Cover

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Practical Management of the Side Effects of Psychotropics Drugs

edited by

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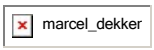

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To my parents

and

my mentors in skepticism

Professor Lubomír Hanzlíček, M.D.

and

Professor Sam Gershon, M.D.

Series Introduction

After the second World War, when psychiatry had just "proven itself" by its successful impact on soldiers suffering from what we now call posttraumatic stress disorder, we had little to offer in the way of treatments except for asylum and support, conversation, simple sedation, and shock therapy. We then discovered the behavioral effects of chlorpromazine (Largactil), reserpine, and iproniazid during the late 1950s and early 1960s. In the years since, we have been inundated with an ever-expanding number and variety of new psychoactive agents. Such drugs now make up the majority of prescriptions and account for a significant portion of health care expense. Most of the prescribing is done by general physicians and internists, often with little training or experience in accurate diagnosis of psychiatric illnesses. In addition, general physicians, particularly in these days of managed care, are less likely to see these patients regularly or to spend enough time talking to them. This commonly results in inadequate dosing, failure to recognize side effects, rapid changes of medication, and the use of inappropriate polypharmacy. This trend is reinforced by insurance company and HMO biases against the use of specialists in their effort to control costs.

These various pressures mean that many patients—particularly those with mild depression, for example, who respond to simple reassurance and

situational change, or patients who are good responders to low-dose medication—never get to a psychiatrist. The specialist is more likely to treat the less responsive patient, or the patient who is already in trouble because of his or her illness or prior treatment. Such patients are more likely to require greater attention, higher doses of medication, and appropriate polypharmacy, and are more likely to experience troublesome, troubling, or dangerous side effects. Balon and his contributors lead us through the wilderness of drugs and their side effects, and point the way toward safer and more effective care of our patients. It is interesting to note that a recurrent theme is the importance of asylum and support, conversation, simple sedation, and shock therapy. Most patients, with or without side effects from the medications they may require, also need thoughtful psychotherapeutic education and care to find their way back into the mainstream of life. This volume in the series alerts us to the dangers, helps us handle them safely, and suggests ways of resuming treatment in a manner designed to obviate difficulties.

William A. Frosch

Preface

Clinical psychopharmacology is a rapidly developing field. Due to the rapid development of new drugs with fewer side effects and pressures from third- party payers to find new, cost-effective treatments, psychiatrists are now medicating conditions traditionally treated by psychotherapy alone, such as dysthymia (1), posttraumatic stress disorder (2), and some personality disorders (3). Psychiatrists now focus on the quality of life of their patients with emphasis on how side effects of medications influence their quality of life (4,5). Psychotropic drugs have many side effects, which, if not tolerated well, can have a major deleterious effect on quality of life.

Many side effects can be quite bothersome, leading to noncompliance and thus to therapeutic failure. Successful management of the side effects of an effective medication is a very important part of good clinical practice. Various texts have reviewed and summarized the side effects of psychotropic drugs (6); however, a practical, clinically oriented management guide has not been available. This book intends to fill the void.

General issues in the management of side effects are addressed, such as diagnosis, patient education, legal issues, and clinical management of side effects of all the major classes of psychotropic drugs used in North America. The chapters describe in detail the major side-effect profiles of different

classes of psychotropic drugs, explaining possible mechanisms of action, differential diagnosis, clinical management, and possible legal aspects of the management of side effects.

This book will assist psychiatrists and other physicians who prescribe psychotropic medications, such as family physicians and internists, in their practice of clinical psychopharmacology.

As psychiatrists, our ultimate goal is to improve the quality of life of our patients. We hope this book will be a useful tool in achieving this goal.

Richard Balon

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1 General Issues in the Management of Side Effects of Psychotropic Drugs

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I. INTRODUCTION

The use of psychotropic drugs has been on the rise over the last three decades, and more than ever, psychotropic drugs are used widely in modern medicine. The majority of psychotropic drugs were originally prescribed only by psychiatrists; however, most of them are now used by other medical disciplines. Examples include anxiolytics, which are prescribed more frequently by primary care physicians than by psychiatrists; antidepressants, which are widely prescribed by primary care physicians, internists, and to some degree (i.e. trazodone) by urologists; and stimulants, prescribed by pediatricians.

Psychotropic drugs, like any medication, are not completely free of side effects. The majority of side effects of psychotropic drugs are mild and tolerable, although some can be fatal—e.g., agranulocytosis with clozapine and less frequently mirtazapine. As psychotropic drugs usually do not affect one single neurotransmitter system and their effects are not localized to the brain only, their side effects are usually the result of their effect on various neurotransmit-

ter systems and organs. In the Physicians' Desk Reference (1), a description of a drug includes a long list of side effects compiled by the respective pharmaceutical company. Lately, we have seen the development of psychotropic drugs with ‘‘less severe’’ or “less frequent” side effects. Thus, the side-effects profile has become an important part of the marketing strategy of pharmaceutical companies. Nevertheless, within a few years after a new psychotropic drug is introduced to the market, there are usually many reports of various side effects. A recent example includes the rush of articles on the side effects of fluoxetine in the early nineties followed by a number of publications on the side effects of other selective serotonin reuptake inhibitors (SSRIs). Clearly, side effects have been and will probably always be part of the treatment regimen with psychotropic drugs.

The incidence of side effects is difficult to estimate. For instance, estimates of the incidence of sexual dysfunction associated with antidepressants varies from 1.9% [fluoxetine (1)] to 96% [clomipramine (2)]. The estimate of incidence depends on various factors, including the specific side effect, dosage of medication, concomitant medication, age, individual sensitivity, and other factors.

The management of side effects of psychotropic drugs should be an important part of the treatment plan. The evaluation of side effects is frequently a part of the quality-of-life assessment. The frequency and severity of side effects may play a role in the effectiveness and cost analysis of the treatment with a particular psychotropic drug. There is an ongoing discussion comparing the effectiveness and tolerability of SSRIs and tricyclic antidepressants (TCAs). Common lore is that SSRIs have less frequent and less severe side effects than TCAs. However, TCAs may be more effective in treating severe depression. Also, SSRIs are usually also more expensive. However, in a recent study (3) comparing clinical, functional, and economic outcomes of initially prescribed fluoxetine, imipramine, and desipramine in a primary care setting, “Patients assigned to receive fluoxetine reported fewer adverse effects, were more likely to continue the original medication, and were more likely to reach adequate doses than patients beginning treatment with either tricyclic drug. The fluoxetine group reported marginally better clinical outcomes after one month, but these differences were not statistically significant and disappeared by the three-month assessment. Quality-of-life outcomes in the three groups did not differ. Total health care costs over 6 months were approximately equal for the three groups, with higher antidepressants costs in the fluoxetine group balanced by lower outpatient visit and inpatient cost.” As there is no clear guidance on the initial selection of these drugs, “patient's and physician's preference are an appropriate basis for treatment selection.”

Thus, taking into consideration a side-effects profile may play an important role in the selection of an antidepressant, but cost and effective factors, together with the physician's and patient's preference, could be equally important.

This chapter reviews several general issues pertinent to the side effects of psychotropic drugs and their management.

II. DIAGNOSIS AND ASSESSMENT

The correct diagnosis and assessment of side effects is an essential part of medication management. Many side effects of psychotropic and other drugs are similar to symptoms of psychiatric disorders. Well-known examples include neuroleptic-induced akathisia, which resembles psychotic agitation, or depression associated occasionally with propranolol. In addition, psychiatric disorders have symptoms that may be interpreted as side effects of medication. Examples include decreased sexual desire in depression or headaches in depression and/or anxiety disorders. As Dunner (4) pointed out, the assessment of treatment-emergent side effects can be confounded by factors related to the illness as well as factors related to the treatment. Other confounding variables include, among others, comorbid psychiatric or medical illness, treatment of a comorbid illness, substance abuse, caffeine intake, smoking status, and individual sensitivity.

One is never sure how best to assess treatment-emergent side effects (4). Careful baseline assessment—or pretreatment—of all symptoms should be the first step. For instance, the lack of baseline inquiry of sexual functioning obscures an assessment of treatment-emergent sexual side effects. A global inquiry alone may result in missing important emergent symptoms (4). However, according to Dunner (4), “going through a systematic list may result in too many symptoms being scored because of the inclusion of symptoms of the illness as well as side effects of treatment.” One should also never underestimate the power of suggestion in some patients. Thus, an abbreviated “list” of symptoms tailored to the most specific or well-known side effects of the chosen medication should be part of the baseline evaluation. For instance, an inquiry prior to starting a SSRI should focus on nausea, diarrhea, headaches, insomnia, anxiety/nervousness, and sexual dysfunction, while an inquiry prior to starting a TCA should include constipation, dry mouth, problems with urination, headaches, and sexual dysfunction. Disappearance of treatment-emergent symptoms with discontinuation usually confirms the diagnosis of a side effect. However, discontinuation of the medication is not always the most suitable

diagnostic method for the assessment of side effects. As side effects of psychotropic drugs are typically dose-related, a medication increase—associated worsening or medication decrease—associated improvement in a side effect may also help to confirm the diagnosis.

An effort to make the assessment of side effects more objective and to quantify them led to the development of several scales to measure specific side effects. These scales include the Abnormal Involuntary Movement Scale (AIMS) (5) for the assessment of abnormal movements and tardive dyskinesia as well as the Barnes Akathisia Scale (6), the Simpson-Angus Scale for Extrapyramidal Side Effects (7) for assessment of tardive dyskinesia and parkinsonian side effects, the Changes in Sexual Functioning Questionnaire (8), and a host of other scales to assess sexual functioning during treatment with antidepressants (9,10).

III. PATIENT EDUCATION AND COMPLIANCE

Patients who are frequently hesitant to take psychotropic medication quite often discontinue medication on their own, resulting in noncompliance with the medication regime. For instance, about half of patients recovering from a relapse of schizophrenia stop their medication within a year. There are various reasons for noncompliance, such as denial of the illness; use of alcohol or street drugs; family or therapist opposition; changes in the social network, supervision, or treatment system; negative symptoms in schizophrenia; and side effects (11). In a study by Van Putten (12), almost half of the patients took less antipsychotic medication than the amount prescribed. The reluctance to take antipsychotic medication was significantly associated with extrapyramidal symptoms, most notably a subtle akathisia. These findings were replicated in the same institutional setting using a test-dose model (13,14). Other side effects—such as sedation, weight gain, sexual dysfunction, and other side effects interfering with the patient's social roles—also interfere with patient's willingness to comply with treatment with psychotropic medications (15).

In one of the first reviews on treatment adherence, Blackwell (16) summarized early studies on side effects and dosage deviation or cessation. In some studies patients ceased to take their medication or deviated from their prescribed dose because of side effects. Blackwell (16) also emphasized the importance of patient education and illustrated the amount of resistance toward patient education from both physicians and patients. Seltzer et al. (17) reported that, following a course of lectures and data sheets, “educated” patients tended to be more compliant on outpatient follow-up and were less fearful of

side effects. Pollack and Rosenbaum (18) stated that an explanation of the mechanisms of side effects and their management can allay patient concerns and decrease the sense of helplessness generated by side effects.

Discussing side effects and educating patients about them is an important part of the pharmacotherapy. Several recent articles discussed the issues and strategies of patient education. Bauer and McBride (19) pointed out that the person being treated possesses important and clinically relevant characteristics that will have an impact on both the course of the disease and the treatment behavior and that we, as clinicians, never actually treat an illness directly. Rather, we collaborate with individuals being treated, who themselves implement the treatment. They discussed an example of the treatment of bipolar disorder with lithium and asked who decides the value of experiencing increased urinary frequency, tremor, acne, and weight gain. It is clearly the individual treated. Bauer and McBride (19) suggested the implementation of a personal cost-benefit analysis around specific treatment decisions. Frank (20), in her discussion of enhancing treatment outcomes, provided specific suggestions about patient education, such as educating the patient and the family. She stated that the acute onset of side effects is a major obstacle to adherence, particularly if no benefit has yet been felt by the patient. She added that proactive strategies for managing side effects should be in place and should be readily triggered when the patient communicates bothersome effects. Furthermore, the education process must be ongoing; it cannot be accomplished in a single presentation or with a single handout or discussion (20).

Stimmel (21), in his review on counseling patients with depression, outlined a practical guide on side-effects counseling. According to him, side effects can be discussed in a rather positive way to minimize overconcern. Instead of either informing the patient of all the possible side effects of the medication listed in the Physicians' Desk Reference or by virtually not mentioning any side effects, he suggests reviewing common, expectable side effects and informing patients what to do should any occur. According to Stimmel (21), it is very important that every side effect mentioned be followed by patient instruction on what to do if the effect occurs. He suggests that merely listing possible side effects will likely increase concern and worry about them. He highlights positive examples of how to discuss the side effects such as sedation, with a patient. Sedation could be presented as a beneficial effect that helps the patient sleep. He also suggests that, ‘‘If daytime sedation becomes a problem, the patient should know that the prescriber can be contacted to modify the dosing schedule to minimize the effect . . . Anticholinergic effects should be described as usually only bothersome . . . and . . . patients can be

advised that anticholinergic effects are always worse in the first 2 weeks of treatment, with some tolerance developing with continued use of the same dosage." Stimmel (21) also addresses the frequent argument that counseling about side effects can cause patients to develop those side effects, thus making it better to discuss them only after they occur. He uses the example of orthostatic hypotension to negate such an opinion. Other suggestions: sertraline should always be taken with food, as food increases its bioavailability by 40%; nausea is dose-related and dosing after meals is often helpful; and initial counseling about drug-induced sexual dysfunction is generally not recommended but necessary when asked about by the patient. However, others consider the last suggestion impractical in view of the recent publicity about sexual dysfunction associated with antidepressants.

Obviously, there are different ways to educate patients about side effects. The central part of the process is the discussion of risks and benefits and informed consent (22). Patients should be treated courteously, without being patronized, adjusting the information to their level of education and understanding. The prescribing physician's creativity and knowledge are other important steps in the process of educating patients about side effects.

IV. ROLE OF PATIENT'S PERSONALITY

The role of a patient's personality in a physician's prescribing practices and in the management of side effects has not been well studied. However, one might foresee the problems due to patient's personality as it emerges during treatment with psychotropic drugs. Knowledge of personality pathology and defense mechanisms (e.g., denial, regression) might be useful in planning pharmacotherapy.

For instance, a patient with comorbid paranoid personality or paranoid traits may be suspicious about medications as well as the physician's intentions. He or she may resist taking any medication. A paranoid patient may have a tendency to misinterpret the side effects and demand medication discontinuation.

Patients with a comorbid antisocial personality may be noncompliant because of side effects. Patients with an underlying narcissistic pathology may pose a special problem as they may feel that "they know better." They may be resistant to pharmacotherapy, argue with the treating physician, and try to handle the side effects on their own.

Patients with an underlying borderline pathology may present a very difficult problem. They may frequently resist psychopharmacological treat-

ment, intentionally or unintentionally. They may stop the medication abruptly because of any side effect. They may also use the issue of side effects in splitting the treating physician and therapist (see "Collaboration with Other Disciplines'' at the end of this chapter). Borderline patients may require repeated education about the possible side effects and their management. Patients with histrionic personality disorder or histrionic traits may mix up exact times and feel guilty, and they may also miss doses when the dosing schedule is too rigorous. A seductive histrionic patient may also try to please the treating physician by minimizing the side effects.

A person with a comorbid obsessive-compulsive personality disorder or obsessive-compulsive personality traits will need exact instructions as to how to take medication, including exact dosing times, to feel comfortable. He or she will require very detailed discussions of side effects before the treatment begins. An obsessive-compulsive patient will also be careful to watch for side effects and discuss them in detail during treatment. However, the obsessive- compulsive patient is usually more compliant.

In conclusion, one must consider overt personality pathology in treatment planning as well as side effects management. One might tailor the instructions and information about the medications and their side effects to a patient's underlying personality pathology.

V. MANAGEMENT OF SIDE EFFECTS

Many articles have reviewed general management strategies of side effects associated with different classes of psychotropic drugs (18,23,24), with various types of side effects [e.g., hematological (25), cutaneous (26), ophthalmological (27), sexual (28)], side effects in special populations [e.g., the medically ill (29,30), patients with AIDS (31)], emergencies caused by side effects (32), and the prevention of side effects (22).

Keks (24) stated that side effects can be minimized by optimizing clinical strategies, including choosing the appropriate drug, slow titration, and dosage reduction. Blackwell (23) listed three general strategies for dealing with the contribution of side effects to noncompliance in depressed patients: monitoring plasma levels of antidepressants, once-daily regimens, and education. In some cases, measurement of plasma levels allows accurate titration to a safe therapeutic level. In general, however, as Blackwell (23) pointed out, there is a poor and inconsistent relationship between side effects and plasma levels. Hollister (33) concluded a long time ago that the routine monitoring of plasma levels is not useful. According to Blackwell (23), there are several

practical considerations involved in the second general strategy: a once-a-day regimen. When drug is taken at bedtime, some of the side effects are not troublesome during sleep (e.g., dry mouth or blurred vision) (23), and the sedative effects may eliminate the need for an additional hypnotic drug. However, as Blackwell (23) warns us, the advantages of a once-a-day regime may have been exaggerated. Some side effects may be more marked with a single large dose.

Balon (28) outlined general management strategies for handling sexual side effects of antidepressants. Slightly modified, these strategies could be adapted as general strategies for the management of all side effects:

1. Waiting for spontaneous remission or improvement. As Pollack and Rosenbaum (18) pointed out, "time on a given dose is often the greatest healer of adverse effects."

2. Reduction to the minimal effective dose. Pollack and Rosenbaum (18) suggested that, after the patient achieves a satisfactory and stable clinical response, one should embark on a systematic but gradual effort to determine the lowest effective dose, as side effects are usually dose-dependent. However, balancing the minimal effective dose and a subtherapeutic dose can be difficult. In addition, studies from Pittsburgh (34,35) indicate that maintenance therapy of depression should be done with a full-dose antidepressant therapy; thus decreasing the dose may not always be the option.

3. Once-daily, preferably nighttime regimen. This approach has advantages and disadvantages, already discussed.

4. Using secondary pharmacological agents or "antidotes." This strategy has been used to manage the various side effects of different drugs, e.g., extrapyramidal (benztropine, amantadine), sexual (stimulants, yohimbine, cyproheptadine, and others), anticholinergic (e.g., bethanechol), and orthostatic hypotension (fluorohydrocortisone).

5. Drug holidays. This strategy has been used in children treated with psychostimulants and in sexual side effects associated with SSRIs (36). However, using drug holidays in patients treated with antidepressants requires caution, as withdrawal may occur. This approach may also encourage noncompliance, and its long-term effects are not known.

6. Switching to another drug with a more favorable side-effects profile. This approach could be used for switching the oversedated patient to a less sedating drug, switching a patient with a sexual dysfunction to a drug not associated with sexual dysfunction, or switching a patient from an antidepressant causing severe jitteriness to an antidepressant causing less jitteriness.

Keshavan (22) outlined "ten commandments'' of wise drug prescribing that may help in preventing side effects: (a) know the patient well before

beginning treatment; (b) offer a treatment package, not just a prescription; (c) educate the patient; (d) choose the right medicine; (e) ensure that the patient takes the medication; (f) use as few drugs as possible; (g) tailor the treatment to the patient's needs; (h) familiarize yourself with the drug; (i) have a high index of suspicion (for side effects); and (j) consider the patient's viewpoint.

Last but not least, one should never forget the possibility of drug interactions, not only among psychotropic and other prescribed medications but also among psychotropic medication and over-the-counter medications.

VI. LEGAL ISSUES

The prescription of psychotropic medication exposes the psychiatrist to significant professional liability claims (37). As Wettstein (38) warns in his chapter, no article or chapter should be a substitute for an attorney in a specific case. The same holds for this chapter. The outlined issues are generally applicable in various situations; however, the reader is advised to consult an attorney for appropriate legal advice on specific legal problems and a clinical legal consultant for advice about specific clinical problems as needed.

Negligence and informed consent are the two main areas pertinent to liability when prescribing psychotropic medication. Prescribing psychiatrists risk negligence liability in a variety of areas, which include (39,40) (a) failure to take an adequate history; (b) failure to obtain an adequate physical examination; (c) failure to obtain an adequate laboratory examination; (d) lack of indication for prescription; (e) contraindication for prescription; (f) prescription of an improper dosage; (g) prescription for an improper duration; (h) failure to recognize, monitor, and treat medication side effects; (i) failure to abate drug reactions and interactions; and (j) failure to consult with other physicians. However, in each of these areas, four elements are required to prove negligence:

1. Duty: A psychiatrist has a legal duty to care for the patient according to the standards of care. The use of medication should be justified based on the patient's symptomatology and medication administration should be continuously monitored.

2. Dereliction: A psychiatrist, like any physician, is not required to practice without error; he or she is, however, required to exercise reasonable care. Courts are less tolerant of errors of fact than errors of judgment (41). There has to be a demonstrated dereliction of duty. Errors of judgment will not result in a successful suit if the psychiatrist acted in good faith and exer-

cised the requisite care in obtaining necessary information, formulating a diagnosis, and treating the patient's condition (41).

