ventricular fibrillation, and asystole (97,117,118). Arrhythmias may occur

during acute cocaine intoxication or in the context of metabolic acidosis from prolonged seizures or hyperpyrexia. Arrhythmias related to myocardial ischemia and infarction are frequently described, and arrhythmic effects of cocaine may not be limited to adults. A study of children exposed to cocaine during the prenatal period documented supraventricular arrhythmias and ventricular ectopy in excess of that seen in a historical control cohort (119).

Cardiomyopathy: Patients who suffer coronary artery ischemia secondary to cocaine use may develop an ischemic cardiomyopathy, with a reduction in left ventricular ejection fraction and resultant congestive heart failure (120). An additional mechanism that has been proposed on the basis of animal and human data is that cocaine may produce cardiomyopathy through direct toxic effects, with a depressed left ventricular function due to the effects of high levels of circulating catecholamines on myocardial cells (121,122). Acute myocarditis related to the long-term use of freebase cocaine has been demonstrated by endomyocardial biopsy. While the association of myocarditis with cocaine use has not been clearly established, one case report demonstrated that the inflammation from myocarditis could successfully be treated with prednisone and azathiaprine (118).

Aortic dissection: Several cases of acute aortic dissection attributed to cocaine abuse have been reported. These cases include examples of involvement of both the ascending and thoracic aorta (123,124). Similarly to the case of ischemic heart disease, these patients generally presented with substernal chest pain. Successful management included emergency surgical intervention (125,126). Mechanisms for cocaine-induced aortic dissection may include underlying hypertensive disease, in addition to the acute elevation of systemic blood pressure and catecholamine release following cocaine use (127,128).

Obstetric Complications

As high as 15% of a sample of pregnant women in an urban setting who were evaluated by urine toxicology screening were found to have abused cocaine (129–131). When compared with non-users, cocaine abusers have been found to be less likely to receive prenatal care, have decreased pregnancy weight gain, increased previous history of spontaneous abortions, more sexually transmitted diseases, and an increased number of prior low birthweight infants (132–134). Studies have documented preterm labor and delivery and an increased risk of abruptio placentae and intrapartum placenta previa in association with cocaine use (135–137).

Adverse perinatal outcomes associated with in utero cocaine exposure include fetal distress in labor with stained amniotic fluid, low gestational age, low birthweight, low birth length, and small head circumference (138–140). A neonatal withdrawal syndrome described in infants with positive cocaine toxicology includes tachycardia, tremulousness, poor feeding, and seizures (141). In utero cocaine exposure has also been associated with an increased incidence of congenital malformations of the genitourinary tract and heart (142). Maternal cocaine abuse has also been associated with congenital syphilis, intrauterine and neonatal death, and sudden infant death (143,144).

Negative neurological and developmental outcomes have been identified in infants with perinatal cocaine exposure. One study reported that infants exposed to cocaine only

in the first trimester had birthweight, birth length, and head circumference similar to drug-free controls, but those exposed to cocaine throughout pregnancy had significantly smaller measurements (131,144). Another study confirmed the association between cocaine use and lower mean weight and head circumference, but did not demonstrate significant differences in motor tone or mental and psychomotor development (145). Cocaine users have been reported to be more likely to use other drugs, including opiates, marijuana, tobacco, and alcohol, thus increasing the risk of negative outcomes related to these drugs (146). A more recent study of infants prenatally exposed to cocaine revealed that, at three months of age, they demonstrated no significant cognitive effects and only mild psychomotor abnormalities (147). In a study of newborns in New York City, Joyce et al. (148) demonstrated that infants exposed to cocaine and other illicit drugs were hospitalized seven days longer than infants not exposed, at a cost of over $7500.

Despite prior compelling data, a recent systematic review looking at outcomes in early childhood after prenatal exposure to cocaine found that, amongst children aged 6 years or younger, there was no significant evidence that prenatal cocaine exposure was associated with adverse developmental effects that are different from those associated with prenatal exposure to other risk factors such as alcohol, tobacco, or marijuana (149).

Nevertheless, given the prevalence of cocaine abuse during pregnancy and the existing evidence of adverse perinatal outcomes associated with its use, screening of women for cocaine use during pregnancy is key. Identification of cocaine use during pregnancy should lead to intensive prenatal care and substance abuse and social service referral for these women. In addition, infants with a documented cocaine exposure history should have neurodevelopmental follow-up.

Other Complications

Gastrointestinal complications of cocaine have been described in case reports (150). Intestinal ischemia and perforation have been associated with cocaine use (151–153) and should be considered in cocaine users who present with severe abdominal pain. Cocaine-induced hepatotoxicity has been well documented in experimental animals (154,155) and has also been reported in humans (156,157). It is postulated that cocaine may cause direct hepatotoxicity through its interaction with the cytochrome P-450 system and through the production of free radicals (158). Acute myoglobinuric renal failure has been reported in cocaine users (159,160) who may present with agitation, seizure, hyperthermia, tachycardia, tachypnea, altered mental status, metabolic acidosis, renal failure with rhabdomyolysis, and multisystem failure.

Opioids

Unlike alcohol and cocaine, opioid use has not been associated with major organ-specific comorbid conditions. The major comorbidities associated with opioid use are those associated with acute intoxication and withdrawal and those associated with injection drug use (as discussed in the next section).

Opioid intoxication and toxicity, which can result from either an accidental or intentional overdose, typically presents with the triad of lethargy or coma, pinpoint

pupils, and respiratory depression (161). Depending upon the severity of toxicity, patients are usually managed with a combination of supportive measures such as fluids, respiratory support including mechanical ventilation, and the use of naloxone (161,162). Unlike alcohol withdrawal, opioid withdrawal is associated with minimal morbidity (162). Common signs and symptoms, including abnormalities in vital signs, rhinorrhea, diaphoresis, muscle cramps, and craving may be managed with clonidine or opioid substitution with methadone or buprenorphine (162,163).

Although relatively uncommon, heroin use has been associated with medical comorbities including renal disease (i.e., glomerulosclerosis, amyloidosis, or rhabdomyolysis-induced renal failure) (164–166), hypotension (167), seizures (168), hypersensitivity reactions (169), and acute myelopathy (170). With the exception of renal disease, which is described primarily in injection drug users, most of the complications have been described only in case report format. Heroin has also been associated with problems in pregnancy (171), as well as with a neonatal abstinence syndrome (172) and child developmental difficulties (173). Other than the neonatal abstinence syndrome, many of the difficulties related to heroin use in pregnancy may be more the result of various factors such as high-risk behaviors, polysubstance use, and poor nutrition, which are correlated with drug use in general rather than with the heroin use itself.

Cannabis

Similar to the case of opioids, the literature on the comorbid medical complications of cannabis use is sparse (174). Other than the psychiatric disorders discussed elsewhere in this book and the route-related complications noted in the next section, cannabis use has been associated with little specific medical comorbidity (175). For example, cannabis has been implicated as a cause of temporary decreases in serum testosterone and sperm count (175) as well as gynecomastia in males (176) and motor vehicle accidents (177).

DISORDERS ASSOCIATED WITH ROUTE OF ADMINISTRATION

The comorbidities associated with the oral consumption of alcohol were reviewed earlier in this chapter. This section will focus on the comorbidities associated with injection and inhaled drug use (see Table 3).

Table 3 Comorbity of Substance Abuse Associated with Specific Routes of Administration

Route	Comorbidity[a]	Symptoms
Injection	Bacterial infections	
	Skin	
	Cellulitis	Redness

	Abscess	Swelling
	Heart (endocarditis)	Fatigue, shortness of breath
	Lungs (pneumonia)	Cough, shortness of breath
	Bone (osteomyelitis)	Bone pain
	Joints (septic arthritis)	Joint pain/swelling/redness
	Brain (meningitis, abscess)	Headache, mental status changes
	Viral infections	
	Acute hepatitis (A, B, C, delta)	Fatigue, anorexia, nausea, etc.
	Chronic hepatitis (B, C)	Fatigue, edema, bleeding
	HIV	See Chapter 15
	Other infections	
	Tuberculosis	Cough, shortness of breath
	Syphilis	Genital sores
	Gonorrhea/chlamydia	Genital discharge, pain
Inhalation	Atelectasis	Dyspnea, cough, sputum production
	Pneumomediastinum	Chest pain
	Pneumothorax	
	Hemothorax	
	Talc granulomatosis	
	Asthma	

[a]Patients may be asymptomatic or symptomatic for many of these problems.