3. Direct causation: The negligence must be the cause of the harm and the harm must be foreseeable.

4. Damages: There must be an actual damage due to deviation of care, including, for instance, the cost of treatment and loss of wages.

An example of all four elements of malpractice would be a patient with a first episode of psychotic depression treated prophylactically with only haloperidol for 2 years who developed subtle abnormal movements of his jaw but had never been asked by his psychiatrist about any abnormal movements nor had the AIMS scale been administered during those 2 years. This example demonstrates lack of duty, as there was no care according to the standards of care; dereliction of duty, as no routine evaluations of possible abnormal movements were done; direct causation; and damage.

Psychiatrists are also subject to litigation for failure to obtain informed consent to treatment with psychotropic medication (40). According to Justice Cardozo, every adult "has a right to determine what shall be done with his own body." Informed consent is an ongoing process, and informed consent discussions, especially those related to side effects, should be repeated periodically depending on the clinical situation. Informed consent comprises three elements: information, competence, and voluntariness.

According to the legal doctrine of informed consent, in addition to obtaining the patient's consent to treatment, the prescribing psychiatrist must also inform the patient or his or her legal guardian about the nature of the proposed treatment; its risks, benefits, and alternatives; as well as the risks and benefits of alternative therapies, including no treatment (38). Side effects are one of the risks of treatment, and those that are more serious or common should be discussed with the patient (e.g., the possibility of tardive dyskinesia during the treatment with antipsychotic medication). Informed consent disclosures are dictated by state laws, which describe whether disclosure should be governed by what psychiatrists ordinarily disclose to patients in such circumstances or by what reasonable patients would want to hear in such circumstances. Documentation of an informed consent is crucial. It is prudent to briefly document in the patient's chart that informed consent was obtained and side effects were discussed. Written informed consent for nonexperimental medication is usually not required and its use remains the subject of debate. Most legal experts do not recommend using written informed consent forms in any medical practice in which standard or routine medication is prescribed (38). However, many state agencies, hospitals, and community mental health centers require a written informed consent form at least for treatment with

antipsychotic drugs. This usually involves a standard form completed by the prescribing psychiatrist and signed by both psychiatrist and patient. When the written informed consent form is used, the psychiatrist must still discuss with the patient the relevant informed consent issues, both initially and also periodically thereafter (38). These forms are frequently time-limited and usually need to be renewed every year. In sum, when not required by law or policies of the agency, it is better not to use them, as they are frequently mistakenly used to substitute the process of informed consent.

It is also necessary to obtain the informed consent of the legal guardian or parent of a child to start treatment with psychotropic medication. Again, some agencies use standard forms for documenting informed consent. The most common and severe side effects, their management, and precautions must be discussed with parents and/or guardians.

VII. GENERIC DRUGS

There is not much known about the difference in side effects between brand and generic preparations of psychotropic drugs. Bernstein (42) described several patients complaining of greater anticholinergic effects with the generic preparation of amitriptyline even though they felt less well from the standpoint of mood. These patients responded less favorably to the generic form but suddenly felt better when treatment with Elavil was resumed. Generic drugs are not always bioequivalent to the brand preparation and there is not always bioequivalence among various generic preparations of the same psychotropic drug. From the standpoint of monitoring side effects and plasma levels, it is probably better to use brand preparations.

VIII. COLLABORATION WITH OTHER DISCIPLINES

The practice of collaborative treatment or medication backup—i.e., psychopharmacology provided by a psychiatrist and psychotherapy provided by another mental health professional—is increasingly common. It has positive and negative aspects. One positive aspect is the increased amount of clinical information available provided that there is true collaboration between the psychopharmacologist and the therapist. The therapist may be seeing the patient more frequently and may be able readily to appreciate the side effects, their onset, and course. Bush and Gould (43) presented an example in which the psychopharmacologist was concerned that a patient's irritability was a side effect of fluoxetine.

However, after meeting with the therapist, it was revealed that the patient was typically irritable. Akathisia or jitteriness may be more apparent during a 45- minute psychotherapy session than during a short medication review.

In-service presentations on the side effects of psychotropic medications may be a useful way to educate therapists about the most common side effects of psychotropic drugs and to foster their cooperation in reporting side effects, referring patients back to the psychopharmacologist, and thus fostering compliance.

A collaboration with the primary care physician is similarly important. The information about the medication prescribed as well as laboratory and other tests results could provide invaluable information for the management of side effects.

IX. MANAGEMENT OF PREGNANT PATIENTS WITHOUT THE USE OF MEDICATION

As Altshuler and Szuba (44) pointed out, "although it is generally believed that pregnancy is a time of emotional well-being, many women develop or have a recurrence of psychiatric illness during this time. The risks associated with leaving a woman untreated during pregnancy are potentially substantial and must be weighted against the risks of exposing the fetus to the potentially teratogenic medications." Medications should be avoided during pregnancy if possible, especially during the first trimester. However, psychiatric illness may have severe negative consequences that need to be managed during pregnancy. Various psychotropic medications are relatively safe during pregnancy—e.g., antipsychotics, tricyclic antidepressants, and SSRIs—especially after the first trimester (although long-term behavioral toxicity is not well studied and documented). Other medications (e.g., mood stabilizers and benzodiazepines) have teratogenic potential.

Various nomnedication management strategies could be implemented during pregnancy when the use of medication is contraindicated or when the risks to the fetus outweigh the risks to the mother.

Electroconvulsive therapy (ECT) should be considered in suicidal, severely depressed, and psychotic patients. It is efficacious and safe during pregnancy (45) and appropriate in a setting where risk from the disorder demands expeditious treatment. Electroconvulsive therapy should be administered to pregnant women in the context of a comprehensive treatment team, which includes a psychiatrist, obstetrician, and anesthesiologist.

General strategies of nonmedication management for women with psychiatric illness include (general guidance; Adele Viguera, MD, personal communication):

• Elimination of caffeine, nicotine, alcohol

• Adequate sleep

• Use of relaxation/behavioral techniques

• Cognitive behavioral therapy

• Marital therapy when necessary

• Support groups

• Detailed patient education

• Reduction of psychosocial stressors

• Close communication with obstetricians

• Modern era physicians' availability (beeper)

These strategies could be used in the management of various psychiatric illnesses. The general goal in managing any psychiatric illness during pregnancy should not necessarily be to maximally control the symptoms but rather to reduce those symptoms that jeopardize the mother and fetus. Finally, it is very important to document every step taken in decision making when treating a pregnant woman. Documentation of patient's consent and participation in decision making may also be useful.

X. CONCLUSION

The management of side effects of psychotropic drugs is a complicated process that requires knowledge of psychopharmacology and its principles, consideration of patient's personality, empathy, good communication skills, and creativity.

Pertinent issues in management are:

• Diagnosis and assessment

• Education of the patient

• Informed consent

• Management itself, which may include:

1. Waiting for spontaneous remission or improvement

2. Reduction to the minimal effective dose

3. Once-daily, preferably nighttime, regimen

4. Using secondary pharmacological agents or “antidotes”

5. Drug holidays

6. Switching to another drug with a more favorable side-effects profile

Using brand preparations of psychotropic drugs may be preferable for monitoring side effects. Educating the therapist about the most frequent side effects seems to be a good strategy for patients in collaborative treatment. Communication with primary care physicians could also provide invaluable information for the management of side effects.

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2 Management of Side Effects of Antipsychotic Drugs

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I. INTRODUCTION

The advent of antipsychotic medications represents a revolution in the management of schizophrenia and other psychotic disorders. However, the use of these medications is still limited by several significant side effects, ranging from mild to moderate discomfort to irreversible neurological disorders. The nature and severity of adverse effects vary from one antipsychotic to another and depend on effects of the drug on specific neurotransmitter systems (such as dopaminergic, serotonergic, cholinergic, and noradrenergic systems). The newer, ''atypical'' antipsychotic drugs appear to be unique in causing less frequent neurological side effects. However, they are not free from causing a variety of nonneurological side effects. Apart from substantial distress, these side effects also lead to impaired compliance in many patients, compounding the morbidity. Clearly, the clinician needs to be well informed about the use of antipsychotic drugs in order to improve treatment compliance and quality of life in these patients. In this chapter, we review the clinical features, diagnosis, pathophysiology, prevention, and management of the various antipsychotic-

induced adverse effects. We emphasize practical clinical aspects and limit basic pharmacological issues to those with direct clinical relevance.

II. NEUROLOGICAL SIDE EFFECTS

Many of the serious neurological side effects of antipsychotic drugs result from blockade of the dopaminergic D2 receptor. A variety of acute extrapyramidal syndromes (EPS) may result. These include acute dystonia, parkinsonism, akathisia, and neuroleptic malignant syndrome. These disorders share some aspects of pathophysiology and have similar approaches to treatment, including the use of anticholinergic medications. Long-term treatment with antipsychotics causes emergence of chronic extrapyramidal syndromes such as tardive dyskinesia. In general, conventional antipsychotic drugs are more likely to result in EPS; high-potency drugs such as haloperidol and fluphenazine carry the highest risk, low-potency drugs such as chlorpromazine and thioridazine have the lowest risk, and medium-potency drugs such as perphenazine and thiothixene are intermediate in this regard. Newer, atypical antipsychotic drugs such as clozapine, risperidone, olanzapine, and quetiapine are notable for their relative freedom from these risks, and these benefits are related to their unique pharmacological characteristics (Tables 1 and 2).

A. Parkinsonism

1. Clinical Features and Diagnosis

The cardinal features of this syndrome include the triad of muscular rigidity, tremors, and bradykinesia (slowness of movement). Older and female patients are at increased risk. The tremor is more prominent in the distal part of the upper extremities, present at rest, and is measured at four to six oscillations per second. Although cogwheel rigidity is easier to diagnose and can even be helpful in establishing an adequate antipsychotic dose (1), more subtle parkinsonian EPS can be difficult to identify. Akinesia may be mistaken for improvement when it develops several weeks into the treatment or during the treatment of a previously agitated patient. After acute psychotic symptoms have subsided, the psychomotor retardation and masked facies due to parkinsonism are sometimes misdiagnosed as postpsychotic depression (2). The drug-induced parkinsonian syndrome may also be mistaken for the negative or deficit syndrome of schizophrenia.

The rabbit syndrome is an unusual variant of drug-induced parkinsonism

Table 1 Adverse Effects of Antipsychotic Drugs

	Extrapyramidal	Sedation	Anticholinergic	Prolactin Elevation	Orthostatic Hypotension	Weight Gain
Conventional						
Low potency						
Chlorpromazine	++	+++	+++	+++	+++	++
Thioridazine	+	+++	++++	+++	+++	+b
Mesoridazine	+	+++	++++	+++	++	++
Molindone	++	++	++	+++	++	—b
Medium potency						
Loxapine	+++	++	++	+++	++	—b
Perphenazine	+++	++	++	+++	++	++
Thiothixene	+++	++	++	+++	++	++
High potency						
Fluphenazine	++++	++	++	+++	++	++
Trifluoperazine	+++	++	++	+++	++	++
Haloperidol	++++	+	+	+++	+	++
Atypical						
Risperidone	++	+	—	+++	++	+
Olanzapine	+	++	++	+	+	++a
Clozapine	—	+++	++	—	+++	+++
Quetiapine	—	++	—	—	++	+a
Sertindolec	+	+	—	—	—	+a
Ziprasidoned	+	—	+	+	++	—

Key: + = low; ++ moderate; +++ = high; ++++ extremely high severity; — = minimal to none.

aWill need more data once drugs are used for a longer period of time.

bWeight loss reported.

cAbbott Labs has withdrawn its IND voluntarily from the F.D.A., so it is unlikely to be available in the USA.

dNot marketed at the time of submission to press.

Table 2 Atypical Antipsychotics—Relative Receptor Antagonism (Selective Receptors)

Receptor Antagonism	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasidone
D2	+	+++	++	+	++/+++
5HT2A	++	++++	+++	++	++++
5HT2A/D2 ratio	+++	++	++	++	++++
Muscarinic	+++	—	++	—	+/—
H1 (histaminergic)	+++	—	++	++++	++
Alpha1 adrenergic	++	+++	+	++	++/+++
Norepinephrine and serotonin reuptake inhibition	—	—	—	—	++

Key: + = low; ++ moderate; +++ high; ++++ very high; — = minimal to none.

characterized by perioral lip tremor (3). This condition can occur at any time during neuroleptic treatment and responds well to antiparkinson treatment.

2. Pathophysiology

The pathophysiology of antipsychotic-induced parkinsonism involves decreased activity of the nigrostriatal dopaminergic system. A compensatory increase in the cholinergic activity occurs as well and may account for some of the symptoms.

3. Management

The three critical steps in the management of Parkinson's syndrome include reduction in antipsychotic drug dosage, anticholinergic medications, and possibly changing the antipsychotic. Antiparkinsonian medications such as benztropine, biperiden, amantadine, and trihexyphenidyl are generally effective at reducing the parkinsonian side effects of antipsychotics (Table 3). With the exception of amantadine, these agents can produce disturbing anticholinergic side effects; they are most useful during the acute phase of treatment and should probably be continued for no more than several weeks, since some tolerance develops to EPS in most patients.

Antipsychotic dosage reduction remains the mainstay of treatment for persistent drug-induced parkinsonism. The need for continuation of antiparkinsonian medications should be periodically reevaluated. Whenever appropriate, switching to an atypical antipsychotic drug should be considered.

B. Akathisia

1. Clinical Features and Diagnosis

Akathisia is the inability to remain seated. Objectively this manifests as fidgetiness, restlessness, moving constantly in the chair, criss-crossing of the legs while seated or pacing the room or ward. Subjectively, patients describe “nervousness,” “restlessness,” “tingling,’’ “nervous legs,” “nervous stomach,” etc. Questioning regarding recent neuroleptic drug initiation, dose increase, or addition of other drugs that elevate neuroleptic levels may point to the diagnosis in addition to observing the objective and subjective signs described earlier. Special questions regarding calf muscle restlessness may help zero in on the diagnosis (4).

Acute akathisia is a particularly distressing side effect; it has been associated with suicidal and homicidal impulses and other impulsive acts. There-

Table 3 Medications Used in Antipsychotic Drug-Induced Extrapyramidal Syndromes

Mechanism	Drug	Dose Range (mg)	Comments
Antihistamine	Orphenadrine (Norflex)	150-250	Mild stimulant; less effective in tremor
Antihistamine/anticholinergic	Diphenhydramine (Benadryl)	25-200	Very sedating
Anticholinergic	Trihexyphenidyl (Artane)	1-15	Less sedating; shorter half-life Less effective for tremor; has been "abused" by patients
Anticholinergic	Biperiden (Akineton)	2-6	
Antihistamine/anticholinergic	Benztropine (Cogentin)	1-6	Effective for tremor and rigidity; long half-life
Beta blocker	Propranolol (Inderal)	20-120	Effective in akathisia
Dopamine agonist	Amantadine (Symmetrel)	100-300	Useful in patients sensitive to anti cholinergics (e.g. the elderly)

fore, rapid diagnosis and management are critical. Differentiating this condition from psychotic agitation is important, as opposite management strategies are applied. Restless legs, a neurological condition, shares similar clinical features but is more often limited to evening and lying down hours and is physically painful, unlike akathisia. Anxiety is usually differentiated from akathisia by the presence of autonomic symptoms and occurs in the absence of neuroleptic use. Late-onset or tardive akathisia may be similar to the acute form but is more resistant to treatment. Pseudoakathisia is seen in chronic patients, who are seen with objective features of akathisia but have no subjective complaints.

2. Pathophysiology

The pathophysiology remains unclear, though dopaminergic, adrenergic, cholinergic, serotonergic, and gamma aminobutyric acid (GABA) -ergic mechanisms have been implicated. Low serum and brain iron has been implicated as well (5).

3. Management

Management involves a high index of suspicion. Lowering the dose of a high- potency neuroleptic or switching to a low-potency neuroleptic or one of the newer atypical agents may be an option. If a higher dose of the high-potency neuroleptic is needed to treat the psychosis at the expense of akathisia, propranolol in doses of 20 to 120 mg/day may be effective in acute akathisia. Patients' pulse and blood pressure may need to be monitored. Where propranolol cannot be used, lorazepam (1 to 4 mg/day) or benztropine (2 to 6 mg/ day) may be effective. Periodic evaluation with a view to discontinuing antiakathisia medications is desirable but may be difficult to achieve in all cases. Clozapine may be particularly useful in persistent or tardive akathisia; use of clozapine monotherapy has been associated with a low prevalence of akathisia (6). The newly available atypical antipsychotic agents may be useful, too. The Barnes Akathisia Scale (7) is a simple and easy-to-use scale (less than 5 min) that can help to assess the impact of drug treatments for akathisia.

C. Dystonia

1. Clinical Features and Diagnosis

Dystonia refers to sustained muscular spasms. The young male adolescent is at a high risk for developing this disturbing side effect. The muscle groups

involved include the ocular muscles (oculogyric crisis), neck (torticollis), facial and laryngeal muscles, extremities, and spine. The experience of dystonia can be painful and frightening. Dystonic reactions can even be life-threatening when laryngeal musculature is involved. As might be expected, the experience of acute dystonic reactions may negatively impact a patient's later compliance with medication, leading some clinicians to temporarily medicate certain patients (i.e., those with past histories of dystonic reactions) prophylactically with anti- parkinsonian medications. Fortunately, the risk of this side effect decreases with continued treatment. However, in some patients, persistent dystonia may emerge following chronic exposure to antipsychotic drugs (tardive dystonia).

The diagnosis is fairly straightforward and is made based on the history of characteristic muscle spasms in temporal relation to antipsychotic treatment. The rapid and dramatic response to anticholinergic drugs is also valuable in the diagnosis. Unfortunately, however, several cases are misdiagnosed in emergency departments as hysterical reactions, tetanus, and even meningitis. Recurrent dystonia that does not respond to standard treatments (below) should raise the suspicion of nonneuroleptic-related neurological disorders such as Wilson's disease, Huntington's disease, and idiopathic torsion dystonia.

2. Pathophysiology

The pathophysiology of dystonia remains unclear; it has been hypothesized to result from either an increase or a decrease in striatal dopaminergic function. It is observed that dystonia is associated with decreasing blood levels of antipsychotics. Thus, the concentration of the drug is high enough to block dopamine receptors but insufficient to block cholinergic receptors, leading to a relative excess of acetylcholine (8).

3. Management

Dystonia responds promptly and often dramatically to anticholinergic drugs such as diphenhydramine 25 to 50 mg, benztropine 2 mg, or biperiden 2 mg (Table 3). These medications can be administered orally or intramuscularly. Benzodiazepines are also effective. Laryngeal dystonia is an emergency and should be treated with benztropine up to 4 mg intravenously over a 10-min period. Treatment of tardive dystonia is generally unsatisfactory, but tetrabenazine and reserpine may be modestly effective (9). Clozapine is worth considering as an option for patients with tardive dystonia who have to continue antipsychotic treatment (10).

D. Tardive Dyskinesia

Involuntary athetoid and choreic movements characterize neuroleptic-induced tardive dyskinesia. Athetoid movements are slow and small in amplitude and described as sinuous and/or writhing. Choreic movements are faster, erratic, and of larger amplitude. These are mostly irregular in rhythm over time.

1. Clinical Features

Women over the age of 50 and patients with unipolar and bipolar mood disorders face a greater risk of tardive dyskinesia. Tongue movements are commonly seen and involve tongue thrusting (“flycatcher's sign”), worm-like movements of the tongue to push the cheeks out (‘‘bon-bon sign”). These are elicited by having the subject open his or her mouth for 30 to 60 sec with the tongue resting on the floor of the mouth and then having the subject stick the tongue out and hold it there for 30 sec while being asked to touch each finger to the thumb in one or both hands. This maneuver can activate some latent dyskinetic movements of the tongue. Other orofacial areas that are involved include the jaw, lips, eyes, and lower face. Movements may take the form of side-to-side jaw movements, puckering or pursing of the lips, lip smacking, frequent eye blinking to the point of blepharospasm in some, throat-clearing and grunting noises suggesting laryngeal muscle involvement. Contortions of the lower face and neck muscles are seen in more severe cases. Dysrhythmic and involuntary movements can be seen in the fingers, toes, and wrists. A severe form of tardive dyskinesia often coexisting with severe dystonias may involve the trunk and proximal extremities and can result in severe disability, with impaired gait and ambulation and difficulties in both swallowing and speaking. A rare form of life-threatening dyskinesia involving the respiratory muscles (diaphragmatic, intercostal, and pharyngeal) has been described previously.

In rapidly progressive tardive dyskinesia or in young patients, the differential diagnosis includes Huntington's disease, Wilson's disease, Sydenham's chorea, and Parkinson's disease. Torsion dystonia and other rare neurological disorders must be ruled out by appropriate history as well as tests and consultation. Neuroleptic-induced Parkinson's may frequently coexist with tardive dyskinesia, as may tardive akathisia, tardive tics, and tardive Tourette's syndrome; these and can complicate the diagnoses.