Injection Drug Use

In addition to HIV infection, a number of other important medical comorbidities have long been associated with injection drug use (178). These conditions typically include a variety of infectious diseases related to the penetration of the skin with the introduction of contaminants, the results of local trauma, and lifestyle-related comorbidities.

Bacterial Infections

Bacteria from contaminated needles or from skin may enter through the bloodstream and implant on abnormal cardiac structures, such as valves, resulting in endocarditis (179). Typically, persons with endocarditis present with an acute febrile illness, a variety of non-specific constitutional symptoms, and possibly a new cardiac murmur. Blood cultures are typically positive and echocardiography may reveal valvular, usually right-sided, vegetations. The tricuspid valve is the primary site of infection in injection drug users and in these cases infective endocarditis is not associated with peripheral emboli;

instead, patients will present with clinical manifestations of septic pulmonary emboli (180). *Staphylococcus aureus* is the most common organism isolated, although streptococcal and gram negative organisms may also be found (181). Therapy for endocarditis is directed towards the organisms isolated on blood culture. While there is evolving discussion regarding the choice and duration of antibiotic therapy, recent data support the use of nafcillin or oxacillin with the addition of gentamycin for two weeks in the treatment of right-sided staphylococcal endocarditis (182–184). During therapy, patients need to be monitored closely for complications such as valvular failure and systemic emboli.

A high proportion of patients may present with bacteremia without clinical evidence of endocarditis (185). IDUs are well known to be at increased risk for other serious bacterial infections, such as pneumonia, osteomyelitis, and central nervous system infections that may be associated with bacteremia (186). Bacterial pneumonia is typically caused by *Streptococcus pneumoniae* or *Haemophilis influenzae* and is among the most common causes of fever in this group of patients (187).

Bacterial infections in IDUs may be localized to soft tissues such as skin, subcutaneous tissue, and muscle, without being associated with bacteremia. Frequently, these infections occur at injection sites and result in cellulitis or abscesses. The bacteria causing these skin infections usually exist as normal skin flora, but they can also be more unusual organisms from contaminated needles. One study of the bacteriology of skin and soft tissue infections in IDUs found that 67% of isolates from IDUs originated from the oropharynx, compared to 25% of controls. In addition, a wider variety of organisms was identified in IDUs (188). While skin and soft tissue infections are amongst the most common causes of fever in this population, one study found that only 42% of patients with a skin or soft-tissue infection had fever and 19% had bacteremia (189). Localized infection can often be treated with oral antibiotics such as dicloxacillin while skin abscesses frequently require surgical drainage. Patients with localized infection that does not respond to oral antibiotics, or patients with signs of systemic infection, may need treatment with intravenous antibiotics. Patients who use hygienic injection techniques, such as skin cleansing with alcohol, may protect themselves from these infections (190).

Hepatitis

The viral hepatitides including hepatitis A (HAV), B (HBV), and C (HCV), are important medical comorbidities among IDUs. Patients with acute hepatitis complain of fatigue, anorexia, nausea, vomiting, dark urine, and light stools. Patients with chronic hepatitis may present with more nonspecific symptoms, complications of advanced liver disease, or they may be asymptomatic.

While HAV is transmitted primarily via the fecal-oral route, studies have shown that the transmission of HAV is associated with needle sharing (191). There is evidence, however, that the lower socioeconomic status of IDUs may be a stronger contributing factor to the transmission of HAV than the drug use itself (192). Although infection with HAV does not have a chronic course, 15% of individuals infected with this virus will have relapsing symptoms for six to nine months following infection. Given the high rate of coinfection of HAV with HBV and HCV in IDUs, found in one study (191) to be 43%

and 81%, respectively, and given the increased risk of complications, particularly with HAV and HCV coinfection, routine HAV vaccination is recommended in IDUs.