In younger populations exposed to neuroleptics, there is a 4 to 5% annual incidence for the first 5 years, and it appears to level off for most patients. The elderly have a much higher annual incidence when exposed to neuroleptics (35

to 50% in one year). In mild to moderate cases, there is some fluctuation in the expression of dyskinetic movements over time. Severe cases may appear progressive before stabilizing.

Neuroleptic withdrawal and emergent dyskinesias are frequently reversible after 6 to 8 weeks, though some are irreversible. Increasing the antipsychotic dose may temporarily suppress the dyskinesia; however, it may eventually resurface.

2. Pathophysiology

The pathophysiology of this condition remains unclear. The prevailing hypothesis of dopamine receptor supersensitivity secondary to prolonged neuroleptic dopamine receptor blockade has its share of proponents and opponents. Nonadrenergic excess and reduced GABA activity are also implicated.

3. Management

Management involves assessing the risks versus benefits of discontinuing the neuroleptic and, in select cases, careful appraisal of nonneuroleptic etiology. The most widely and easily used (5 min) scale to assess tardive dyskinesia is the Abnormal Involuntary Movement Scale (AIMS) (11). Vitamin E, an antioxidant, in doses of 1200 to 1600 IU has shown modest effectiveness in early cases of mild to moderate tardive dyskinesia (12). Whether it can prevent tardive dyskinesia remains unanswered. In the current era of the psychopharmacology of psychoses, the advent of the atypical agents holds particular promise for tardive dyskinesia and related syndromes of dystonia and akathisia. Clozapine has ameliorative or “masking” effects (13). Several patients who subsequently are withdrawn from clozapine show no further evidence of dyskinesias, though some show bizarre limb-axial, trunkal, and neck dystonias that abate in time, either with reintroduction of clozapine or with olanzapine. Only longer exposures to the newer agents (post-clozapine) will indicate if they, like clozapine, have a lower tardive dyskinesia burden than the older neuroleptics. Preliminary data suggest that olanzapine and risperidone may, in fact, have a 5- to 10-fold lower burden of dyskinesia at 1 to 2 years as compared with haloperidol (14).

E. Neuroleptic Malignant Syndrome (NMS)

1. Clinical Features and Diagnosis

The neuroleptic malignant syndrome is a serious complication of antipsychotic treatment characterized by severe muscular rigidity, hyperthermia, fluctuating

autonomic dysfunction, confusion, elevated creatine phosphokinase (CPK), and leukocytosis. NMS usually occurs within 2 weeks of neuroleptic initiation or increase. Several cases of this potentially fatal condition have been reported, but the incidence of clinically recognized cases appears to be relatively rare. NMS is considered a spectrum disorder; the incidence of the full syndrome is estimated to be around 0.02 to 2.4%, and mild cases may occur in up to 12% of antipsychotic-treated patients (15). The following are the risk factors for NMS: male gender, mental retardation or organic mental disease, affective disorder, use of high-potency antipsychotic drugs in large and rapidly increasing doses, and coadminstration of lithium. NMS has been reported rarely following treatment with clozapine and risperidone. NMS can also be triggered by abrupt discontinuation of dopamine agonists such as L-dopa or amantadine.

The diagnosis of NMS can be challenging. The following conditions must be considered in the differential diagnosis: (a) heat stroke: NMS can be distinguished from heat stroke by the presence of muscle flaccidity and dry skin (16); (b) anticholinergic syndrome; (c) lithium intoxication; (d) lethal catatonia, a febrile form of catatonia associated with schizophrenia that may occur in the absence of antipsychotic use; (17) and (e) malignant hyperthermia, a familially transmitted illness that manifests itself with clinical features very similar to those of NMS (18).

2. Pathophysiology

The mechanism of NMS is not yet clearly elucidated, but dysregulation of dopamine function is clearly involved. Observations of NMS caused by dopamine-blocking agents as well as discontinuation of dopamine agonists are in support of this possibility. The similarity between NMS and malignant hyperthermia have been noted, but muscle biopsies have not demonstrated any link between these conditions (18).

3. Management

Treatment of NMS involves termination of antipsychotic medication as well as supportive and symptomatic care in an inpatient setting. Symptomatic treatment involves treatment of concurrent infections, electrolyte imbalance, fever, and the autonomic imbalance. Cold wet packs are helpful in controlling fever. Dantrolene is an effective treatment, given in a dose of 0.8 to 2.5 mg/kg body weight every 6 hr (up to 10 mg/kg daily). When the patient stabilizes, oral dantrolene can be instituted (100 to 200 mg daily). If the recovery is inadequate, bromocriptine may be added, beginning with 2.5 mg tid and up to 20 to 30 mg/pday.

F. Cognitive and Psychiatric Side Effects

Traditional neuroleptic drugs have been known to impair certain cognitive functions, especially in the areas of selective attention, concentration, and working memory. However, separation of the illness effects from the medication effects has been difficult. The advent of the newer atypical agents such as clozapine, risperidone, olanzapine, and quetiapine has resulted in a resurgence of interest in this area of research. It has been suggested that some of the improvements noted with clozapine have to do with improvements in specific cognitive functions, especially those putatively linked to the prefrontal cortex. Several, though not all, studies support this contention for clozapine, risperidone, olanzapine, sertindole, quetiapine, etc. Interesting but, at this time, unanswered questions include whether improvements in cognitive function are nonspecific—i.e., whether improvements in overall psychopathology are associated with improvements in certain cognitive domains or whether the newer antipsychotic agents with different pharmacological profiles (for instance, strongly antimuscarinic agents such as clozapine and olanzapine versus weakly antimuscarinic agents such as risperidone and quetiapine) will turn out to have differential effects on cognitive abilities of patients with psychoses. Indeed, there is some recent evidence that risperidone may have a favorable effect on working memory in treatment-resistant schizophrenia (19). Again, whether these tests of cognitive ability (such as impairments in selective attention or working memory) translate to our ability to predict functional improvements for patients (for instance, driving ability, ability to carry out simple tasks like cooking for themselves or taking a bus, and, ability to make progress in group, vocational, and other therapies) are important questions that remain unanswered at this time. Practical considerations may include limiting or discontinuing anticholinergic agents (for instance, benztropine) if possible, using one of the newer agents, and—in those cases where antimuscarinic properties are problematic—using one of the less antimusearinic agents.

A curious side effect noted with clozapine and risperidone is the emergence of obsessive-compulsive symptoms (20). Whether this simply reflects an improvement of the psychoses and a revelation of the underlying neuroses or if it is related to the mechanisms of the newer agents is unclear. Interestingly, these agents have been used along with the newer antidepressants to treat refractory obsessive-compulsive disorder. The use of low doses of SSRIs in addition to clozapine and risperidone seems to help some individuals. There is no clear relationship to dose of clozapine or risperidone, though the obsessive compulsive symptoms are transient in some cases and may not require additional treatment. This effect seems to emerge earlier in the case of risperi-

done (weeks) than that of clozapine (months). In a preliminary study, olanzapine did not appear to increase the frequency of obsessive-compulsive symptoms in schizophrenia (21).

G. Epileptogenic Effects

Some antipsychotic drugs decrease seizure threshold, and this may be associated with the appearance of diffuse slowing in the electroencephalogram (EEG). Low-potency antipsychotics such as chlorpromazine, loxapine, thioridazine, and especially clozapine are associated with a higher risk of epileptogenicity (22). The risk of seizures with clozapine is dose-related: seizures occur in about 1 to 2% of patients taking <300 mg/day, 3 to 4% of patients on 300 to 600 mg/day, and about 5% or higher in those on >600 mg/day. Clozapine and other low-potency antipsychotics should be avoided in patients with a history of seizure disorders. If a patient on antipsychoties develop seizures, temporary discontinuation of the antipsychotic, dosage reduction, and/ or switching to a high-potency drug should be considered. An anticonvulsant such as valproate can be initiated if the above approaches are not feasible or are ineffective. Carbamazepine is best avoided with clozapine.

III. CARDIOVASCULAR EFFECTS

Among the antipsychotics, low-potency drugs such as chlorpromazine and thioridazine have significant effects on cardiac conduction. Psychotropic drug effects on cardiac conduction and repolarization have been implicated as a possible cause for some cases of sudden death noticed in patients receiving antipsychotic drugs. Thioridazine has been blamed the most, since this calcium-channel blocker often causes ECG changes, notably T-wave abnormalities. QT prolongation has been described with pimozide (23). Sertindole is also associated with QTc prolongation. However, the causal relationship between antipsychotics and the rare occurrence of sudden death in psychiatric patients is not clearly established (24).

Postural or orthostatic hypotension is particularly common with low- potency antipsychotic drugs and occur relatively early during therapy. The mechanism of this adverse effect is alpha-adrenergic blockade. Symptoms include dizziness and fainting and can be particularly troublesome in the elderly, who may be prone to falls. The condition needs to be monitored by checking the recumbent and vertical blood pressure before and periodically after institution of treatment. Management of postural hypotension involves the use of

lower doses and gradual titration; patients should be warned of the side effects. They should be advised to get up slowly from bed and to raise the foot end of the bed. In some cases, stockings may help. When these conservative measures fail, use of vasopressor agents such as levophed or salt tablets (1–3 gm/day) or mineralocorticoids such as fludrocortisone (0.1 mg/day) may be indicated.

Another side effect, often seen with the atypical antipsychotics such as risperidone (25) and sertindole (26), is nasal congestion. This may be related to the alpha-adrenergic blocking effects of these drugs and not due to anticholinergic effects as is often believed.

IV. ENDOCRINE SIDE EFFECTS

Antipsychotic drugs consistently elevate prolactin levels by dopaminergic D2- receptor blockade, since dopamine is inhibitory to prolactin release. Such prolactin elevations are responsible for the breast enlargement and galactorrhea often observed during treatment with antipsychotic drugs. Increased prolactin levels also lead to decreases in levels of luteinizing and follicle-stimulating hormones, which may, in turn, lead to amenorrhea and decreased orgasm in women and reduced testosterone secretion in men. There is no clear evidence that hyperprolactinemia due to antipsychotics increases risk of breast cancer. Some tolerance may develop during long-term antipsychotic treatment. Among the atypical antipsychotic drugs, olanzapine is associated with a lower likelihood of causing prolactin elevations than risperidone (27); quetiapine like clozapine poses no risk of sustained prolactin elevation (28,29).

Weight gain is common with antipsychotic drugs, especially with low-potency drugs, particularly chlorpromazine, clozapine and olanzapine. The mechanisms involved include antiserotonergic and antihistaminic effects. Further, the dry mouth and thirst caused by the anticholinergic effects may increase intake of high-calorie drinks. Patients should be advised to avoid these and drink water instead. Molindone and loxapine are among the few antipsychotics reported to cause the least weight gain; it may even cause weight loss. Risperidone and ziprasidone may be less likely to cause weight gain than olanzapine and clozapine (27,30). Weight gain poses a risk for Type II diabetes mellitus and cardiac disease. Frequent counseling, monitoring, and possible switching to an agent with less weight gain potential may be options.

V. SEXUAL SIDE EFFECTS

Problems with desire (libido and impotence) and the mechanics of the sexual act (erectile dysfunction, premature ejaculation, retrograde ejaculation, delayed ejaculation, priapism) have been attributed to the older and some of the newer antipsychotic agents in small case series or case reports (31). Most of the conventional antipsychotic drugs can cause sexual dysfunction; the incidence of these side effects is often underestimated (they could be seen in as many as 40 to 50% of patients) (32), since many patients do not report them unless asked. These side effects may relate to the dopamine antagonist, anti- alpha-adrenergic, and possibly anticholinergic activity of these agents (33). An increase in prolactin levels has been associated with amenorrhea and galactorrhea. Newer agents like clozapine, olanzapine, and quetiapine produce minimal to mild transient increases in prolactin levels, and this may translate to diminution or absence of prolactin-related side effects. Sertindole has been shown to induce decreased ejaculatory volume in men, though this seems to resolve spontaneously in most men even with continued treatment. Priapism is less common with the neuroleptic drugs than with antidepressant drugs and has been reported in anecdotal reports for most of the older drug classes. Data are sparse for the newer agents. However, recent evidence suggests that sexual dysfunction may be least common with quetiapine and clozapine (28,29), transient with olanzapine, and more common with risperidone (27). Sertindole causes decreased ejaculatory volume in men, a side effect attributable to this drug's α1-adrenergic antagonist effect (26). These side effects are gaining importance as physicians, health care providers, and patients are talking and asking about specific symptoms more openly. Presumably, sexual side effects are a significant if unrecognized cause of noncompliance or failure to adhere to treatment.

Management involves the reduction of antipsychotic dose to the minimum effective range as well as changing to a different class of the older drug; one of the newer agents may be a treatment option. Dopaminergic agonists such as bromocriptine and alpha 2-adrenergic antagonists like yohimbine may be helpful but must be weighed against the potential risk of worsening the underlying psychiatric condition. Use of a specific agent such as cyproheptadine before intercourse may be another option that is sometimes helpful. Imipramine, in a dose of 25 to 50 mg/day, has been found to be effective in the treatment of retrograde ejaculation caused by thioridazine (34). Bethanechol, 30 mg 1 to 2 hr before coitus, may also be helpful. Consultation with a urologist with a specific interest in sexual dysfunction may be warranted in difficult situations.

VI. HEMATOLOGICAL/IMMUNOLOGICAL EFFECTS

While agranulocytosis is the one side effects that is well recognized with clozapine, with an annual risk just under 1%, there are other hematological and immunological side effects with the older and newer agents. The risk of agranulocytosis and neutropenia is 10-fold higher with clozapine than with older neuroleptic agents. The newer agents such as olanzapine, quetiapine, risperidone, sertindole, and others do not pose this risk, based on available data. Several of the older agents and clozapine have been associated with anemia (aplastic, hemolytic, etc), eosinophilia, thrombocytopenia or thrombocytosis, purpura, etc. Practical management concerns would include being wary of combinations of drugs that could possibly have additive effects on the hemopoietic system: for instance, clozapine and carbamazepine, clozapine and mirtazepine (a new antidepressant) should be avoided, and care to monitor the blood count in patients taking clozapine and valproate is advised. In the United States, clozapine is the only drug with the mandatory weekly white cell monitoring, although testing has become biweekly after the first six months. In the others, monitoring of laboratory parameters as well as observing for unexplained fever, malaise, lassitude, mouth ulcers, and sore throats, especially early in treatment (first 5 months), with clozapine and related drugs may help detect latent leukopenia or agranulocytosis. Discontinuation of the drug and consultation with a hematologist and/or an infectious disease specialist may be needed if there is a need to hospitalize the patient during the vulnerable period. Granulocyte colony stimulating factors have been successfully used by hematologists to reverse the bone-marrow suppression with clozapine; sometimes this intervention is combined with reverse isolation as well as prophylactic antibiotic and antifungal agents in a hospital setting (35).

Immunological side effects may also include rare cases of hypersensitivity to the older agents, rarely to the newer one. Also, the induction of antinu- clear antibodies and other antibodies with the use of chlorpromazine and related antipsychotic agents could result in a diagnosis of drug-induced lupus requiring discontinuation of the offending agent and trying a different agent preferably from a different drug class or one of the newer agents. Chlorpromazine as well as some of the older and newer agents like clozapine are rarely associated with immune-mediated hepatitis, pancreatitis, and serositis (pleural effusions, and pericardial effusions). A high index of suspicion and immediate discontinuation and consultation may be ways to minimize the negative consequences of these rare but sometimes fatal reactions.

VII. DERMATOLOGICAL EFFECTS

Antipsychotic agents frequently cause uncomfortable skin reactions both acutely and in the long term. These may include three types: allergic skin reactions, photosensitivity reactions, and pigmentary changes.

A. Allergic Reactions

Like most other drugs, antipsychotic drugs can cause maculopapular rashes. These are erythematous and itchy and appear on the face, neck, chest, and limbs typically between 2 and 10 weeks after beginning treatment. The reactions occasionally may be severe and manifest with exfoliative dermatitis, localized or generalized urticaria, and erythema multiforme; angioneurotic edema, which can be life-threatening, has also been described. The allergic skin reactions promptly subside with discontinuation of the drug (36). However, since phenothiazines are excreted slowly, the rashes may occasionally persist. For this reason, a treatment-free interval of about a week should be allowed before beginning another antipsychotic drug. The possibility of a "cross allergy" to the newly started drug should also be kept in mind (37). Antihistamines and topical steroids may often be required. Alternative treatments of the psychotic illness, perhaps with nonantipsychotic drugs or electro- convulsive therapy, may also have to be considered.

B. Photosensitivity Reactions

These reactions are thought to result from interactions between certain drugs and light, resulting in the generation of free radicals with adverse biological effects. The reactions are commonly seen in areas of the body exposed to sunlight and resemble sunburns in appearance. Low-potency antipsychotics, most commonly chlorpromazine, result in photosensitivity in about 3% of patients (38). Treatment involves limitation of exposure to the sun; sunscreens (usually containing paraaminobenzoic acid, or PABA) and protective clothing are also helpful. Patients should be educated about these side effects, especially during the summer months. Switching to a high-potency antipsychotic drug may be necessary in some cases, or to one of the newer agents.

C. Cutaneous Pigmentation

Chronic use of antipsychotics, especially low-potency drugs such as chlorpromazine, may result in discoloration of the skin, particularly in sun-exposed

areas. Haloperidol and other high-potency antipsychotic drugs are less prone to cause this side effect (39). Alteration in melanin metabolism by phenothiazines has been implicated (40). The skin changes may range from a tan color to purple; pigmentary changes in the eye are frequently associated. The reaction is rare, about 1% in frequency (40), and may be dose-related. The pigmentary skin changes cause a good deal of cosmetic embarrassment. Long-term treatment with high-dose antipsychotics should therefore be avoided. Avoidance of excessive exposure to direct sunlight is important; reducing the antipsychotic drug dose and switching to high-potency agents or to the newer agents are helpful measures.

VII. OPHTHALMOLOGICAL SIDE EFFECTS

A serious complication, associated with thioridazine use in doses of over 800 mg per day is irreversible retinal pigmentation. Difficulty in nocturnal vision is an early symptom of this sequel that should arouse suspicion. This condition may worsen even after the medication is discontinued and can lead to blindness. Chlorpromazine, when used in large doses for long durations, may cause a benign pigmentation of the eyes, especially in the cornea and lens. Vision is not impaired and the retina remains intact. The best management of the ophthalmological complications is prevention, and the chronic use of large doses of aliphatic phenothiazines such as thioridazine and chlorpromazine should be avoided (41). Quetiapine in doses that far exceed human doses has been reported to be associated with cataracts in dogs when administered for 1 year. Similar studies in monkeys were negative, and the relevance of these observations to humans is unknown. The package insert recommends a slit- lamp examination or direct ophthalmology to check for cataracts around the time of initiation of the drug and periodically thereafter.

IX. ANTICHOLINERGIC SIDE EFFECTS

Antipsychotics, in particular low-and medium-potency drugs, can cause peripheral anticholinergic effects such as dry mouth, and nose, blurred vision, urinary retention, constipation, and, rarely, paralytic ileus. These side effects can be worse when antipsychotic drugs are used in combination with anticholinergic drugs. Most of the anticholinergic side effects can be addressed by reduction of the antipsychotic drug and by switching to a less anticholinergic antipsychotic. Patients who complain of dry mouth benefit

from frequent sips of water, and constipation responds to usual laxatives. Cholinergic agents such as pilocarpine and bethanechol can help in cases of paralytic ileus and urinary retention. Among the newer agents, clozapine is strongly antimuscarinic, risperidone and quetiapine have practically no antimuscarinic activity, and olanzapine is intermediate.

X. HEPATIC EFFECTS

Jaundice and liver function alterations were described during chlorpromazine therapy soon after introduction of this drug (42). Transient increases in hepatic enzymes occur frequently (22 to 50%) following initiation of treatment with most antipsychotics; these are usually benign and do not necessitate stopping the antipsychotic (43). Transient elevations of liver enzymes are also seen with clozapine (44), olanzapine (45), and quetiapine (28). Chlorpromazine is most frequently implicated in hepatotoxicity, since it has been the most widely prescribed antipsychotic and also has been available longer than most other antipsychotic drugs. Clinical jaundice is rare (about 1% of the patients). Jaundice has also been reported in patients treated with thioridazine, fluphenazine, perphenazine, promazine, mepazine, clozapine, and haloperidol. There are no published reports of jaundice caused by thiothixene or other thioxanthene derivatives.

A. Clinical Features and Diagnosis

In most cases, the liver enzyme elevations are asymptomatic. Rarely, jaundice or other evidence of hepatic dysfunction appears during the first month after beginning antipsychotic treatment. Most patients recover in about 8 weeks, although laboratory values may take longer to recover (3 to 18 months). Rarely, a patient may develop chronic biliary cirrhosis (43,46). The laboratory picture is usually similar to that of obstructive jaundice with elevations in conjugated bilirubin and alkaline phosphatase levels. The hepatotoxic reaction is idiosyncratic and unrelated to age, sex, dosage, or prior hepatic disease.

B. Pathophysiology

Histopathological examination of the liver in cases of hepatotoxicity reveals evidence of cholestasis in the canaliculi, hepatocytes, and Kupffer cells. The patterns of cholestasis are centrilobular or central and midzonal. In addition, some degree of inflammation, sinusoidal eosinophilia, and focal necrosis may

be seen (43). The time course, eosinophilia, and rare occurrence after a single dose point to an immunogenic hypersensitivity reaction. However, it has been suggested that the higher incidence of liver enzyme elevations and necrosis may point to a cytotoxicity mechanism. Both mechanisms may be operative in clinically significant cholestasis independently or acting in concert. Chlorpromazine may form free radicals that inhibit transport systems (Na+, K+- ATPase activity), which, in turn, may impair biliary flow. These cytotoxic effects may lead to membrane alterations that then trigger a hypersensitivity response. It has been suggested that the pathology and mechanisms may be the same in haloperidol-induced liver disease.

C. Management

Although some patients may recover despite continuation of the treatment, it is prudent to stop the antipsychotic drug. A nonphenothiazine antipsychotic, such as thiothixene, provides an effective alternative, but treatment resumption should await normalization of liver parameters. Liver function should also be closely monitored after institution of such treatment. The drugs should be used cautiously in patients with already existing liver disease. Patients on antipsychotics who develop fever, jaundice, or flu-like symptoms should have appropriate liver function tests as well as a complete blood count and differential count done promptly. Newer agents such as risperidone may provide alternative treatment options.

XI. DRUG INTERACTIONS

The clinician should be alert to the possibility of drug-drug interactions when using antipsychoties concomitantly with other medications (Table 4). Smoking can reduce plasma levels of antipsychotic drugs. This may be particularly relevant to clozapine and olanzapine, which are largely metabolized by the cytochrome P450 1A2 isoform; smokers may need higher doses of these medications, and the doses will need to be reduced upon cessation of smoking. The concomitant use of antiparkinsonian drugs may delay absorption of antipsychotic drugs and decrease blood levels. The addition of anticholinergics to low-potency antipsychotic drugs predisposes to the risk of serious anticholinergic toxicity and should therefore warrant caution. Coadministration of tricyclic antidepressants and antipsychotic drugs lead to higher blood levels of both drugs; this is related to mutual inhibition of enzymatic metabolism. Such combinations may also lead to additive anticholinergic and sedative ef-

Table 4 Drug Interactions with Antipsychotics

Drug	Mechanism	Clinical Outcome
Anticholinergic agents	Additive actions	Increased anticholinergic side effects.
Antidepressants (SSRIs or TCAs)	Mutual inhibition of metabolism; antidepressants increase antipsychotic blood levels and vice versa	Increased side effects especially anticholinergic and orthostatic. Possibly increased EPS.a
Lithium	Increased tissue lithium uptake; increased levels of antipsychotics	Increased neurotoxicity; confusion and disorientation; may increase EPS.
Antacids and cimetidine	Decreased absorption of antipsychotics	Decreased antipsychotic effects; delayed response.
Carbamazepine	Carbamazepine increases enzymatic metabolism of antipsychotics	Decreased antipsychotic levels; positive symptoms may increase about 2–4 weeks after introduction of carbamazepine.
	Increases risk of agranulocytosis	Concomitant use of clozapine contraindicated (both agents may cause agranulocytosis).

aExtrapyramidal syndromes.

fects. Low-potency antipsychotics and pimozide used in combination with tricyclics can increase the likelihood of cardiac side effects and prolongation of the QT interval. Inhibition of the 1A2 enzyme by fluvoxamine leads to increased levels of clozapine, olanzapine and haloperidol; on the other hand, 3A4 may be induced by carbamazepine and alprazolam, leading to the need for higher doses of these medications. A detailed discussion of these interactions is offered in a review by Nemeroff et al. (1996) (47).

XII. CONCLUSIONS

Effective management of antipsychotic drug-induced adverse effects involves early identification of the side effect followed by prompt intervention. Failure to do so can lead to considerable distress to the patient, potential noncompliance with treatment, and even medicolegal difficulties for the treating clinician (48). Fortunately, the majority of antipsychotic drug—induced adverse effects are preventable. The following guidelines for wise prescribing can help to prevent unneeded iatrogenicity:

- Choose the antipsychotic drug with the least problematic side-effect profile for a given patient.
- Identify potential risk factors for adverse effects before beginning treatment (e.g., history of seizure disorder) before beginning clozapine and preexisting cardiac disease before starting low-potency anti- psychotics.
- Use minimum effective doses of medication; begin with small doses and titrate dose gradually; educate patient regarding early recognition of side effects.
- Avoid polypharmacy whenever possible; monitor blood level whenever appropriate; check side effects periodically and whenever dose changes are made.
- Intervene promptly and early whenever side effects appear; consider atypical antipsychotic drugs especially when extrapyramidal side effects are significant.

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3 Management of Tricyclic Antidepressant Side Effects

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I. INTRODUCTION

The tricyclic antidepressants (TCAs) derive their name from their three-ring structure: a central ring bounded by two benzene rings. They have been proven to be effective in the treatment of depression disorder, anxiety disorder, panic disorder, attention-deficit disorder, enuresis, and sleep disorder, thereby reaching a huge number of patients of all ages. The shortcomings of TCAs are their lack of effectiveness in about 20% of patients and the occurrence of a number of side effects. Their action on NE and 5HT systems have been known to be responsible for their therapeutic action, and acetylcholine, histamine, and alpha-adrenergic blocking effects lead to a host of side effects.

While toxicity is an important factor, many insurance companies and the public hospitals insist on using TCAs as first-line drugs in order to contain costs of medication. SSRIs are permitted only when TCAs fail to produce an improvement. For enuresis and pain disorders, tricyclics are the first-choice drugs. TCAs are the most widely used antidepressants.

II. GENERAL MANAGEMENT OF SIDE EFFECTS

Ideally, the patients must be educated about the side effects of the TCA before their initiation. Explanation of side effects reduces the discouragement and increases the confidence in the clinician if the side effects do occur. Indeed unanticipated side effects negatively influence patients' perceptions of medications and contribute to noncompliance (1). The side-effect profile of the particular antidepressant prescribed to the patient should be explained. The patient should also be told that it is impossible to predict precisely what specific side effects a given individual will experience with a particular TCA.

Many TCA-induced side effects and the symptoms of depression are indistinguishable. These include headache, dry mouth, insomnia, anxiety, constipation, weight loss, fatigue, reduced libido, and lethargy (2,3). It is important to categorize any symptom the patient offers among the depressive symptoms or the TCA-induced side effects.

Often, there is a correlation between the side effects and biological action of drugs. For example, an antidepressant with a predominant alpha-adrenergic-blocking effect can be anticipated to produce postural hypotension. However, not all the patients who receive TCAs develop side effects, and even those without anticholinergic effects can produce symptoms such as dry mouth and constipation. In addition, idiosyncratic side effects can occur.

III. SPECIFIC SIDE EFFECTS

A. Gastrointestinal

1. Dry Mouth

Dry mouth is a frequently occurring and troublesome anticholinergic side effect of TCAs. A number of medical conditions such as diabetes, dehydration, primary disease of salivary glands, autoimmune disease, and depression itself may cause dry mouth. These medical disorders need to be ruled out prior to regarding dry mouth as a drug induced symptom. Decreased saliva contributes to dental disease (4) and difficulty chewing and speaking.

a. Treatment. Even though dry mouth is not considered dangerous, some patients cannot talk or swallow. Difficulty in articulation may lead to a ecrease in their interactions. The best method of preventing dry mouth is to avoid the most anticholinergic preparations and to prescribe those that are least anticholinergic. Among the TCAs, the most anticholinergic are amitriptyline, protriptyline, and clomipramine and the least anticholinergic are nortriptyline,

desipramine, and maprotiline. Adequate hydration is necessary as inadequate fluid intake further reduces salivary flow. Salivary stimulants such as lemon or citrus drops can increase salivary flow. A plastic squeeze bottle containing salivary substitutes having the viscosity and electrolyte composition of the whole saliva may be kept at the bedside; this is particularly helpful for nocturnal xerostomia.

In order to prevent dental disease, instruct the patient to avoid sugared gums, candies, and drinks. Water, ice sips, or sugarless candies and drinks are useful. Brushing and flossing teeth after each meal and before retiring to bed reduce the risk of plaque formation. Daily use of mouthwash using commercially available gels and rinses will soothe, lubricate, irrigate, and moisturize dry oral mucosa. A semiannual dental checkup should be a routine in those on TCAs. Peripheral cholinergic drugs can improve the TCA-induced dry mouth (5). Bethanechol 25 to 50 mg three to four times daily is useful for dryness of mouth and other parts of the body. Yohimbine has been used for dry mouth (6) with equivocal results.

2. Constipation

Constipation is due to decreased colonic movement as a result of anticholinergic activity. This side effect is a manifestation of depression; is more frequent in the elderly, the immobile, and the sedentary; and occurs in patients with dietary changes and with dehydration; therefore proper diagnosis is imperative. Patient education, diet, and medications are essential initial steps. Regular sleeping and eating habits, daily activity such as simple walking, and the use of a heating pad to the abdomen are useful. Unfortunately, a depressed patient may not be able to comply with these suggestions. The use of bulk agents is encouraged in all the patients. They are instructed to add one to three teaspoons of bran to cereal or morning drink daily unless excessive cramping or diarrhea occurs. Use of fruits, including prunes and vegetables, as well as consumption of 1 L of water daily, is recommended. Various hydrophilic colloids have long been used as adjuncts in the management of constipation (7). Preparations of psyllium seed (Metamucil) up to three times a day are started prophylactically in high-risk elderly, immobile, and dehydrated patients. Stool softeners such as docusate sodium or (Colace) 100 mg bid, Regulex 100 mg bid, and Surfak 240 mg bid are the first line of active treatment if education, diet, and bulking agents are not successful. These are gradually discontinued as a regular bowel habit returns. Harsh irritant and osmotic laxatives are avoided, as their chronic use contribute to colonic atony and perpetuation of constipation (7). However, they do have a place in the temporary relief of

constipation, and a glycerin suppository or an oil retention enema may have some limited use in softening fecal impaction. The assistance of gastroenterologist may have to be resorted to in difficult cases.

3. Appetite and Weight

The weight gain induced by amitriptyline, imipramine, and nortriptyline is usually between 1 and 3 lb per month (8), but occasionally patients may gain as much as 20 lb or more. There is an initial rapid phase, followed by a slower but continuous linear increase during the maintenance phase (9,10). The weight gain can be quite high, producing discomfort. Amitriptyline is the most commonly cited offending agent (9), although other TCAs produce this effect (11). According to various studies, weight gain and carbohydrate craving can be observed among 25 to 50% of subjects (8,11). Discontinuation of TCAs usually results in a slow process of weight loss until the pretreatment weight is achieved (9). Some seriously obese patients may lose only a portion of the extra weight (12). Unfortunately, which patients will be at higher risk for weight gain cannot be predicted. No correlation has been noted between weight gain and pretreatment weight, prior weight loss in the course of depression (8), or response to antidepressant treatment (10). It is reasonable to assume that changes in eating behavior result from TCA action on neurotransmitters in the hypothalamus (13). Both serotonin (14) and histamine (15) play a role in promoting satiety, and their antagonists may cause overeating. Among the TCAs, amitriptyline is the most potent blocker of the H1 histamine receptor, followed by nortriptyline and imipramine. In contrast, desipramine has minimal antihistaminic properties, which may explain the reduced effect of desipramine on appetite as compared with other TCAs (16). As weight gain is observed in TCA-treated patients with panic disorder, enuresis, pain syndrome, and depression, this side effect is independent of diagnosis.

a. Treatment. Patients should be educated about the possibility of craving for sweets and increased appetite and the need to maintain a balanced diet. Weight gain can be controlled by suggesting a low-carbohydrate diet and exercise. These precautions can prevent or minimize weight gain. If food craving is severe and weight gain is rapid or substantial, it may be necessary to switch to a different antidepressant, such as desipramine or fluoxetine.

Rarely, weight gain is the result of accumulation of fluids, producing edema, as in the syndrome of inappropriate antidiuretic hormone (SIADH) (17). In cases with fluid accumulation, support stockings and occasionally administration of a thiazide diuretic (e.g., hydrochlorthiazide 50 to 100 mg daily) may be helpful. In SIADH, the offending agent has to be stopped and

low sodium corrected immediately. Occasionally, the addition of anorectic agents, such as dextroamphetamine or dexphenfluramine, is helpful. The latter has recently been available in the market for the treatment of obesity. This drug, in doses of 15 mg twice daily, may be helpful in patients who have gained excessive weight. There is no absolute contraindication to combining this drug with TCAs. In fact some treatment-resistant depressed patients may benefit from the combination. However, there is a risk of pulmonary hypertension, manifesting itself as shortness of breath, ankle edema, chest pain, and fainting spells. If any of these symptoms occur, dexphenfluramine has to be discontinued immediately.

B. Neurological Side Effects

1. Sedation

This frequently encountered and annoying side effect is pharmacologically related to the antihistaminic and anticholinergic effects of TCAs. While sedation can be advantageous in agitated and insomniac patients, it is nevertheless undesirable in a number of situations including the operation of heavy machinery, driving an automobile, and learning in school.

In many instances, sedation occurs initially but gradually dissipates to a varying degree or the patient learns to live with it. Some patients start drinking coffee to counteract the impact of the sedation. In some patients, this side effect needs an active intervention. A single night dose of TCA may alleviate the daytime sedation. If it still persists, a decrease in dosage may be required. While the sedation may be decreased by a lowered dosage, the therapeutic response may be diminished to nonresponse or a relapse may occur in already responding patients. Another alternative is to switch to a less sedating preparation. Among the tricyclics, amitriptyline, doxepin, clomipramine, and trimipramine are the most sedating; nortriptyline, desipramine, and protriptyline are the least sedating. In cases where the patients are unable to tolerate the sedation, TCAs need to be discontinued and an SSRI gradually substituted.

Pharmacological strategies to improve sedation include administration of dextroamphetamine 5 to 30 mg daily in the morning and at noon along with the TCA. Switching to an activating antidepressant, such as bupropion 75 to 300 mg daily, may improve depression without sedation (18).

2. Ocular Side Effects

Common complaints are decreased vision, blurry vision, and difficulty reading. The dryness of the eyes can cause problems in contact lens wearers (19).

Bethanechol may not be useful (20) and pilocarpine drops may produce accommodative spasms with secondary angle glaucoma (21), follicular conjunctivitis (22), and cataract formation (23). In the long run, corrective lenses are useful, but not early in treatment, prior to fixing the dose. Aggravation of narrow-angle glaucoma, a genetic disease, by TCAs is infrequent (24). Nonirritant, soothing eyedrops such as Visine can improve irritation due to dryness.

3. Delirium

This is described as a frequently occuring side effect of TCA (25), particularly in patients over the age of 40 (25,26). Preskom and Simpson (27) noted that among those with high levels of TCA, 43% manifested delirium. Clinically, delirium begins with evening restlessness and pacing followed by sleep disturbance. This progresses to forgetfulness, agitation, illogical thoughts, disorientation, memory impairment, and delusions. Delirium with disorientation, loss of memory, ataxia, flushed and dry skin, and psychosis can occur. Peripheral anticholinergic signs are present in only 10% of these patients (26). TCA levels in the peripheral blood do not correlate directly with central anticholinergic delirium.

a. Treatment. Distinguishing between the worsening of the psychosis and the drug-induced delirium is the first step, as worsening requires an increased dosage while the anticholineric delirium requires discontinuation of medication.

Once the diagnosis of delirium is made, the offending agents should be discontinued and the patients given supportive treatment. Nutrition and electrolyte balance should be assessed and maintained. If psychosis is predominant, antipsychotic drugs with the least anticholinergic properties, such as haloperidol or risperidone, can be administered. Blood pressure monitoring is required for risperidone. Intravenous physostigmine 1 to 2 mg repeated after 20 to 30 min if no clinical improvement occurs can be used to reverse anticholinergic delirium (28,29). As physostigmine has a number of side effects that may complicate both the prognosis and management of toxic patients, its use should be reserved for intractable and severe cases only. Monitoring of blood levels may help to detect those patients with high TCA levels and delirium.

4. Extrapyramidal Symptoms

TCAs can induce fine rapid tremor of the upper extremities and tongue (30,31). Coffee and anxiety both increase the tremors. Tremors can occur at a particular

dose and a dose reduction can produce the disappearance of these tremors. However, decrease in dose can exacerbate depression in some cases.

Akathisia, dystonia, akinesia, and dyskinesias are occasionally reported in association with amoxapine (32–34). Zubenko and collaborators (35) have described the occurrence of an akathisia-like syndrome with imipramine and desipramine. This syndrome appeared in 5 of 1000 neuroleptic-free patients treated with antidepressants. Clomipramine, amitriptyline, and doxepin along with estrogen (36) can produce akathisia. TCAs are moderate inhibitors of dopamine-sensitive adenylate cyclase (37), which accounts for their antidopaminergic effects. Estradiol also has a potent antidopaminergic effect on prolactin release (38). Estrogen can then enhance the antidopaminergic effect of TCA. There are a few anecdotal reports of akathisia and facial dyskinesias during treatment with other TCAs (39,40).

Bucco-facio-lingual dyskinesias with associated limb and truncal choreoathetotic movements have been noted during treatment with amitriptyline (39) and clomipramine (41). In a review of the existing literature, Yassa et al. (42) reported 24 cases of tardive dyskinesia arising during antidepressant treatment. Of these patients, 11 were receiving imipramine, amitriptyline, nortriptyline, or clomipramine.

a. Treatment. The treatment of fine tremors depends on the diagnosis. Therefore, the first step is to assess the blood level of the TCA. Reduction of the dose to bring normalize the blood level may be necessary. If the TCA level is within the therapeutic range, administer propranolol 10 to 20 mg three or four times daily. If there is no improvement after dosage adjustment and/ or administration of propranolol or the dosage reduction results in loss of therapeutic effect, the medication may have to be discontinued and another agent administered.

TCA-induced akathisia is difficult to treat. Benzodiazepines such a diazepam 5 mg or lorazepam 1 mg may alleviate the immediate problem. If akathisia persists, diphenhydramine 25 to 50 mg may also be useful. In persistent cases and in patients who develop tardive dyskinesia or dystonia, the offending agent needs to be discontinued and another antidepressant started.

5. Myoclonus

About 40% of the patients receiving imipramine (43) and other TCAs (44– 46) develop myoclonus. Often, it is mild and consists of two to three very brief muscle jerks of the lower extremities, usually in the evening during relaxation. In 9% of patients, myoclonus may be more severe, with repetitive jaw

jerking causing stuttering, sudden arm jerking resulting in dropping things, and nocturnal myoclonus precipitated by tactile or auditory stimuli. In cases of overdose, myoclonus occurs frequently (47).

a. Treatment As noted above, most of the patients manifest benign myoclonus and do not require any treatment. In those with severe myoclonus, this side effect disappears upon drug discontinuation (48). If TCA therapy is essential for a patient with drug-induced myoclonus, addition of clonazepam, valproic acid, or carbamazepine and careful vigilance may be helpful. Addition of lithium to tricyclic therapy may initiate myoclonus, and patients on this combination should be watched (49).

6. Seizures

All tricyclics can induce seizures. Burley (50) estimated that 1.4% (28/2218) of patients on imipramine had seizures. Peck et al. (51), in reviewing earlier trials, found an incidence of 0.6% if the dose was over 200 mg/day and 0.1% (3/2986) if the dose was below 200 mg/day. Seizures have been seen not only in adults but also in children treated with this agent for nocturnal enuresis (52–54). Clinical trial data have indicated a seizure rate of 0.7%, similar to the incidence in normal population (51,55,56). A systematic study (57) indicated that the incidence of TCA-induced seizure was 2.2%. It has also been noted that most seizures occur in patients taking 200 mg/day of maprotiline (58,59). Because of the strong dose relation to seizures, the maximum dosage of maprotiline was decreased from 225 mg/day to a ceiling dose of 150 mg/day for outpatients and from 300 mg/day to 225 mg/day for inpatients.

a. Treatment. A careful history of seizures should be obtained prior to initiation of TCA therapy. In those with seizure disorders and depression, maprotiline and clomipramine should be avoided. If a person develops seizures, three conditions should be considered: drug-induced seizures, syncopal attacks secondary to orthostasis, or drug-induced SLKDH.

An electroencephalogram (EEG) may not be helpful in diagnosing drug- induced seizures but is useful to reveal an undetected primary seizure disorder. With the patient in the supine and standing positions, blood pressures should be obtained to rule out orthostasis. Soon after the seizure is reported, it is wise to estimate the blood TCA level to ascertain whether the seizure was the result of a high or therapeutic level of TCA in the blood. Blood electrolytes should also be checked. Low sodium levels should be corrected, followed by estimation of urine osmolality and serum ADH levels.