IDU is a significant risk factor for the transmission of HBV, accounting for 15% of the cases in the U.S. HBV is an important cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma. In the U.S., there are 1.25 million individuals with chronic HBV infection, approximately 300,000 new HBV infections per year, 15,000–30,000 of them developing chronic infection each year, and two to three patients per 1000 dying annually secondary to fulminant hepatitis (193). Still, it is estimated that 50% of active IDUs have serological evidence of prior exposure to HBV, and the majority of these cases show evidence of active viral infection. In addition, approximately 70% of IDUs are infected with HBV within five years of their injecting drugs (194). One study of 255 IDUs in Europe demonstrated a 61% seropositivity for hepatitis B surface antibody (indicating past exposure) and a 7% incidence of hepatitis B surface antigenemia (indicating current infectivity) (195).

The hepatitis D virus (HDV) or delta virus is dependent on HBV for replication (196). Hepatitis caused by the delta virus is the least common form of chronic viral hepatitis, but the one most likely to progress to cirrhosis (197). HDV can co-exist with HBV either as a coinfection, with acquisition at the same time as the HBV infection, or as a superinfection of a chronic HBV carrier, typically an injection drug user (198,199). Coinfection with HDV carries a higher risk of severe acute disease but a lower risk of chronic infection, while superinfection with HDV carries a higher risk of severe and chronic disease. While HDV accounts for a minority of the cases of HBV-related acute hepatitis, it has been estimated that more than 50% of cases of acute liver failure in patients with HBV are due to delta virus rather than HBV alone (200). The risk factors for HDV infection are similar to those for HBV, particularly injection drug use. Since HDV requires the presence of HBV infection, HDV can be prevented either by HBV vaccination or post-exposure prophylaxis in the cases of exposure to HBV.

Recently hepatitis C has emerged as a major viral pathogen, particularly in the subpopulation of IDUs. Formerly designated non-A, non-B hepatitis (NANBH), HCV is the most common chronic blood-borne infection in the U.S., with HCV antibodies detected in 1.8% of the U.S. population (201). Of the approximately four million people in the U.S. who have a positive antibody status, 74% have a detectable HCV ribonucleic acid (RNA). There are an estimated 36,000 new infections reported each year, and HCV has become the most common cause of chronic liver disease, with 40% of chronic liver disease being HCV-related (201). In the U.S., HCV infection is the primary reason for liver transplantation and accounts for 8000 to 10,000 deaths per year (202).

The majority of patients with acute HCV infection are asymptomatic. Seventy-five to 80% of patients with acute HCV will become chronically infected (201). Progression of chronic HCV is variable and typically follows an indolent course, with the time from exposure to manifestation of clinical disease often being many years (203). Progression depends in part on the presence of coinfection with other viruses such as HIV or HBV, as well as exposure to alcohol or other hepatotoxins. There is abundant data to support the finding that heavy alcohol consumption has a deleterious effect on the course of chronic HCV infection. One study revealed a 34% increase in the rate of progression of liver fibrosis in individuals consuming >50 g/day of alcohol (204). A further study not only

found a two- to threefold greater risk of cirrhosis and decompensated liver disease in patients with significant alcohol intake (>40 g/day for women, >60 g/day for men), but also noted a more rapid rate of development of cirrhosis in the subjects with greater alcohol consumption (205). In general, cirrhosis develops in 20% of all patients with chronic HCV within 20 years (206). Hepatocellular carcinoma develops in one to five percent of patients with chronic HCV infection, and in one to four percent of patients per year in the setting of cirrhosis (201). In patients with evidence of compensated cirrhosis, the five-year survival is 91%, which is reduced dramatically to 50% in those with decompensated cirrhosis.

IDU is the major risk factor for HCV transmission in the U.S., accounting for 60% of new cases and 20 to 50% of cases of chronic infection (201,207). Approximately 80% of injection drug users will develop positive HCV antibodies after one year of drug use. As many as 90% of users are infected with HCV after five years of injecting drugs (194). In the setting of sharing needles and injection paraphernalia, nearly all injection drug users will become infected after eight years of use.

Because of the common risk factors for acquiring HCV and HBV in the IDU population, many injection drug users will have antibodies to both viruses, with approximately five percent of them having both infections and active liver disease (199). The coexistence of HCV and HBV viruses is a common cause of acute and chronic liver disease. Coinfection with HBV and HCV has also been shown to increase the rate of progression of liver disease in these patients, with evidence of increased severity of the histological lesions on biopsy. One study examining the prevalence of coinfection with HCV and HBV found that 33% of patients with HCV had occult HBV infection, and 33% of those patients had cirrhosis. In contrast, 19% of patients who had HCV infection alone had cirrhosis (208). Studies have shown that the two viruses appear to inhibit each other at the molecular level while enhancing the cytopathic effects, thereby increasing the severity of the histological lesions (209,210). One survey revealed that HBV core antibody, a marker of past infection, was detected in 80% of IDUs and that HCV antibody was found in 90% of these patients, indicating the high prevalence of both viruses in IDUs and the need for education on routes of transmission (211).

Management of hepatitis in IDUs involves careful assessment and close medical follow-up. Individuals with chronic liver disease (i.e., chronically elevated liver enzymes) need to be followed longitudinally, with a focus on avoiding, when possible, potential hepatotoxins (e.g., alcohol, some medications). All drug users should be screened carefully for hepatitis with serologic studies and liver function tests. A critical aspect of preventive care for patients with hepatitis is vaccination for other viral hepatitides. On the basis of serological results, the patient should be vaccinated to prevent superinfection with HAV or HBV, leading to further hepatic injury (212). One prospective study showed that, while patients with chronic HBV who acquired HAV infection had a relatively benign course, patients with HCV who were superinfected with HAV had a significant risk of developing fulminant hepatic failure (213). Therefore, vaccination against HAV is recommended in HCV-infected patients without detectable HAV antibody (214).

Patients without evidence of HBV surface or core antibodies should receive the HBV vaccination series. Coinfection with HBV and HCV can increase the rate of progression

of liver disease, with biopsy evidence of increased severity of the histological lesions (209). Given that the majority of IDUs have antibodies to HCV and are at risk for coinfection with HBV, vaccination against HBV is indicated (215). The FDA recently approved a combined HAV and HBV vaccine consisting of inactivated HAV and recombinant HBV surface antigen protein (Twinrix). The use of this new vaccine, which combines components previously used in the single antigen vaccines, is indicated in IDUs (216). Other recommended vaccinations include pneumococcus, influenza, and tetanus (212,217,218).

Tuberculosis

Although substance abuse in general is associated with an increased risk of tuberculosis, there is a greater concern for tuberculosis in IDUs, particularly those with HIV disease (219). Substance use-related factors that contribute to the increased risk of tuberculosis include malnutrition, poor and crowded living conditions, and alcohol abuse, along with IDU and HIV disease. For example, alcoholism has been thought to promote the reactivation of tuberculosis in infected individuals through malnutrition and alcoholinduced immune dysfunction. In addition, patients with alcohol dependence are likely to be noncompliant with therapies for tuberculosis (220). Drug use itself was recognized as a risk factor for tuberculosis before the recognition of HIV disease in drug users (221). One study found that, in the absence of AIDS, substance abuse might account for additional deaths among patients with tuberculosis (222).

Managing tuberculosis in IDUs with HIV disease is a particularly complex issue. Tuberculosis infection is more difficult to diagnose because skin testing is less reliable in individuals with immune dysfunction (219). In addition, in this setting active tuberculosis may present atypically, such as in the case of extrapulmonary disease (223). Compliance with both prophylactic therapy, in the case of a positive purified protein derivative (PPD) skin test, and therapies for active disease can also be problematic in drug users. Drug treatment programs such as methadone maintenance may be an effective means by which to enhance compliance with tuberculosis therapies in this population (219,224).