C. Behavioral Effects

1. Mood Symptoms

TCA-induced mania is not uncommon even though there is a dispute over whether this is related to the not yet manifest bipolarity or due to the drug per se. Mania can occur in bipolar patients as well as in those without prior history of bipolar disease. In addition, some patients develop a rapid-cycling bipolar disorder (60,61). There is equivocal evidence that TCAs may induce rapid cycling. A majority of patients who developed mania while on TCAs for the treatment of depression later developed rapid cycling (62–65).

a. Treatment. While definitive answers in this area are still awaited, it is prudent to use caution in treating bipolar depressed patients who may develop mania while on TCAs. These patients are susceptible to developing rapid cycling. When TCAs are to be used in patients with bipolar disorder, they should be combined with a mood stabilizer. If a patient develops rapid cycling, it is worth stopping antidepressants and observing the response. Similarly, TCAs should be discontinued if mania develops in a patient with unipolar depression.

2. The "Jitteriness" (Early Tricyclic) Syndrome

This is a state of unpleasant psychomotor excitation that develops early in the course of treatment with TCAs. It is usually observed in about 30% of patients with panic disorder or depression who are receiving a noradrenergic agent, such as desipramine, protriptyline, or imipramine (65–68). Shortly after ingesting a standard dose (e.g., 25 to 50 mg of desipramine or imipramine), the patient experiences a sudden onset of inner restlessness or a "wired" feeling, irritability, increased energy, and insomnia (68,69). The jitteriness syndrome may be heterogeneous. In some cases, it may reflect an autonomic hyperadrenergic "speed-like" reactivity with increased energy and anxiety (31,70); in others, it may manifest as an akathisia-like motor restlessness (35,70,71).

a. Treatment. First consider the differential diagnosis, which include worsening of depression, akathisia, nocturnal myoclonus, and hypomania. Management includes starting with a small dose of TCA in the panic disorder patient. Most patients develop tolerance to this behavioral side effect. The dose is then gradually increased based on the response and side effect. It is possible that jitteriness may reappear with every dose increment. Some patients can never tolerate more than 10 mg of imipramine or desipramine (68– 70), but a few may experience a complete blockade of panic attacks on these

low doses (68,69). In patients who develop jitteriness with a particular dose, a decrease in dose may be useful. In some, addition of a benzodiazepine or beta blocker may alleviate the problem (31,68,69) without any dose adjustment. Discontinuation of TCAs and initiation of therapy with other types of antidepressant drugs may be necessary in those who cannot obtain relief of this syndrome by other means.

D. Sexual Dysfunction

This is the most troublesome side effect for young patients. Anticholinergic properties of TCAs may adversely affect erection/lubrication and orgasmic ejaculatory functions (72). Alpha-adrenergic blockade would interfere primarily with ejaculation and less often with emission, leading to orgasmic ejaculatory dysfunction (73). Significant sedation, disruption of recognition, and impaired concentration caused by some of these compounds are also likely to interfere with arousal and sexual drive. Interference with the endocrine axis and neurotransmitter receptors, both centrally and peripherally, might influence arousal and sexual drive (74). Elevated prolactin levels have been implicated in sexual dysfunction and reproductive failure in some patients, probably secondary to antidopaminergic action (75,76). Since gynecomastia is a known side effect of antidepressants, the assumption that, like antipsychotics, these drugs increase prolactin levels is plausible (77). However, most patients on TCAs do not have elevated prolactin levels (78) and monoamine oxidase inhibitors (MAOIs) may even suppress prolactin (79).

However, studies in this area are complicated by preexisting sexual abnormalities. For example, in a carefully conducted European study (80) with clomipramine, sexual functioning was documented in patients before the depressive episode, after the onset of illness, and following drug treatment. It was found that 69% of males and 57% of females had their sexual activity impaired by depressive illness per se. The addition of clomipramine interfered with obtaining and maintaining an erection in about 20% of male patients. Ejaculation was impaired in about 11%.

A number of TCAs including amitriptyline (81–83), imipramine (5,81,82,84–86), protriptyline (5,84), and desipramine (81,84) have been implicated in sexual side effects. Amoxapine can produce decreased libido, impotence, and painful ejaculatory inhibition in males (73,87,88) and orgasmic inhibition in females (89,90). Hyperprolactinernia (91–94) and the dyskinetic reaction induced by amoxapine might interfere with sexual function (96).

a. Treatment. It is important to understand patients' sexual functioning prior to the initiation of antidepressant therapy. A systematic inquiry will provide a clearer picture than asking whether the patient has had any sexual side effects. Such a history needs to be obtained periodically during therapy as well. If sexual dysfunction occurs, further assessment is indicated. The patients social situation, general health and use of other drugs are taken into account. Subsequent management includes dosage reduction or waiting for tolerance to develop.

Counteractive agents include bethanechol 10 to 20 mg before sexual activity or 20 to 30 mg daily, cyproheptadine 4 to 12 mg daily, amantadine 100 to 200 mg daily, and Yohimbine 5.4 to 16.2 mg prior to intercourse or 5.4 mg three times daily. Among antidepressants, only bupropion and nefazodone are considered to produce sexual side effects less often, and they are the ones to be used if a substitution is necessary (96,97). The efficacy of sildenafil citrate is worth exploring.

E. Withdrawal Phenomena

Abrupt discontinuation of TCAs results in a typical withdrawal syndrome in up to 50% of cases (98). It usually occurs with doses of at least 150 mg of imipramine (31) or an equivalent dose of one of the other TCAs (99). The severity of the withdrawal seems to be correlated with the total daily dose ingested (100). Symptoms may be experienced from as early as a few hours after missing one dose (101,102) to 2 weeks after discontinuation (103).

The most common complaint is of a flu-like syndrome: nausea, vomiting, diarrhea, abdominal cramps, malaise, cold sweats, chills, dizziness, and headaches (31). Insomnia is also common, accompanied at times by a resurgence of vivid and occasionally frightening dreams (100). Some authors describe pronounced anxiety (104) and even panic attacks (105) accompanied by signs of autonomic hyperactivity such as tachycardia, hypertension, sweating, and restlessness. Other extremely rare presentations are the onset of a parkinsonian syndrome (hypokinesia and cogwheel rigidity) (100), akathisia- like restlessness (106), and delirium (107). There are several reports describing “paradoxical” mood responses upon abrupt discontinuation of TCAs (108– 111). These vary from transient remission of depression in nonresponders to hypomania and mania. One patient developed rapid-cycling bipolar illness (112). A few patients needed to be hospitalized for the treatment of serious mania (108). Some of the patients involved had a personal or family history

of bipolar illness but others did not. One patient's mania responded to readministration of the discontinued antidepressant (112), suggesting a true withdrawal phenomenon as opposed to a natural course of illness.

a. Treatment. The best way to prevent withdrawal is to be aware of this possibility during patient encounters. Patients should be taught that they should not stop the drug abruptly. The educated patient will participate in the treatment by asking questions if the drug is abruptly discontinued. The only exception is the appearance of severe side effects necessitating immediate withdrawal, such as repeated seizures or cardiac conduction abnormalities.

F. Cardiovascular Side Effects

1. Conduction Disorders

Cardiovascular side effects include slowing of conduction, hypotension, and tachycardia. Generally, the tertiary amine derivatives are more cardiotoxic than secondary amine derivatives.

Conduction delays leading to first-degree heart block and bundle-branch patterns occur at therapeutic plasma concentrations of TCAs (113–118). These are manifest by flattened T waves, prolonged QT intervals, and depressed ST segments on the electrocardiogram (ECG). Some use the QRS widening as a monitoring parameter for assessing the cardiovascular complications, either at or slightly above therapeutic plasma levels (119–122).

A number of early studies found evidence of TCA-induced impairment of left ventricular function (116,123,124). However, the method used to assess left ventricular function was the systolic time interval, a measurement that is dependent partly on the QRS duration.

a. Treatment. Patients over the age 50 or anyone suspected of a cardiac problem should have an ECG prior to the initiation of treatment and a follow-up ECG once a year as well as whenever clinically indicated. Children on TCAs should preferably be monitored with weekly ECGS. Pulse and blood pressure should be checked if symptoms referable to the cardiovascular system occur. In addition, a complete physical examination is conducted and an ECG recorded. As TCAs have quinidine-like action, other drugs that have a similar action should not be given simultaneously without proper precautions.

Patients with congestive heart disease or conduction disorders of the heart should not receive TCAs, as other cardiac-safe drugs are now available. If a conduction disorder is detected while the patient is on a TCA, discontinue the TCA and monitor cardiac status until the side effect dissipates.

2. Orthostatic Hypotension

One of the most frequent and potentially serious side effects of TCA treatment is orthostatic hypotension manifesting in light-headness upon standing up and occasionally a syncopal episode. The risk of serious sequelae increases dramatically with advancing age. A study examining 100,000 Medicare recipients over the age of 65 revealed the occurrence of 1300 hip fractures. Further analysis revealed that hip fractures were two to three times more common among individuals receiving tricyclic drugs over a period of 2 years (125). By far, the most studied drug in this context is imipramine (126–129). However, several studies (130–133) indicate that a similar orthostatic effect exists for other TCAs. Nortriptyline carries a reduced risk of orthostatic hypotension (120,134–136). For all TCAs, orthostatic hypotension generally is not found to be dose-dependent (126,130,137).

The mechanism by which TCAs induce orthostatic hypotension is complex. Interestingly, a significant risk factor for the development of orthostatic hypotension with imipramine may be the diagnosis of depression itself. When treated with imipramine, patients with heart disease and melancholia are at significantly greater risk for orthostatic hypotension than patients with heart disease alone (138,139).

a. Treatment. The patients should be instructed to get up slowly, gradually moving from lying down to sitting up and then to standing and walking. Elastic bandages may prevent stasis in the lower extremity and improve orthostasis. The next usual treatment is the reduction in the dose of the TCAs. This carries the risk of a relapse with no guarantee that the low blood pressure will be normalized. If the patient has responded well to a TCA and the hypotension has been a problem, concomitant administration of stimulants may be beneficial. Both dextroamphetamine and methylphenydate may enhance antidepressant activity and improve orthostasis. Other pharmacological options include sodium chloride injections (140) or fludrocortisone 0.2 to 1 mg daily (141), both of which increase intravascular volume.

G. Overdose

It is a paradox that TCAs are very effective agents in alleviating suicidal ideation and depression, yet they are frequently used in fatal overdoses. They remain the common cause of death from prescription drugs noted in depressed and suicidal patients. In overdoses, they are highly concentrated in the myocardium and have profound toxic effects. Of the 2 or 3% of overdoses that result in death, most patients die from cardiac complications (142).

Sinus tachycardia is the earliest and the most common symptom of TCA overdose. The etiology of sinus tachycardia is multifactorial—blockade of NE uptake and anticholinergic effect. Electrophysiologically, TCAs inhibit the fast sodium channel, resulting in slowing of depolarization in cardiac conduction tissue. Widening of the QRS, ventricular ectopy, and slow idioventricular rhythm follow sequentially. The final manifestation is hypotension. This is due to direct myocardial depression, alpha-adrenergic blockade, and inhibition of NE uptake. TCA overdose carries a significant mortality involving a risk of generalized seizures and cardiovascular disturbances. All these can lead to pulmonary edema. Central nervous system (CNS) manifestations include coma. The excitation is a part of anticholinergic syndrome. Seizures are self- limited and occur after 6 to 8 hr following the overdose. Patients presenting with hypotension have a three times higher risk of pulmonary complications. Gastrointestinal effects are decreased motility, delayed gastric emptying, and prolonged transit time. This makes decontamination particularly important. Diagnosis of overdose is clinical and the blood levels are not helpful, as there is no correlation between the clinical picture and the severity of overdose.

a. Treatment. There is no way of predicting the course and outcome of the overdose. Therefore every patient is condition should be considered potentially serious and must be evaluated immediately. Management is supportive. Airway, respiratory, and circulatory support, gastric decontamination, as well as the treatment of seizures and of myocardial conduction difficulties are important. Supplemental oxygen, cardiac monitoring, pulse oximetry, intravenous access, and baseline ECG are needed. Arterial blood gas and chest x-ray are necessary in patients needing alkalinization therapy. For CNS toxicity, use of naloxone, thiamine, and dextrose is warranted. Flumanezil is contraindicated as seizures may develop with this drug. Physostigmine should not be given to comatose patients because its use may lead to cardiac complications.

Gastric evacuation of ingested TCA is useful if it is performed soon after ingestion. Some 6 to 22% of the total ingested drug can be removed by gastric evacuation. Ipecac is not indicated because it may induce persistent vomiting. Charcoal decontamination is indicated in all cases of overdose. Charcoal (1 g/kg body weight) is given with a single dose of the cathartic sorbital. Bosse et al. (143) assigned patients to three methods of treatment: (a) activated charcoal, (b) saline lavage followed by activated charcoal, and (c) activated charcoal followed by saline lavage. All three methods resulted in similar outcomes.

Hypotension develops in 33 to 50% of patients. The use of vasopressors or inotropic drugs is indicated when intravenous sodium bicarbonate is ineffective. Substantial evidence shows that intravenous sodium bicarbonate and/or

hyperventilation will reverse cardiotoxic effects. Indications for intravenous sodium bicarbonate include acidosis, hypotension, prolonged cardiac conduction, ventricular dysrhythmia, and cardiac arrest. Sodium bicarbonate seems to improve hypotension within 1 hr and to correct QRS prolongation in most patients (144); it improves mental status in about 50%. Careful monitoring of pH is necessary with bicarbonate and hyperventilation therapy (145). Class 1B drugs such as lidocaine and phenytoin are recommended for the treatment of ventricular arrhythmia. Complete heart block and refractory symptomatic heart block are indications for temporary use of a pacemaker.

Seizures must be treated promptly to prevent lactic acidosis. Diazepam is the most suitable agent. A retrospective study (146) indicated that 24 of the 388 patients overdosed with TCAs had seizures. Cardiac repercussions of these seizures were frequent and severe. In the postictal period, broadening of the QRS complex and hypotension requiring massive alkalinization therapy, vasopressors, and cardioversion were observed. These patients had normal blood pressures and QRS complexes prior to seizure. This raises the question whether prophylactic treatment of alkalinization is advisable.

H. Other Side Effects

1. Urinary Symptoms

Symptoms of urinary hesitancy, strain being necessary to void, loss of force, or decreased caliber of the urinary stream are common side effects of TCAs. Urinary retention can occur in both sexes. Treatment options for urinary hesitancy would include decreasing the dose of TCA, switching to a less anticholinergic TCA, or adding a peripheral cholinergic agent to the drug regimen. Bethanechol exerts a selective action on the intestines and bladder without any effect on the cardiovascular system (5,147,148). It is better to start bethanechol with a small dose and increase it until response occurs or side effects develop. For treating urinary complaints, 10 to 100 mg daily may be appropriate. In cases of retention, immediate urological consultation and discontinuation of TCA are necessary. The side effects of bethanechol are abdominal cramps, diarrhea, tremor, rhinorrhea, and excessive tearing.

2. Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH).

TCAs have been reported to produce SIADH (149–153) meeting the criteria of hyponatremia, hypoosmolality, lack of maximal urinary sodium retention, and urinary osmolality greater than that of serum (154).

a. Treatment. This condition requires prompt recognition and early treatment in order to prevent serious consequences such as convulsions and permanent lesions of the basal ganglia lesions. Any person who has a seizure while on a TCA should have his or her electrolytes checked. Hyponatremia needs intervention. If the diagnosis is SIADH, the TCA should be stopped immediately and endocrinological consultation obtained.

IV. CONCLUSIONS

TCAs are frequently employed drugs that produce a number of side effects. In order to minimize patient discomfort and enhance compliance, the physician should be aware of these side effects and treat them rapidly and effectively. Such interventions are useful for effective treatment of depression and other disorders.

Whenever possible, patient education and initiation of treatment with small doses are helpful. In suicidal patients, it is wise to provide only a week's supply at a time.

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4 Management of Side Effects of Monoamine Oxidase Inhibitors

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I. INTRODUCTION

The effectiveness of monoamine oxidase inhibitors (MAOIs) as antidepressants has now been clearly established beyond doubt. While doubts were raised in the earlier years about their relative efficacy compared with tricyclic antidepressants (TCAS) in classic melancholic depression, direct comparisons with tricyclics and metanalyses of studies over the past forty years have indicated that MAOIs are generally as effective as TCAs in the treatment of endogenous depression in outpatient settings (1). Several studies conducted at the beginning of the past decade (2–5) have also established what was historically well recognized by European clinicians: MAOIs are more effective in alleviating depression in individuals who are hypersensitive to rejection and whose depressive episodes are marked by reverse vegetative symptoms such as hypersomnia and hyperphagia. MAOIs are clearly effective in panic disorder (6) and may be superior to other available drugs in reducing phobic anxiety. Among the available psychotropics, MAOIs appear to be most efficacious in the treatment of generalized social phobia (7,8).

It is important to recognize that the MAOIs have been available for forty years, have withstood the test of time, and have demonstrated an unquestionable efficacy in depression and phobic disorders. However, MAOIs have never gained the kind of popularity that selective serotonin reuptake inhibitors (SSRIS) have achieved in primary care practices due to the complexities involved and the amount of information that a physician has to learn to prescribe these medications. Even in psychiatric practices, MAOIs have never attained the status of first-line agents owing to the risks involved, such as life-threatening interactions with certain foods and drugs. Despite all the negative aspects of MAOI therapy, it should be borne in mind that some patients respond only to MAOIs, and for this select group, these drugs have been life-savers. With the availability of selective and reversible inhibitors, such as moclobemide, the MAOI class of drugs are enjoying popularity again in Europe and several other countries. In the United States, currently, only two MAOIs, phenelzine and tranylcypromine, are available, and in this chapter we limit our discussion mostly to these two drugs.

II. PHARMACOLOGY OF AVAILABLE MAOIs

The enzyme monoamine oxidase (MAO) is widely distributed in the human body. The isoenzyme, MAO-B, is more abundant in the brain and MAO-A is more active in the gut. It is important to note that both forms of MAO are present in the human brain, where they exert different actions. MAO- A selectively deaminates serotonin and norepinephrine, whereas dopamine, phenylethylamine, tyramine, and benzylamine are substrates for the MAO-B isoenzyme. In the central nervous system, the most important function of MAO appears to be regulation of neuronal cytoplasmic concentrations of monoamine neurotransmitters by deamination of these amines in presynaptic terminals and cell bodies. Hence, when the MAO is inhibited by a medication, there is a net increase in the vesicular and cytoplasmic concentrations of serotonin, norepinephrine, and dopamine, with the greatest increase for serotonin (9). A variety of adrenergic and 5-HT receptor adaptations take place after a few weeks of treatment with an MAOI, and some of these changes may explain certain benefits as well as late-emerging adverse effects.

Of the three MAOIs available in the United States—phenelzine (Nardil), tranylcypromine (Parnate), and selegiline (Eldepryl)—only the first two are approved as antidepressants, whereas seleoine, a selective MAO-B inhibitor, is approved for use as an adjunct in Parkinson's disease. Isocarboxazid (Marplan), another nonselective MAOI used for many years, is no longer marketed

by its manufacturer. Structurally, phenelzine is a hydrazine derivative, whereas tranylcypromine has an amphetamine-like structure. The classical MAOIs, phenelzine and tranylcypromine, both in use for many years, are inhibitors of both MAO-A and MAO-B enzymes, and both are irreversible inhibitors, which means that after discontinuation of the drug, there is lag period of about 10 to 14 days before MAO physiological activity is restored. Tranylcypromine may be more quickly reversible than phenelzine, but not as easily reversible as moclobemide, a selective MAO-A inhibitor, which is currently available in many countries in Europe and elsewhere including Canada but not the United States. Several other moclobemide-like compounds, collectively termed reversible inhibitors of MAO-A (RIMA) are being developed and tested. The popularity of these new-generation MAOIs appears to be related more to their relatively favorable safety profile rather than greater efficacy.

III. DOSING

The starting dose for phenelzine is 15 mg bid, which can be increased to 45 mg/day after about 3 days if orthostatic hypotension is not a serious problem. The therapeutic dose of phenelzine for a young adult patient is 60 to 90 mg/ day in two or three divided doses, and this dose may be generally reached in about 2 to 3 weeks after starting the medication. For tranylcypromine, the starting dose is 10 mg tid, which can be increased by 10 mg every week to attain an average effective dose of 40 to 60 mg/day, generally split into two or three doses (Table 1). Some clinicians have reported using 60 to 100 mg/ day of tranylcypromine to treat refractory cases of depression. Plasma levels of both phenelzine and tranylcypromine have not been well studied and generally do not seem to help predict treatment response (10). As is the case with most medications, smaller doses of MAOIs should be used for elderly patients. Starting doses of phenelzine and tranylcypromine in the elderly are 7.5 mg/day and 5 mg/day respectively, with up to 45 mg/day for the former and 20 mg/day for the latter. Dose escalation should be slower in geriatric patients.