All patients with substance use disorders should be screened annually for tuberculosis. Latent tuberculosis is defined as a skin test with a positive PPD but without active disease, as evidenced by a negative chest radiograph and negative sputum culture. Those individuals with evidence of latent infection should be offered prophylactic therapy. Treatment options for latent tuberculosis include isoniazid (INH) for 9 months (for HIV seronegative or seropositive patients); INH for 6 months, rifampin and pyrazinamide for 2 months; or rifampin for 4 months. Current guidelines also advocate the use of rifampin and pyrazinamide daily for 8 weeks as an effective alternative regimen (225). Patients infected with both HIV and latent tuberculosis have a much greater risk of progression from latent infection to active disease and, therefore, should be treated early in the latency stage. Patients with active disease require therapy with multiple drugs and thus need to be followed very closely, in some cases with directly observed therapy (DOT) (219).

Active tuberculosis is defined as having a positive PPD and a positive chest X-ray or sputum culture. The choice of medications and the duration of treatment are dependent on

the level of drug resistance in the region in which the patient lives. Treatment options for active tuberculosis in areas with less than 4% INH resistance include INH, rifampin, and pyrazinamide daily for 8 weeks, followed by INH and rifampin daily for 16 weeks. In areas with greater than 4% INH resistance, patients should receive INH, rifampin, and pyrazinamide for 8 weeks and INH and rifampin for the following 16 weeks, with the addition of ethambutol or streptomycin until the susceptibility pattern of the organism is known (226).

Fever in Injection Drug Users

When a patient who is actively injecting drugs presents with a febrile illness, the clinician faces the challenging task of finding the source. A thorough history and physical examination, along with laboratory studies such as a complete blood count, liver enzymes, cultures of body fluids, and chest radiograph, are often required to fully evaluate the patient. Even when these steps are taken, a source may not be found. In a study done in the Boston City Hospital emergency department, physicians had significant difficulty predicting which patients were bacteremic or had endocarditis (227). Often, when initial evaluation is unrewarding, close follow-up, including hospitalization, may be necessary until a source is found. Other less acute sources of fever such as tuberculosis, viral illnesses including HIV and hepatitis, and opportunistic infections in HIV-infected patients, need to be considered as well.

Inhaled Drug Use

After injection use, inhalation is the second most common route of administration of illicit drugs. Both cocaine and heroin can be smoked by mouth or “snorted” intranasally. While not as prevalent as that seen as a result of tobacco use, the comorbidities associated with inhalation of illicit drugs are important. In addition, although most of the published literature on the complications of inhaled drug use describes problems seen in cocaine users, the documented shift of heroin use from injection to inhalation is likely to result in more reports of similar problems in heroin users (228).

Chest pain, dyspnea, cough, sputum production, and hemoptysis are important pulmonary symptoms with which users of free-base or “crack” cocaine present for medical evaluation. Chest radiographs have been helpful in the diagnosis of underlying pulmonary abnormalities, and findings such as atelectasis, pneumomediastinum, pneumothorax, and hemopneumothorax have been reported (229). Toxic combustion products from using crack cocaine have been shown to reduce mucociliary clearance and cause bronchiolar damage in both animals and humans, resulting in atelectasis. In addition to these toxic effects, immunologically mediated adverse effects of cocaine have also been postulated (230). Cannabis inhalation has also been associated with pulmonary toxicity (231).

Spontaneous pneumothorax and pneumomediastinum due to inhalation of cocaine have been described. Pneumothorax may result from rupture of visceral pleural blebs, whereas pneumomediastinum may occur when air dissects centrally along the bronchiovascular sheaths into the mediastinum. Pulmonary talc granulomatosis and exacerbation of asthma

have also been associated with cocaine inhalation (232,233).

Inhalation of both heroin (234) and marijuana (235) has also been associated with asthma. In addition, marijuana has been shown to contain many of the same carcinogens seen in tobacco (175), leading to a concern about the potential of widespread cases of lung cancer in marijuana smokers. This concern has not yet been realized, perhaps due to the small number of marijuana smokers and the fact that they tend to smoke relatively few marijuana cigarettes per day (175).

Intranasal cocaine use can cause nasal symptoms that mimic allergic or vasomotor rhinitis. In more severe cases, septal perforations may occur as a result of "snorting" (236,237). Irritation from adulterants, ischemia secondary to the vasoconstrictive effects of cocaine, and direct trauma may lead to these sino-nasal complications. In a study using a logistic-regression analysis, intranasal cocaine use was found to be a significant risk factor for HCV infection among the HCV-positive subjects (238), with possible etiologies including sharing of straws or episodes of epistaxis during cocaine use.

MODELS OF MEDICAL CARE FOR SUBSTANCE ABUSERS

The medical comorbidity seen in substance users provides a major challenge to the health care system with respect to how to approach the multiple problems in this patient population. Preoccupation with the acquisition and use of drugs and the impaired judgment that results from drug use make it exceedingly difficult to provide both disease treatment and preventive services to patients with substance use disorders. In addition, given the fragmented and chaotic lives of many substance abusers, receiving treatment for their substance use disorder as well as for their concurrent medical or psychiatric conditions may not realistically be possible. Therefore, the benefits of linkage of treatment of substance use, medical, and psychiatric disorders would address the problems that arise when the substance use disorder is not addressed in the primary care or mental health setting, when the comorbid medical or psychiatric conditions are not addressed in the substance abuse treatment setting, or when the patient receives care in all these settings but there is a lack of communication between them (239).

Three health "systems" approaches that have applicability to substance users as a whole (240) have been described to address the medical needs of HIV-infected drug users. In the "distributive" model, which is currently widely used, patients with substance use disorders are distributed to a variety of sites throughout the health care system. "Mainstreaming" of patients has appeal, in that these systems already exist and nothing new is required. However, this "usual care" approach is generally recognized as inadequate for many substance abusers. Barriers to the effectiveness of this approach include provider-patient mistrust and provider uncertainty of how to manage substance use disorders.

Two other models have been described that include innovative approaches to providing primary care to substance-using populations. In the "primary assessment and triage" model, special programs have been developed in which substance abusers receive a comprehensive substance abuse and medical evaluation at one site and are then referred

for ongoing drug abuse treatment and primary medical care at selected programs in the community (241). In the "drug treatment linked to primary care" model, both types of services are provided "under one roof" (242). Both of these models recognize the need for comprehensive and coordinated services for this population. The "linked" model provides for initial and longitudinal care for patients. A recent randomized controlled trial looking at the provision of primary medical care within an addiction treatment program found that subjects with substance abuse-related medical conditions treated in the integrated model had a significantly higher rate of abstinence than patients treated in the usual treatment model in which primary care and substance abuse treatment were provided separately (243).

An extension of the "linked" model is the practice of providing substance abuse treatment within a primary care office-based setting. This model has been shown to be successful in patients with alcohol problems in terms of primary-care physicians providing screening, brief interventions, and longitudinal care (244–246). In addition, this model has proven to be a feasible and effective option in the treatment of opioid dependence. The Food and Drug Administration's recent approval of buprenorphine for maintenance treatment of opioid dependence provides an additional viable option for treatment in the primary care setting (247). Two randomized controlled trials looking at the provision of office-based opioid dependence treatment (248,249) found equal or superior results with methadone or buprenorphine in this setting when compared with those seen in the provision of care offered in a traditional narcotic treatment program. Therefore, this model of care provides integration of treatment for substance use disorders and related medical conditions while aiming to broaden access to care by bringing new patients into treatment. Ultimately, the determination of which model is best will depend on the level of need and access to services for individual patients.

CONCLUSIONS

Comorbid medical disorders are of major importance in the care of substance-using patients. The presence of medical comorbidities is commonly the stimulus for patients to seek treatment and, as such, needs to be addressed as part of the treatment plan. Clinicians providing services to substance abusers need to be aware of these problems, be able to recognize them when they occur, and have access to the resources necessary to address them. Models of medical care for substance users have been developed in which drug treatment and medical services are provided in an integrated fashion. Careful attention to the medical needs of patients with substance use disorders will benefit both their substance use behavior and their general medical wellbeing.

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Index

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