IV. ADVERSE EFFECTS AND MANAGEMENT

Orthostatic hypotension is a relatively common side effect of MAOIs. This is a particularly troublesome problem in the first month or two after treatment is started (11). While tricyclic antidepressants (TCAS) are also associated with

Table 1 Adverse Effects of MAOIs Currently Available in the United States

Most Common	Somewhat Common	Less Common
Insomnia	Myoclonic jerks	Hypertensive reaction
Afternoon sedation	Parasthesias and muscle	Hyperpyrexia
Orthostatic hypotension	pains	Hepatotoxicity
Weight gain	Sleep movements	SIADH
Sexual dysfunction	Dry mouth	Hypoglycemia
	Constipation	Stuttering
	Peripheral edema	Photophobia
	Agitation	Confusion
	Hypomania	Psychosis
		Hallucinations
		Dystonia

orthostatic hypotension, MAOIs seem to induce this problem more commonly and to a greater degree. This problem may be somewhat less with tranylcypromine than with phenelzine (12). Orthostatic hypotension abates with time in some patients, but not always. Reducing the dose can lessen the problem, but this strategy may lead to reduced efficacy of the drug and hence is not always successful. Dividing the daily dose into several smaller doses is an effective strategy. For example, a patient taking phenelzine 30 mg bid is less likely to be troubled by unsteadiness resulting from postural hypotension if the dosing is changed to 15 mg four times a day, although this can be cumbersome and reduce compliance. Some clinicians believe that this approach may work better for tranylcypromine and less so for phenelzine. Increasing fluid intake sometimes helps this problem. Older patients may benefit from wearing support stockings and abdominal binders (13). Florinef (fludrocortisone), about 0.05 to 0.1 mg/day in two divided doses, can effectively reduce MAOI-induced postural hypotension, but not always. In using Florinef, one should keep in mind all the potential problems associated with use of a mineralocorticoid, such as fluid retention, electrolyte imbalance, and edema. There have been reports of successful use of salt tablets in combating MAOI-induced hypotension in the first 2 months (14). It is important to instruct the patients at the beginning of treatment to be careful when getting up from a supine position, particularly early in the morning. Sitting on the edge of the bed and shaking legs for a minute can reduce the risk of falls secondary to postural hypotension. A small cup of coffee or tea in the morning has been found to be quite helpful

by some of our patients for alleviation of the unsteady feeling in the morning. However, patients on MAOIs should refrain from excessive caffeine use because of the potential for hyperstimulation. Interestingly, in one study, orthostatic hypotension was eliminated in a group of 61 patients treated for migraine headaches with phenelzine, when a beta-blocker, atenolol, was added (15). The authors have reported that hypertensive reactions were also less frequent when the two drugs were combined. We need further experience with this combination to determine whether addition of a beta-blocker is a safe and an effective strategy for alleviation of postural hypotension in depressed

patients receiving an MAOI.

Although orthostatic hypotension may be more problematic, insomnia is the most frequent complaint of patients receiving MAOIs. Tranylcypromine tends to have a more stimulating effect, perhaps because of its amphetamine- like structure; the hydrazine compound, phenelzine, also causes insomnia frequently. Both initial and middle insomnia are common complaints. MAOI- induced insomnia does not appear to ease with continued treatment. Taking the last dose before 2 P.M. can reduce the severity of insomnia for some patients. On the other hand, we have known some patients whose insomnia got better when a larger chunk of the MAOI total daily dose was administered at bedtime. In the first 2 to 3 months, it may be necessary to juggle the dosing times until the appropriate dosing schedule is figured out for the given patient. Trazodone, 50 to 75 mg at bedtime, has been found to be helpful and safe at this dose for many patients experiencing MAOI-induced insomnia (16,17). Benzodiazepines can also be quite effective in combating initial insomnia; however, their use as sedatives should be limited to short periods due to their potential to cause physical dependency. Low-dose amitriptyline (about 50 mg) given at bedtime has produced impressive results in combating MAOI-induced insomnia; high doses can be risky. Imipramine should not be used in combination with an MAOI. Sedation, particularly in the afternoon hours, is also reported frequently, especially in those receiving phenelzine. Afternoon somnolence may not always resolve after insomnia at night is alleviated with a bedtime sedative (18). Switching to another MAOI can be tried with the usual precautions.

Sexual dysfunction is seen at a relatively higher frequency with MAOIs than with TCAs (19). Anorgasmia and delayed ejaculation are the most common of these problems. Impotence is also a frequent complaint of male patients on MAOIs. The reported incidence of sexual complaints is higher for phenelzine than for tranylcypromine (12,20). While sexual dysfunction is seen more commonly in men receiving MAOIs, a large proportion of female patients also report such complaints (19). The mechanism of sexual dysfunction with

MAOIs is not well understood. Erectile dysfunction may be related to the adrenergic effects of these drugs, while serotonergic alterations are thought to be responsible for orgasmic and ejaculatory dysfunction. Decreasing the dose sometimes helps to minimize the problem, but there is a risk of worsening of the illness for which the medication is prescribed. Spontaneous remission of anorgasmia after a few weeks has been reported in a small group of patients (21). If the sexual dysfunction has not resolved after 2 months, and it is not possible to decrease the MAOI dose, one of the following interventions may be tried. Cyproheptadine, a 5-HT2 antagonist, 4 to 8 mg, taken an hour before sexual activity, helps to alleviate this problem in some patients, although controlled studies are lacking (22). Patients frequently complain of sedation with cyproheptadine and there is also the potential risk of recurrence of depression after addition of this agent (23). In a case report, MAOI-associated impotence reversed with bethanechol 30 to 40 mg/day (24). One should keep in mind that sexual dysfunction may be a consequence of the depressive illness itself, and it is important to distinguish this from problems that are medication-induced. Such an assessment requires a careful undertaking of sexual history. For an excellent discussion on this topic, readers are referred to a recent review paper by Harvey and Balon (25).

Although patients report dry mouth and constipation, these are mild in comparison with similar side effects of TCAS. Patients also complain of urinary hesitancy which, although not likely related to cholinergic receptor blockade, may respond to low-dose bethanechol (5 to 10 mg bid or tid). Interestingly, MAOIs have minimal or no anticholinergic activity in laboratory studies.

Weight gain is generally a late-emerging side effect of MAOIs, the mechanism of which is not well understood. It may be secondary to increased craving for sweets, the propensity of MAOIs to induce edema, or both. Patients should be advised to reduce consumption of junk foods and other high-calorie snacks and to exercise on a regular basis as much as their physical health permits. Phenelzine appears more likely to cause weight gain than tranylcypromine (12). This problem may be even more frequent in patients treated simultaneously with a tricyclic and an MAOI (26). Switching to another MAOI may stop further weight gain, but this strategy is not always successful. Of the two available MAOIS, phenelzine belongs to the hydrazine class whereas tranylcypromine is a nonhydrazine compound. In switching from one to another, a 2-week washout is mandatory.

Needle-prick sensations in the extremities are reported by patients taking MAOIS. Muscle pains and twitches have also been frequently reported during MAOI therapy. MAOIs can interfere with the metabolism of vitamin B6 (pyri-

doxine), and deficiency of this vitamin may be responsible for such adverse effects (27,28). Supplementing about 100 mg/day of pyridoxine can alleviate the problem in many patients.

Some patients complain of nocturnal myoclonic jerks or symptoms similar to those of restless-leg syndrome (29). Clonazepam 1 to 2 mg at bedtime almost always helps to alleviate this problem.

MAOIs may rarely exacerbate shortness of breath in patients with preexisting obstructive lung disease. A patient in our clinic, a middle-aged male smoker with bronchitis whose depression had partially responded to tranylcypromine after several unsuccessful antidepressant trials, could tolerate up to 50 mg/day of the MAOI but would experience difficulty breathing whenever a further dose increase was attempted. We suspected that this was related to the propensity of MAOIs to occasionally induce edematous reactions.

Iproniazid, the first MAOI that was found to have a mood-elevating effect in the 1950s (30), was initially introduced as an antituberculosis drug. This hydrazine-class MAOI was later discontinued because of the high incidence of hepatotoxicity associated with it. Hepatotoxicity is seldom associated with tranylcypromine treatment. There has been an occasional report of elevation of liver enzymes with the hydrazine compound phenelzine; however, the problem is quite rare and routine liver function tests are not indicated. Nevertheless, hepatotoxicity should be kept in mind when the patient complains of nausea, malaise, and low-grade fever. It is prudent to avoid using MAOIs in those with cirrhosis and chronic liver disease.

In general, MAOIs appear to be quite benign compared with TCAs with regard to their effects on cardiac conduction. Tranylcypromine does not seem to induce any major changes in cardiac electrophysiology in individuals with no preexisting cardiac disease (31). There have been reports of shortening of the QTc interval associated with phenelzine treatment. However, routine electrocardiography is not necessary in healthy young adults before starting an MAOI.

Patients may sometimes complain of confusion or feeling drunk during MAOI therapy. Behavioral disinhibition, in the form of antisocial behavior and aggressiveness, has also been noted occasionally in patients treated with an MAOI. Reducing the dose generally eases these problems.

As is the case with other antidepressants, MAOIs have been implicated in switching bipolar depressed patients to hypomania or mania (12,20). Very rarely, these medications have been suspected to have induced psychotic symptoms in vulnerable patients. In both cases, the clinician is advised to discontinue the MAOI and restart, if necessary, at a lower dose.

There have been several reports of MAOI dependence, particularly with

tranylcypromine (32,33). We have noted significant withdrawal problems in the form of behavioral agitation, anxiety, restlessness, and depressed mood when tranylcypromine had to be stopped abruptly for reasons such as emergency surgery. One of our social phobic patients who had significant improvement with tranylcypromine became severely phobic again a week after the medication was discontinued because he was scheduled for surgery. He avoided people and confined himself to his bedroom. His social anxiety lessened again 2 weeks after he resumed the MAOI therapy.

V. HYPERTENSIVE CRISES

What clinicians dread most about MAOIs is their potential to induce acute hypertensive reactions when certain foods are consumed. The offending content of such foods is tyramine, an exogenous amino acid, which is normally catabolized efficiently by MAO-A enzyme present in the mucosa of the stomach and small intestine. In the presence of irreversible MAO inhibition, large amounts of ingested tyramine may become available in the systemic circulation; this is eventually transported to sympathetic nerve endings, where it can displace norepinephrine stored in the synaptic vesicles into the synapse, potentially leading to a hypertensive crisis.

Hypertensive crises can also occur after ingestion of medications that have sympathomimetic properties. Many over-the-counter (OTC) decongestants fall into this category. OTC medications that are contraindicated in patients taking MAOIs include pseudoephedrine, ephedrine, dextromethorphan, phenylpropanolamine, and many others. Cocaine and ‘‘speed’’ can also lead to hypertensive reactions in the presence of MAO inhibition; as such MAOIs should not be prescribed to known or suspected drug abusers. For a detailed list of contraindicated medications, the reader is referred to a textbook of psychopharmacology.

Spontaneous hypertensive reactions when there is no history of recent consumption of a tyramine-rich food or ingestion of a sympathornimetic drug can also occur with MAOIs (34). There have been more reports of such spontaneous reactions with tranylcypromine. Several theories have been put forward regarding the possible mechanisms of this phenomenon. One explanation is that tranylcypromine is converted to amphetamine, which can then interact with newly ingested tranylcypromine, thus leading to a hypertensive episode. However, since spontaneous hypertensive episodes have occurred with phenelzine also, one would suspect that there may be other mechanisms.

At the beginning of MAOI therapy, the clinician should provide the

patient with printed information regarding foods and medications to avoid. The physician should also educate the patient about recognition of the typical symptoms of a hypertensive reaction—sweating, severe headache, palpitations, stiff neck, and photophobia. Generally, such reactions occur within about 2 hrs of ingesting a contraindicated medication or a prohibited food. Patients should be instructed to call their physician or go to the nearest emergency department when they experience such symptoms. Mild to moderate hypertensive reactions usually resolve over 6 to 10 hrs without any specific treatment. For MAOI associated severe hypertension, the drug of choice in the emergency department remains phentolamine (Regitine) given intravanously in 2.5- to 5.0-mg doses every 5 to 15 min until blood pressure control is achieved. The therapeutic goal is 30 to 40% reduction in blood pressure from the pretreatment level. Nitroprusside is also quite effective with a rapid onset and brief duration of action. Nitroprusside is given using an intravenous pump with a starting dose of 0.25 to 1.0 μg/kg/min and the average dose required is 3 μg/kg/min. In general, only short-acting antihypertensive agents should be used because of the potential for precipitous hypotension. In line with the practices of emergency care and primary care physicians in treating hypertensive emergencies, psychiatrists have also been using nifedipine to treat MAOI-induced acute hypertensive reactions in the past 6 to 7 years. Many have found that nifedipine 10 mg PO every hour generally brought down the blood pressure in one or two doses. However, a recent review of nifedipine use for acute lowering of blood pressure has raised concerns about the drug's safety. Citing numerous adverse events and outcomes such as severe hypotension, reflex tachycardia, acute myocardial infarction, and two documented deaths, a recent JAMA article (35) has suggested that the use of nifedipine to treat acute hypertension be abandoned. To our knowledge, there are no reports of adverse events associated with use of nifedipine for lowering MAOI-associated hypertensive reactions. However, in light of the recent controversy in this regard discussed above, psychiatrists should simply advise their patients receiving irreversible MAOIs to go to the nearest emergency department if they experience symptoms of a hypertensive reaction. Some psychiatrists have advised their patients on MAOIs to carry a few 10-mg pills of nifedipine with them just in case they experience a severe headache, which often accompanies an acute hypertensive crisis. However, this may be risky, because orthostatic hypotension can also present with a headache and the latter could be mistaken for a hypertensive reaction. When there is a “spontaneous” hypertensive reaction, it is wise not to rechallenge the patient with the same MAOI.

Most patients are not strictly compliant with dietary restrictions when

they are taking an MAOI (36). Often they develop a false sense of security when no reaction has occurred after they eat a slice of pizza or another tyramine-rich food, which leads to further noncompliance. It is therefore important to remind patients periodically about the importance of adherence to diet. The acute hypertensive reaction is often referred to as "cheese reaction," because most reported reactions have occurred after consumption of aged cheese—is a common ingredient of the western diet. As a rule, the more aged the cheese, the higher its content of tyramine. Aged or pickled meats, poultry, or fish should be avoided by patients receiving MAOIs. It is important to provide the patients with a brief rather than a long list of prohibited foods (Table 3). For an excellent review of the MAOI diet, we recommend a recent paper by Gardner et al. (37). The patients should be reminded to continue their dietary restrictions for 2 weeks after discontinuation of an MAOI.

VI. DRUG INTERACTIONS

A comprehensive discussion of drug interactions during MAOI therapy is beyond the scope of this chapter. However, we wish to emphasize a few important points. Instead of providing the patient a long list of contraindicated medications, the patient should be given a short list of safe OTC medications and told to check with the physician before taking a new medication (Table 2). Patients should be advised to inform their general physician that they are taking an MAOI medication. A Medic-Alert bracelet can reduce the risk of inadvertent administration to the patient of a contraindicated medication. Phenelzine and tranylcypromine should never be used in combination with serotonergic antidepressants that include the selective serotonin reuptake inhibitors (SSRIs), venlafaxine, mirtazapine, and nefazodone. Fatal cases of "serotonin syndrome" have been reported when patients were switched from an SSRI to an MAOI and vice versa without a washout period. A 2-week washout is necessary when switching from an MAOI to an SSRI or vice versa. A 5-week washout is recommended after discontinuation of fluoxetine before an MAOI can be started. For an excellent review of MAOI drug interactions, we refer the reader to a recent paper by Livingston and Livingston (38).

VII. SPECIAL PRECAUTIONS IN THE ELDERLY AND THE MEDICALLY ILL

MAOIs, if indicated, should be used with great caution in geriatric patients. Although not strongly anticholinergic like the tricyclics, MAOIs have anticho-

Table 2 Concomitant Medication Guidelines for Patients Receiving Irreversible MAOIs

Extremely Risky	Risky/Not Recommended	Generally Safe
Indirect sympathomimetics	Anticholinergics	Direct sympathomimetics
Amphetamines	Disulfiram	Epinephrine
Dexamphetamine	Oral hypoglycemics	Norepinephrine
Dextromethorphan	Theophylline	Dobutamine
Methylphenidate	Tricyclics	Albuterol
Pemoline	L-tryptophan	Isoproterenol
Phentermine	Sumatriptan	Miscellaneous
Ephedrine	Levodopa	Acetaminophen
Pseudoephedrine		Aspirin
Phenylpropanolomine		NSAIDs
Phenylephrine		Barbiturates
Street drugs		Benzodiazepines
“Speed”		Lithium
Cocaine		Calcium channel
Phencyclidine		blockers
Serotonergic agents		Nitroglycerine
SSRI antidepressants		ACE inhibitors
Clomipramine		Diuretics
Venlafaxine		Corticosteroids
Nefazodone		Metoclopramide
Fenfluramine		Lidocaine
Dexfenfluramine		Procainamide
Mirtazepine		Ondansetron
Antihypertensives		
α-Methyldopa		
Guanethidine		
Reserpine		
Narcotic analgesics		
Meperidine		

Table 3 Restricted Foods for Patients Receiving Irreversible MAOIs

Avoid Completely	Avoid Large Quantities	Generally Safe
Aged cheeses and related foods such as pizza and lasagna	White wine	Bananas
Aged or pickled meats (e.g., day sausage, salami, pepperoni), poultry, or fish	Canned beer	Fresh cheeses (ricotta, cottage, cream, farmer)
Spoiled meats, poultry, or fish	Vodka, gin	Yeast powder used in baking
Stored beef or chicken liver	Meat tenderizers	Peanuts
Broad (fava) bean pods	Caffeine and dark chocolate	Raisins
Yeast extracts	Ripe avocados	
Sauerkraut	Anchovies	
Soy sauce		
Tap beer, red wine		
Banana peel		

linergic-like effects and hence may aggravate memory impairment in the elderly demented. Restlessness and paranoia have also been noted with MAOI use in the elderly. Tranylcypromine, which is less sedating and probably less likely to cause severe postural hypotension, is preferred by some geriatric psychopharmacologists. Even with proper counseling, the elderly are less likely to follow dietary restrictions because they tend to be forgetful. In this population, there is a greater risk of cerebrovascular accidents from hypertensive reactions owing to the increased fragility of cerebral vessels with aging. Drug interactions are also more likely because the elderly, in general, see several physicians and take several medications for various ailments. Postural hypotension is a more serious problem in geriatric patients than in younger individuals. Therefore family members should also be educated about medication side effects, management of side effects, drug interactions, and dietary restrictions.

MAOIs should be avoided, if possible, in patients with multiple medical problems. In type II diabetics, MAOIs can exaggerate the actions of oral hypoglycemics (39). Weight gain is also an unwanted adverse effect in diabetics. Consideration should be given, when MAOIs are used in patients with cardiovascular illness, to the potential of these drugs to induce severe orthostatic hypotension. For the cardiac patients in general, MAOIs may be safer than TCAs but more hazardous than SSRIs and other newer antidepressants.

VIII. TOXICITY IN OVERDOSE

Overdosing on a 1- to 2-week supply of an MAOI can be lethal. Monitoring for more than 24 hrs is necessary because severe toxic effects may not occur until 10 to 12 hrs after ingestion. Late-emerging severe hypertension poses the most serious risk. Serious central nervous system toxicity—in the form of confusion, hallucinations, hyperpyrexia, and convulsions—is a common manifestation of MAOI overdose.

IX. TCA AND MAOI COMBINED THERAPY

There are several reports in the literature of large groups of patients with refractory depression finally responding to the combination of a TCA and an MAOI after failing multiple trials. A 3 year follow-up, of a group of 25 treatment-resistant patients receiving the MAOI isocarboxazid and the TCA amitriptyline, with periodic attempts to discontinue the MAOI, showed that pa-

tients who needed both drugs were those who had more depressive episodes in the past. No serious adverse events were noted by the investigators of this study (40). In the literature, there are many reports of life-threatening and occasionally fatal reactions when a TCA was started soon after discontinuing an MAOI or when a TCA was added to an MAOI. Imipramine was the culprit in many such reactions. These reactions are not manifest by hypertension; they often present as hyperpyrexia, delirium, and convulsions, somewhat akin to the ‘‘serotonin syndrome.” Interestingly, there is one report of spontaneous hypertensive crisis that was controlled by the addition of amitriptyline (41). Nevertheless, this type of treatment should be limited to special and extremely refractory cases. If the combination approach is chosen, the risk is less when both medications are started together at low doses. For a comprehensive review of the combined use of TCAs and MAOIs, the reader is referred to a review paper by White and Simpson (42).

X. REVERSIBLE INHIBITORS OF MAO-A (RIMAs)

The risk of hypertensive reactions appears to be much less with the newer reversible inhibitors of MAO-A (RIMAs) than with the irreversible nonselective classic MAOIs discussed above. Of the RIMAs, moclobemide is the most studied, although it is not approved in the United States at this time. Moclobemide is a benzamide derivative that is not associated with hepatotoxicity. It binds reversibly to MAO-A enzyme, meaning that when a substrate such as tyramine is available in high concentrations, the substrate is capable of displacing the drug from the enzyme; thus there is less likelihood of a hypertensive reaction (43). Whereas tyramine sensitivity is increased 30-fold with MAO inhibition by tranylcypromine, moclobemide increases tyramine sensitivity by a factor of 4 only (44). Furthermore, after discontinuation of moclobemide, MAO activity is restored to normal within a day owing to its short half-life as well as reversibilty of binding. The starting dose for moclobemide is 150 mg/day and the therapeutic dose is 450 to 600 mg/day in three divided doses after meals. The most common side effects are insomnia and dizziness. Whereas combining an irreversible MAOI and an SSRI is associated with well-documented fatal reactions, moclobemide has been used simultaneously with paroxetine, fluoxetine, fluvoxamine, and sertraline without serious adverse consequences (45–47). Unlike the classic MAOIs, moclobemide does not appear to be associated with marked weight gain (48). Interestingly, while moclobemide appears to have efficacy comparable with that of other available antidepressants, in contrast to the classic irreversible and nonspecific MAOIs,

moclobemide does not seem to be superior to tricyclics in atypical depression. While the newer generation RIMAs appear to be safer than the older generation MAOIs, the years ahead will decide their efficacy in the real-life clinical settings.

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5 Management of Side Effects of SSRIs and Newer Antidepressants

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I. INTRODUCTION

Starting with the release of fluoxetine in 1987, a new class of antidepressants, often described as second-generation agents, quickly came to dominate the treatment of depression. As an example, as of mid-1996, over 40 million people have taken fluoxetine, sertraline, and paroxetine worldwide (1). One of the most important reasons for the remarkably rapid acceptance of these medications as first-line agents has been the perception among both patients and clinicians of the lower side-effect burden associated with these agents. At the same time, however, the newer antidepressants are far from side effect-free. This chapter reviews the side effects seen with these newer agents and suggests proper management strategies should they arise. Antidepressants consist of one clear category—the selective serotonin reuptake inhibitors (SSRIs)—and four other agents that share little similarity and are sufficiently different from the SSRIs to be distinguished from them. Therefore, this chapter treats the SSRIs as one class and discusses the other new antidepressants individually.

The SSRIs discussed are fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), and fluvoxamine (Luvox). The other agents reviewed are bupropion (Wellbutrin), venlafaxine (Effexor), nefazodone (Serzone), and mirtazapine (Remeron).

II. SELECTIVE SEROTONIN REUPTAKE INHIBITORS

The generally accepted clinical notion that SSRIs are better tolerated than the two older classes of antidepressants (tricyclic antidepressants and monoamine oxidase inhibitors) has been borne out by most but not all studies. In double- blind, placebo-controlled studies, discontinuation rates due to adverse events have been estimated as ranging between 10 and 20% for an SSRI compared with 25 and 35% for tricyclics and 5 and 10% for placebo (2,3). Most clinicians would agree with this overall conclusion. In contrast, other metanalyses have estimated far lower differences between SSRIs and tricyclics (4), while still other reviews have found no significant difference in dropout rates due to side effects between SSRIs and tricyclics (5,6).

As with most medications (see discussion in Chap. 1), SSRI side effects are typically dose-related. The extent of tolerance to any specific side effect, however, may vary. For instance, in one fluoxetine study, tolerance was more commonly seen with activation side effects as opposed to sedation (7). Additionally, the disorder being treated also affects side-effect rates. As an example, compared with depressed patients, those with obsessive-compulsive disorder (OCD) seem to tolerate side effects better (without necessarily showing lower rates) and show lower discontinuation rates (8), while patients with anxiety disorders are more sensitive to stimulation effects.

Despite a few individual differences (to be discussed below), the four SSRIs are very similar, with the most common side effects for each agent being virtually identical (within the limits of comparing rates across studies). Table 1 shows the estimated side-effect rates from clinical trials for each of the SSRIs. The rates in Table 1 that are most inconsistent with those seen in open clinical practice are those related to sexual side effects, especially for fluoxetine. (See below for more details.) Since data such as these do not distinguish between mild side effects and those more associated with marked distress and compliance problems, Table 2 shows the discontinuation rates and side effects associated with drug refusal for the four SSRIs. Here too, sexual side effects are probably a more important cause of SSRI discontinuation in clinical practice than in clinical trials.

Table 1 Rates of Side Effects with SSRIs (%)

	Fluoxetinea	Sertralinea	Paroxetinea	Fluvoxamineb	Placeboc
Nausea	21	26	26	40	9–14
Headache	15	20	18	22	16–20
Insomnia	14	16	13	21	6–10
Anxiety/nervousness	9–15	3–6	5	5–12	1–9
Drowsiness	12	13	23	22	6–9
Diarrhea	12	18	12	11	7–9
Dry mouth	10	16	18	14	6–12
Tremor	8	11	8	5	1–3
Anorexia	9	3	6	6	2
Sweating	8	8	11	7	2–4
Sexual dysfunction	2	16	13	8	0–2

aFor depression.

bFor obsessive-compulsive disorder.

cRange across studies.

Table 2 Discontinuation Rates Due to Side Effects Due to SSRIs (in %)

Fluoxetine	Sertraline	Paroxetine	Fluvoxamine
Discontinuation rate			
12b–15a	15a	12b–20a	22b
Most common side effects			
associated with discontinuation			
Nervousness/anxiety/insomnia	Agitation/Insomnia	Somnolence	Nausea
Nausea	Sexual dysfunction	Abnormal ejaculation	Somnolence
Dizziness		Nausea	Insomnia

aStudies of depression.

bStudies of obsessive-compulsive disorder.

III. INDIVIDUAL SIDE EFFECTS AND THEIR TREATMENT

A. Stimulation

Symptoms of jitteriness or activation occur in at least 30% of patients on SSRIs and include restlessness, nervousness, agitation, anxiety, irritability, tremor, and insomnia (10). Stimulation side effects typically develop within the first few weeks of treatment and tend to be dose-related, time-limited, and occur more frequently after a rapid increase in dose (7,10). Fluoxetine has the highest incidence of activation, followed by sertraline, paroxetine, and fluvoxamine.

A number of pathophysiological mechanisms have been proposed to explain stimulation side effects. Animal studies and case reports of neurobehavioral toxicity in patients treated with serotonin-active drugs in combination with an SSRI suggest that excessive serotonin neurotransmission may be involved (10). Noradrenergic and dopaminergic mechanisms are supported by the akathisia-like side effects that are similar to those reported with neuroleptics and occasionally noradrenergic antidepressants. Furthermore, increased dopaminergic neurotransmission resulting from serotonin reuptake antagonism is supported by in vitro studies.

Overstimulation from an SSRI can be especially problematic in patients with prominent underlying anxiety or panic. As an example, in a study of panic patients, 50% of those treated with fluoxetine 20 mg daily dropped out because of adverse effects, mostly increased agitation and jitteriness (11).

Of the potential strategies to treat or prevent SSRI-induced stimulation, beginning treatment with a low dose, especially with anxious patients, should be the first consideration. Panic patients, for instance, are better able to continue treatment if fluoxetine is started at 2.5 to 10 mg/day. (12). The additional use of benzodiazepines (e.g., alprazolam 0.5 to 4 mg daily) or propranolol (10 to 80 mg daily), especially in the first few weeks of treatment, can also be helpful and enhance compliance (10). Often, the anxiolytic can be discontinued after a few weeks without the return of overstimulation.

The SSRIs, especially fluoxetine, can also cause an akathisia-like syndrome that resembles anxiety (13–16). Symptoms include restlessness, constant pacing, purposeless movements of the feet and legs, and marked anxiety. While some patients develop tolerance, for others, these symptoms may persist. Of importance, fluoxetine-induced akathisia can phenomenologically resemble an agitated depression, and physicians must be aware of the risk of turning a nonagitated depression into an agitated one by administering an SSRI (16). It has been suggested that patients with depression may be more vulnerable to developing akathisia than those with mania or schizophrenia (17). Beta

blockers (e.g., propranolol at 10 to 20 mg tid), trihexiphenidyl, or other agents that are effective for neuroleptic-induced akathisia can provide relief of symptoms (13,18,19).

All four SSRIs are associated with insomnia at rates of 15 to 25%, with symptoms generally dose-related (20). Clinical experience suggests that insomnia is most common with fluoxetine, although this is not found in the clinical trial data base (see Table 1). The serotonin reuptake inhibitors have a number of effects on sleep architecture. In studies of depressed patients, paroxetine and fluvoxamine reduced REM sleep and increased REM latency, fluoxetine and fluvoxamine decreased slow-wave sleep, and fluoxetine decreased sleep continuity (21). It has been postulated that the SSRIs' lack of 5HT2A/2C antagonism partly contributes to reduced slow-wave sleep and increased awakenings, since antagonism of these serotonergic receptors increases slow-wave sleep (22–24).

In evaluating sleep disturbance in a patient taking an SSRI, the clinician must first discriminate between insomnia as a symptom of the psychiatric disorder being treated or as a side effect of the antidepressant. With SSRI-induced insomnia, the initial management strategy should be ensuring morning administration of the medication. If insomnia persists, benzodiazepines such as temazapam, alprazolam, zolpidem, or trazodone can be effective treatments. In a double-blind crossover study of 17 depressed patients with insomnia on fluoxetine or bupropion, 67% of those treated with trazodone 50 to 100 mg at bedtime showed improved sleep compared with 13% treated with placebo (25). Trazodone appeared to improve sleep duration, early morning and middle of the night awakening, and subjective sleep quality.

B .Gastrointestinal

Gastrointestinal side effects are among the most common and troublesome adverse events encountered with SSRI use, with symptoms including nausea, vomiting, diarrhea, loose stools, and constipation (26). In clinical trials, SSRI- induced nausea has an incidence of 20 to 40%, with fluovoxamine having the highest reported rate. Although it occurs commonly, less than 10% of patients actually discontinue medication because of nausea (9).

Nausea and vomiting from SSRIs are most likely secondary to enhanced 5HT availability in the gut and/or centrally, which then acts upon 5HT3 receptors (27,28). In animal studies, activation of 5HT3 receptors causes emesis. The tendency for nausea to wear off with time may partially be due to down- regulation of these receptors.

A number of strategies may be used to diminish SSRI-induced nausea.

First, since food slows the absorption process while leaving the extent of absorption unchanged, taking SSRIs with meals may help to minimize some gastrointestinal symptoms (20). Second, since nausea is dose-related, lowering the dose may be helpful. Third, simply waiting a few days to weeks may be effective, since tolerance to nausea tends to develop over time. However, if symptoms occur even at low doses or persist during treatment, cisapride 5 mg bid has been demonstrated to effectively treat SSRI-induced nausea within 3 days without causing diarrhea (27). Cisapride's mechanism of action is thought to be related to 5HT receptor antagonism, most likely at the abdominal visceral afferent neurons and the area postrema, an area of the brainstem located at the base of the fourth ventricle. Effective doses of cisapride for the management of SSRI-induced nausea range from 5 to 20 mg bid; treatment can sometimes be discontinued after a month without recurrence of nausea. However, through a pharmacokinetic interaction of the P450 3A4 system, fluvoxamine and fluoxetine (and nefazodone) may raise cisapride blood levels, resulting in cardiac arrhythmias. Therefore, cisapride should be given only with caution to patients taking any of these antidepressants.

Diarrhea or loose stools, reported in 11 to 18% of patients taking SSRIs, often persists longer than nausea (9). In clinical trials, sertraline was associated with a slightly higher rate of diarrhea than the other SSRIs (shown in Table 1). Paroxetine's mild affinity for muscarinic receptors may diminish its capacity for diarrhea while causing a higher rate of constipation than other SSRIs (20).

Initial treatment strategies for treating SSRI-induced diarrhea include lowering the dose and waiting for tolerance to develop. In addition, Lactobacillus acidophilus, a bacterium involved in the manufacture of fermented milk products, taken in capsule form twice daily, has been reported to relieve persistent sertraline-induced diarrhea within a few days (29). Orally ingested Acidophilus survives gastric acidity, alters intestinal flora, and has been reported to inhibit some enteropathogens. Diarrhea may return when the capsules are stopped.

Hepatitis is a rare reported adverse event with SSRI treatment. In these unusual cases, elevated transaminases can be expected to diminish after drug discontinuation. Mild liver enzyme abnormalities have been reported in only 0.5% of patients treated with fluoxetine (30).

C. Weight/Appetite Changes

Weight gain and weight loss each occur in approximately 4% of patients treated with SSRIs in short-term studies (26). Of note, changes in appetite and

weight may be symptoms of depression or of response to treatment and may not be causally related to SSRI use. Of the SSRIs, fluoxetine is reported to have the most anorectic effect; however, there is no evidence that weight loss is maintained with long-term treatment (20). In a study of 655 nondepressed obese patients treated for 8 weeks with fluoxetine doses of 10, 20, 40, and 60 mg and placebo, the placebo group lost an average of 0.6 + / - 2.3 kg compared to 4.0 + / - 3.9 kg for those taking 60 mg fluoxetine, with intermediate weight loss at lower doses (31). In another study, 21 obese binge and nonbinge eaters were randomly assigned to 60 mg/day of fluoxetine or placebo in a 52 week double-blind trial (32). Patients treated with fluoxetine and behavioral modification lost significantly more weight than patients receiving placebo and behavioral modification. Weight loss occurred mostly in the first 20 weeks of treatment, with the fluoxetine group losing an average of 13.5 kg, or 0.68 kg/wk in this time period vs. 0.6 kg weight gain in the placebo group. Weight loss of only 0.5 kg, or 0.03 kg/wk, was reported in the remaining 32 weeks. Follow-up data suggested that patients regained weight once fluoxetine treatment was discontinued. Fluoxetine's weight-loss properties may be related to the specific inhibition of serotonin reuptake. Animal and human studies have suggested that substances that increase central serotonin levels decrease carbohydrate and overall caloric intake as well as lowering the satiety threshold (32).

In contrast, however, both open case series and clinical experience indicate that over months of treatment with any of the SSRIs, a number of patients gain weight up to 30 lb or more (33). Some patients describe an intense carbohydrate craving, while others have insidious weight gain despite no change in appetite or food intake. While fluoxetine (and probably other SSRIs) may initially lower the satiety threshold, long-term treatment may actually contribute to raising the threshold in some patients (33,34). The mechanism of this long-term effect may be desensitization of postsynaptic receptors, with changes in serotonin neurotransmission opposing those seen in short-term treatment.

Weight changes with fluoxetine (and possibly other SSRIs) may be a function of baseline weight (35). In an open label depression trial using fluoxetine. 20 to 80 mg daily, 39 depressed outpatients were divided into three groups: ideal weight, underweight, or overweight. Overweight patients had a significant weight loss of 3.3 lb in the first 2 months of treatment, while the ideal weight patients gained 4.4 lb over 4 months. The underweight group showed no consistent trends. Weight changes were maintained for at least 6 months. Of note, in contrast to the overweight group, the ideal weight patients

reported reduced appetite and weight loss during the depressive episode. Hence, it is possible that the ideal weight group resumed more normal eating habits when they felt less depressed, thereby contributing to their weight gain.

Initial management strategies for SSRI-induced weight gain include educating patients about this possibility. Patients should be encouraged to monitor carbohydrate and fat intake and engage in a regular exercise program commensurate with a person's health and age. Patients who already gained weight should consider entering behavioral weight control programs or switching to a different antidepressant.

D. Headache

Consistently, headaches are among the most common side effects reported in controlled SSRI studies (see Table 1). Militating against their frequency, however, is the very high rate of headaches in those treated with placebo in these same studies (15 to 20%), typically yielding a drug/placebo difference of no more than 5%. Consistent with this, headache seems an unusual cause for SSRI discontinuation. Implied in the high rate of headaches among placebo-treated patients are the multiple causes of headaches in psychiatric patients that may be incorrectly attributed to the prescribed antidepressant. These causes include the underlying psychiatric disorder being treated, premorbid history of tension headaches or migraines, and specific medical disorders such as hypertension. SSRIs may exacerbate pre-existing migraines or tension headaches, presumably via their serotonin-enhancing properties (36,37). Paradoxically, along with their capacity to cause headaches, SSRIs have also been reported as decreasing migraine headaches (38,39).

For those patients with whom headaches are either caused de novo or exacerbated by SSRIs, few treatment regimens have been established. The universal strategies—decreasing the dose, waiting for accomodation, switching to another antidepressant—should all be considered. (The utility of switching from one SSRI to another as a strategy for managing headaches is unknown.) Altering the time of day of antidepressant administration is unlikely to diminish headaches. Typical headache remedies are the next strategies to consider: relaxation techniques and/or analgesics such as aspirin, acetominophen, or ibuprofen 400 to 800 mg daily. Migraine headaches may be safely and effectively treated with the serotonin 1-D agonist sumatriptan at either 25 to 100 mg orally or 6 mg given subcutaneously (40). Finally, anecdotal experience suggests the occasional efficacy of tricyclics such as nortriptyline or amitriptyline when prescribed in low doses (25 to 50 mg daily).

E. Sexual Side Effects

Clinical experience indicates that sexual dysfunction is among the most prevalent and distressing side effects associated with SSRIs. This conclusion, however, stands in marked contrast to the data recorded in prerelease studies and described in the Physicians' Deck Reference (PDR), which woefully underestimate both the rate and importance of SSRI-induced sexual side effects. As the best example of this, fluoxetine's clinical trial data, published before psychopharmacologists became aware of the problem, indicate a 1.9% rate of sexual side effects (9). Across clinical studies, estimates of the true rate range between 8 and 75% with fluoxetine (41). The best overall estimate is that 30 to 40% of patients on SSRIs will show sexual side effects (42). As with other side effects, however, the rate of sexual side effects causing significant distress is assuredly lower. As an example, mild delayed time to orgasm for a man would be counted as a side effect but might not need to be treated, whereas anorgasmia for either sex would virtually always be distressing and more clinically significant. Nonetheless, most clinicians find that patients regularly request a change in antidepressants because of sexual side effects.

Assuredly, the disparity in sexual dysfunction rates between controlled and clinical studies is explainable by a number of methodological issues, the most important of which is the differing methods of ascertaining side effects (42). For instance, studies in which sexual side effects are specifically asked about show far higher rates than those studies in which only spontaneous complaints are recorded (43). However, in evaluating sexual side effects from SSRIs, it is vital to take into consideration the other causes of sexual dysfunction in these patients, including the effects of the disorder being treated (e.g., depression), relational problems, comorbid drug/alcohol abuse, and comorbid medical disorders (42).

Common sexual side effects reported with SSRIs are those related to alterations in the classical human sexual response cycle. Thus, decreased interest, diminished arousal including erectile dysfunction in men, and delayed time to orgasm (or, when prolonged, anorgasmia), have all been reported. Although not yet validated by systematic study, most clinicians note orgasmic difficulties as the most commonly seen sexual side effects with SSRIs. Other less common sexual side effects include increased sexual arousal and spontaneous orgasm with yawning (42).

Most clinicians and the few studies examining the issue have found similar rates of sexual side effects among the SSRIs (44,45). One double-blind study, however, did find a lower rate of sexual dysfunction with fluvoxamine as compared with sertraline (46).

Since all strongly serotonergic antidepressants (including clomipramine as well as the SSRIs) are associated with high rates of sexual side effects, it is presumed that increased serotonin diminishes sexuality. There is some animal evidence as well as human data supportive of this (41,47,48). Although the antisexual serotonergic effects are generally assumed to be central in origin, serotonergic influences in the peripheral nervous system may also play a role.

As shown in Table 3, management of SSRI-induced sexual side effects includes both general and specific strategies. The success rate for lowering the dose or waiting for accomodation to occur is unknown. Switching to another antidepressant that is known to cause fewer sexual side effects—e.g., bupropion or nefazodone—is a well validated strategy (49,50). It is unclear how frequently switching from one SSRI to another results in improvement in sexual functioning. Transient medication discontinuation (stopping the antidepressant for 48 hr prior to anticipated sexual activity) or simply lowering the dose for a few days is likely to be helpful with all the SSRIs with relatively short half-lives—sertraline, paroxetine and fluvoxamine—but not with fluoxetine (51,52). This technique, however, may risk the reemergence of depression or encourage poor compliance. Additionally, sudden discontinuation of a short half-life SSRI confers the risk of precipitating SSRI withdrawal symptoms (see below).

A number of specific antidotes to reverse sexual side effects have been proposed. No double-blind study has yet validated the efficacy of any of the agents shown in Table 2. Whether as-needed use for any of these agents is as effective as daily dosing is unknown. Clinical experience suggests the use of dopamine agonists or yohimbine. Unfortunately, the only double-blind study in the area found only marginal differences between yohimbine and placebo in reversing SSRI-induced sexual side effects (53). Side effects of dopamine agonists are those related to stimulation side effects. Most clinicians do not use cyproheptadine routinely because of its powerful sedating properties and its capacity to reverse antidepressant effects (42).

F. Somnolence

Paradoxically, in addition to overstimulation, SSRIs are associated with sedation, which may be secondary to antihistaminic effects and/or 5HT reuptake inhibition (18). In clinical experience, fluvoxamine tends to be the most sedating, followed by paroxetine, sertraline, and fluoxetine. In contrast to activation, which appears to be a more transient SSRI-induced side effect, sedation may be more persistent (7).

Should sedation emerge, dose reduction and switching to nighttime dos-

Table 3 Treatment of Antidepressant-Induced Sexual Side Effectsa

Name	Antidepressant Class Causing Side Effects	Side Effects Reversed	Effective Dose
Bethanechol	TCAs, MAOIs	Erectile dysfunction, anorgasmia	10–40 mg as needed or 40–100 mg/day
Cyproheptadine	TCAs, fluoxetine, MAOI (one case)	Anorgasmia	2–16 mg usually as needed
Yohimbine	Fluoxetine, clomipramine	Decreased libido, erectile dysfunction, anorgasmia	5.4–16.2 mg as needed or 5.4 mg three times a day
Dopamine agonists			
Amantadine	Fluoxetine	Anorgasmia	100–400 mg/day
Stimulants (dextroamphetamine, pemoline)	Sertraline, phenelzine	Decreased libido, erectile dysfunction, anorgasmia	Dextroamphetamine 10– 25 mg/day; pemoline 18–75 mg/day
Bupropion	Fluoxetine (one case)	Decreased libido, erectile dysfunction, orgasmic delay	75 mg/day
Buspirone	SSRIs	Decreased libido, anorgasmia	15–60 mg/day or as needed
Gingko biloba extract	Multiple antidepressants	Decreased libido, erectile dysfunction, anorgasmia	120 mg bid

aGeneral strategies: Decrease dose, wait, switch, discontinue transient medication.

Key: TCAs = tricyclic antidepressants; MAOIs = monoamine oxidase inhibitors; SSRIs = selective serotonin reuptake inhibitors.

Source: Ref. 42.

ing should be the first two strategies employed. However, if symptoms persist and are problematic, low doses of a stimulant such as 5 to 20 mg of methylphenidate or 2.5 to 10 mg dextroamphetamine can be prescribed with caution (18). Alternatively, one can switch to a less sedating antidepressant within this class or to venlafaxine or bupropion.

G. Anticholinergic Effects

Compared with the tricyclic antidepressants, SSRIs show minimal interactions with cholinergic receptors and thus display significantly fewer anticholinergic side effects (54). Among the SSRIs, paroxetine has a mild affinity for acetylcholine's muscarinic receptors and is the most likely to cause events such as dry mouth, constipation, and blurred vision (20,23,55). In clinical trials of paroxetine, dry mouth and constipation were reported at incidences of 18 and 14% respectively (9). While the other SSRIs bind insignificantly to muscarinic receptors, side effects typically attributed to cholinergic blockade are seen, presumably due to interactions with other neurotransmitter systems. As an example, in a study of 1378 fluoxetine-treated patients, dry mouth occurred in 14% and visual disturbances, usually blurred vision, were reported in 4% (56).

SSRI-induced anticholinergic side effects can be minimized by starting with a low medication dose, decreasing the dose, or changing to a less anticholinergic agent within this class. If these standard management strategies are ineffective, those employed in treating TCA-induced anticholinergic side effects can be used. For dry mouth, patients should remain well hydrated and use sugarless lemon drops or sugar-free gum to promote increased salivary flow. Items containing sugar should be avoided since they increase dental caries. Artificial saliva preparations of pilocarpine or peripheral cholinergic agents such as bethanechol chloride at 10 to 30 mg qd to tid, to promote salivation, can also be used (57).

For constipation, initial strategies include regular sleep and eating habits, daily activity, and the use of a heating pad to the abdomen. One to three teaspoons of bran added to cereal, four to six prunes daily, the use of cooked or canned fruits and vegetables rather than raw fruits and vegetables, and ingestion of at least a 1 L of water a day may also be tried. Bulk laxatives such as metamucil or docusate sodium can also be used. Although rarely necessary with SSRIs, cathartic laxatives such as milk of magnesia may be used, but only intermittently, as they lose effectiveness with continuous use. Bethanechol 10 to 25 mg bid or tid can also be helpful (57,58).

Visual anticholinergic side effects include cycloplegia, paresis of the

ciliary muscles that act on the lens, and presbyopia, difficulty with near vision secondary to mydriasis (pupillary dilation and sluggish reaction to light). Hence, patients report blurry vision, difficulty reading or eyestrain. In the short term, artificial tear preparations such as 1% pilocarpine drops or bethanechol can be helpful. Visual side effects of SSRIs tend to be mild and to dissipate over time. If visual effects persist once on a stable dose of medication, corrective lenses should be considered (57,58).

H. Cardiovascular Effects

While serotonin has marked and varied effects on the cardiovascular system, the SSRIs have not demonstrated significant cardiovascular side effects (59). In a study of adverse events in 1378 fluoxetine-treated patients, fluoxetine had no significant cardiac toxicity. Less than 1% of patients in this study discontinued treatment because of tachycardia, palpitations, and dyspnea, which occurred early in treatment and were generally related to anxiety (56). While fluoxetine can cause a statistically significant but clinically unimportant slowing of the heart rate (3.3 beats per minute), cardiac conduction and the PR and QRS intervals remain unaffected (56,60). Cases of fluoxetine-associated bradycardia and syncope, atrial fibrillation, and supraventricular tachycardia have all been reported (61–63). However, the incidence and nature of adverse cardiac events were consistent with the population of patients examined and also comparable to those occurring in the placebo-treated group (64). Similarly, neither sertraline nor paroxetine have demonstrated clinically significant effects, on blood pressure, heart rate, intraventricular conduction or electrocardiographic time intervals (60,65). Furthermore, paroxetine's cardiovascular profile does not appear to differ in the elderly as compared with a younger population (65).

I. Hypomania/Mania

It is generally assumed, although not proven, that antidepressants can precipitate manic/hypomanic episodes and/or provoke rapid cycling (66–68). Patients thought to be at highest risk for these side effects are, of course, those with bipolar disorder. Unfortunately, the paucity of well-designed studies on bipolar depression have precluded meaningful generalizations as to the differential capacity of antidepressant classes to cause either mania or rapid cycling. No controlled, well-designed study has systematically examined the efficacy or switch rate of any of the available SSRIs in bipolar depression. However, the early clinical trials for paroxetine and sertraline as antidepressants allowed

the inclusion of bipolar patients. (Trials with fluoxetine and fluvoxamine excluded bipolar individuals.) The rate of manic switches for these bipolar patients treated with one of these SSRIs (3.7%) was significantly lower than that seen in bipolar patients treated with a tricyclic (the usual comparator antidepressant)—11.2%—and no different than the switch rate seen with placebo (4.2%) (69). In a post hoc analysis, Stoll et al. found that bipolar patients taking fluoxetine showed more severe manic symptoms on admission to hospital compared with those taking bupropion or MAO inhibitors (70). Even if these results were replicated (and they have not been so tested), it is unclear whether this finding would apply to the other SSRIs with shorter half-lives.

Studies examining the switch rate to mania/hypomania with different antidepressants prescribed to unipolar depressed patients are also inconclusive. Individual case reports and series indicate the capacity of all antidepressants to cause manic switches in some individuals (71). Using the data from clinical trials, the rate of bipolar switching in a predominantly unipolar population (some bipolar patients may have been included in some studies) treated with SSRIs is 0.72% (69).

Management of antidepressant-induced manic states predominantly reflects common sense, since no studies have examined treatment approaches. For hypomanias, simply lowering the antidepressant dose may suffice. With fluoxetine, its long half-life may require a longer time on the lower dose or a brief medication discontinuation with subsequent resumption on a lower dose. More severely manic states require either antidepressant discontinuation or treatment and/or a mood stabilizer, a high-potency benzodiazepine, or a neuroleptic.

J. Suicidality and SSRIs

In 1990, Teicher et al. published a report of seven patients who developed an intense, violent suicidal preoccupation during treatment with fluoxetine (72). Although all patients had had a prior history of suicidal ideation, none was actively suicidal at the time of starting the SSRI. These patients additionally described agitation and inner restlessness reminiscent of akathisia. Other case reports and small case series described similar phenomena (73–76). The descriptions in these cases highlighted prominent agitation, a frantic internal quality, and sometimes obsessive preoccupation with violent thoughts.

These reports provoked a series of studies examining the capacity of fluoxetine (or other SSRIs) to precipitate or exacerbate suicidal behavior and the possible mechanisms for these clinical events. The large-scale studies (comprising numbers ranging from 500 to 3000) typically compared the rates

of new-onset suicidal ideation/behavior in depressed patients treated with fluoxetine to those in patients treated with other antidepressants and placebo (77– 79). These studies consistently demonstrate that the rate of suicidal ideation and behavior decreases during fluoxetine treatment and that rates of new- onset suicidality in those treated with fluoxetine and other antidepressants are similar.

Large-scale studies, however, do not necessarily preclude a smaller percentage of patients who may have a paradoxical reaction to an SSRI, resulting in new-onset suicidal ideation. A number of mechanisms for this have been suggested (76,80–82). The most common explanations are that when suicidal ideation emerges de novo during SSRI treatment, it may reflect (a) a dysphoric response to the stimulating properties of the antidepressant; (b) an akathisialike syndrome caused by the dopamine-diminishing effects of serotonergic drugs; or (c) an initial decrease in serotonergic neurotransmission secondary to an exaggerated autoreceptor response to the SSRI, with diminished serotonin leading to increased suicidality. In the only clinical study systematically examining any of these hypotheses, Tollefson et al. found no relationship between activation side effects and new-onset suicidality in patients treated with fluoxetine, casting doubt on the stimulation explanation (78).

If new-onset suicidality is seen during treatment with an SSRI, the most commonly considered approaches are stopping the medication or lowering the dose. Those patients who present with simultaneous anxiety/agitation might benefit from a brief trial of a benzodiazepine (82). If the clinical syndrome resembles akathisia, a beta blocker such as propranolol might additionally be effective.

K. Serotonin Syndrome

As a class of powerfully serotonergic medications, the SSRIs have been implicated in causing a central serotonin syndrome, characterized by a group of symptoms including mental status changes, restlessness, myoclonus, fever, shivering, hyperreflexia, and ataxia, occasionally leading to death (83,84). All four SSRIs have been associated with serotonin syndrome, indicating a class effect (85–88). Serotonin syndrome can present in a spectrum of severity. Thus, a number of cases may manifest with only transient muscle twitching, ataxia and diarrhea, while others require admission to an intensive case unit and life-support treatment. The proposed pathophysiology of the serotonin syndrome is excessive central serotonergic activity, possibly through activation of the 5HT-1A receptor in the brainstem and spinal cord (83–84).

In most cases, serotonin syndrome is seen in patients taking two agents

that increase serotonin availability through different mechanisms. With SSRIs, therefore, the largest number of cases have occurred when SSRIs and MAO inhibitors are combined or an antidepressant from one class has been started before the previous agent from the other class has been completely metabolized. Higher antidepressant doses of the MAO inhibitor selegiline (> 10 mg daily) should also not be combined with an SSRI. The risk of a serotonin syndrome when an SSRI is combined with the antiparkinsonian dose of selegiline (10 mg or less) is lower (89). A few other cases of serotonin syndrome have been described when an SSRI is combined with lithium, buspirone, dextromethorphan or tryptophan (84).

The most important treatment of serotonin syndrome is prevention. The key contraindicated combination is that of an MAO inhibitor with an SSRI. After the use of an SSRI, the amount of time needed before an MAO inhibitor can be safely prescribed depends on the half-life of the SSRI. For fluoxetine, a 5-week washout is required; for the other SSRIs, 2 weeks is sufficient. Following the administration of an MAO inhibitor, 2 full weeks should elapse before the prescription of an SSRI in order to allow resynthesis of MAO.

Should it occur, the treatment of serotonin syndrome is predominantly supportive (84,90). The serotonergic medication(s) should be immediately discontinued. Evaluation in the emergency department is appropriate. Symptomatic treatment of the hyperreflexia and myoclonus with benzodiazepines and/ or beta blockers can be helpful. Hyperthermia constitutes a true emergency and should be treated with aggressive cooling measures. Antiserotonergic agents anecdotally reported as effective in ameliorating serotonin syndrome include cyproheptadine, methysergide, and propranolol (84,91).

L. Pregnancy

The literature on the safety of SSRIs in pregnancy is limited. Animal studies of in utero exposure up to 11 times the maximum daily human dose of fluoxetine have shown no harm to the fetus (64). In a study of 74 patients treated with tricyclic antidepressants and 128 patients treated with fluoxetine, neither antidepressant administered in the first trimester of pregnancy was associated with an increased risk of congenital malformations (92). The register kept by the manufacturer of fluoxetine consists of 1500 cases of prenatal fluoxetine exposure without any evidence of a high incidence of congenital anomalies or a clustering of any specific malformation (93). A recent study comparing 228 pregnant women taking fluoxetine with 254 pregnant women not taking an antidepressant found that fluoxetine use during pregnancy was not associated with an increased risk of spontaneous loss or major fetal anomalies (94).

However, women with first-trimester fluoxetine exposure were found to have infants with a higher incidence of three or more minor anomalies and women with third-trimester exposure were found to be at increased risk for perinatal complications. Unfortunately, the study was nonrandomized and could not exclude the role of depressive disorder itself or the higher maternal age of the fluoxetine-treated mothers as contributing factors. Additionally, 30% of the fluoxetine-treated mothers also took other psychotropic medications (95). In contrast, a prospective study of 112 women with fluoxetine use during the third trimester of pregnancy revealed a lack of significant postnatal complications (96). Thus far, children with histories of prenatal exposure to fluoxetine appear to have no adverse effects in neurobehavioral function, including IQ (93). However, further longitudinal studies are needed to clarify this issue.

Data are even more limited for the other SSRIs. In the largest case series, a study of 63 infants with first-trimester exposure to paroxetine found no congenital anomalies (97).

M. Less Common Side Effects

A variety of other side effects, listed in Table 4, have been infrequently associated with SSRIs. The most concerning of these is the tendency to cause skin blushing, or, less commonly, overt bleeding, with manifestations such as ecchymoses, rectal bleeding, and epistaxis (98–102). Laboratory evaluations in these cases do not reveal any consistent findings. Bleeding seems to be a class effect of the SSRIs, since at least three agents have been reported to cause it. Neither the etiology nor the prevalence of SSRI-induced bleeding is known. If symptoms of overt abnormal bleeding occur, the SSRI should be discontinued.

Table 4 Less Common Side Effects from SSRIs

Bleeding/blushing
Hyponatremia
Movement disorders—akathisia, dystonia, tremors, myoclonus, tardive dyskinesia
Bruxism, myoclonus
Cognitive disturbances
Alopecia

Hyponatremia secondary to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) can occur with any of the SSRIs, although its exact incidence is unknown. It may be asymptomatic, discovered by routine laboratory tests, or may become manifest by mental status changes, dizziness, weakness, or even seizures (103–105). In some cases, SIADH occurred within the same patient in conjunction with the administration of two different SSRIs (103,106). In contrast, another patient was rechallenged with the same SSRI that previously caused SIADH but without precipitating hyponatremia (107). Treatment of SIADH includes discontinuing the SSRI and fluid restriction if the hyponatremia is severe or symptomatic.

SSRIs have been reported to cause a variety of movement disorders, most of which are more commonly associated with dopamine blocking agents. Side effects such as akathisia, dystonia, parkinsonian symptoms, tremors and even tardive dyskinesia have all been described (15). The majority of case reports of these side effects involve fluoxetine, which may reflect its relative longevity and popularity among the SSRIs rather than a higher risk associated with its use. The most commonly touted mechanism for these side effects is secondary dopamine blockade via serotonergic agonist influence. Anecdotal treatment of these movement disorders has been consistent with neuroleptic- induced side effects: lowering the dose, stopping the medication, and/or the use of anticholinergic agents, beta blockers (such as propranolol 10 to 20 mg bid or tid), and benzodiazepines.

Some uncommon side effects are likely to be related to the more common problems described above. Thus, myoclonus, occasionally seen with SSRIs, is thought to be due to increased serotonergic tone and is related to the more global and more dangerous serotonin syndrome (108). Similarly, bruxism seems to be a specific manifestation of muscle tension, related to either myoclonus or the movement disorders described above (109).

SSRIs are generally not associated with memory disturbances or other cognitive changes. Most studies examining laboratory measures of information processing capacity and memory retrieval indicate that SSRIs are either neutral in their cognitive effects or occasionally improve performance (110). Nonetheless, occasional case reports and many clinical observations suggest that a small group of patients describe reversible memory disturbances (111,112).

Apathy and indifference without somnolence has been described in patients taking SSRIs (113,114). In the reported cases, changes appeared gradually and did not seem abnormal to patients until they resulted in embarrassment or repercussions. Side effects seemed to be dose-related; a decrease in fluvoxamine dose led to normalization of one patient's behavior within 2 or 3 days

(114). In these unusual cases, therapeutic options include lowering the dose, switching to a different antidepressant, or adding a second medication with stimulating properties such as bupropion or a stimulant.

Finally, alopecia has been reported in association with each of the SSRIs (115–118). The only successful reported treatment has been drug discontinuation.

N. Overdose

Among the most important qualities of the SSRIs (and the other recently released antidepressants) is that, compared with tricyclics and MAO inhibitors, they are markedly safer if taken in overdose (119). Examining a large (n = 234) series of patients who overdosed on fluoxetine, Borys et al. found that when taken without other psychotropic agents, fluoxetine overdoses were uniformly characterized by a good outcome (120). With an average dose of 455 mg (over twenty times the usual therapeutic dose), almost half of those overdosing on fluoxetine alone had no symptoms at all. When symptoms arose, the most common were tachycardia, drowsiness, tremor, vomiting, and nausea. Only 23% of those who overdosed on fluoxetine alone required medical hospitalization with an average length of stay of less than 1 day.

The data base for other SSRIs is smaller but similar; outcomes are overwhelmingly benign (9). Deaths from SSRIs when ingested as single agents have occurred but are rare. Typical overdose symptoms with other SSRIs are similar to those described above for fluoxetine.

Despite the safety of SSRIs when taken in overdose, prudent clinical management for SSRI overdose dictates that the patient be evaluated in the emergency department both to rule out the rare cardiac arrhythmia as well as to explore the need for psychiatric hospitalization to protect the patient from more lethal suicide attempts.

O. SSRI Withdrawal Syndromes

Most recently recognized among the SSRI side effects has been the presence of a characteristic withdrawal syndrome upon drug discontinuation. Clinically, the SSRI withdrawal syndrome comprises two types of symptoms: flu-like and neurological (121,122). Flu-like symptoms (which resemble the tricyclic withdrawal syndrome) include fatigue, nausea, vomiting, malaise, myalgias, insomnia, anorexia, and chills. Distinguishing these from a true influenza syndrome, fever is not present during SSRI withdrawal. Neurological symptoms almost always include dizziness with gait instability, tremulousness, irtitabil-

ity, vivid dreams, and occasionally true vertigo. A more unusual group of neurological symptoms includes unpleasant sensory distortions such as a visual lag after eye movement, visual illusions similar to those associated with migraine headaches, and dysesthesias. The dysesthesias are typically described as paroxysmal sensations resembling electrical shock.

Although no study has systematically explored the issue, clinical experience suggests that the likelihood and severity of the SSRI withdrawal syndrome is inversely correlated with the half-life of the medication (121). Thus, fluoxetine, with its long half-life, is almost never associated with this syndrome; sertraline, infrequently; fluvoxamine, occasionally; while paroxetine has been most consistently implicated in the published cases. Consistent with this, in the largest published series examining SSRI withdrawal (n = 158), rates of a withdrawal syndrome for the four SSRIs were 0, 2, 14, and 20%, respectively.

In the one study with a sufficient number of patients to explore predictors of withdrawal, there was no association of the syndrome with diagnosis, age, or clinical status (relapse vs. not) after withdrawal (121). Patients who had taken the medication for more than 2 weeks were more likely to experience withdrawal symptoms.

The course of the withdrawal is variable. Some patients develop symptoms while still on the medication, but at a lower dose than previously. In other patients, symptoms begin within 2 but up to 5 days after medication discontinuation. Withdrawal symptoms generally fade within 4 to 14 days, although shock-like sensations have been reported to fade over a 3-month period in a few patients.

The mechanism by which SSRI discontinuation causes these withdrawal symptoms has yet to be established. It seems unlikely that the symptoms represent cholinergic rebound (which is the presumed mechanism of tricyclic withdrawal symptoms), since most SSRIs have weak anticholinergic properties. The most likely etiology, of course, would be that chronic use of serotonergic reuptake blockers causes an adaptation in serotonergic receptor sensitivity with subsequent temporary changes in serotonergic function once reuptake blockade ceases. The specific serotonergic receptors involved in these changes are unknown.

Methods of prevention and treatment of the SSRI withdrawal syndrome are still a matter of common sense and guesswork. The first reasonable suggestion is that, with those patients who have taken short-half-life SSRIs for more than a few weeks, the antidepressant should be discontinued by a tapering schedule over at least 1 week or more, with the schedule to be lengthened significantly if withdrawal symptoms appear. Patients experiencing with-

drawal symptoms after drug discontinuation should resume the medication, following which a slower tapering schedule should be instituted. Typically, the withdrawal symptoms disappear upon reinstitution of the medication. Patients who continue to show withdrawal symptoms even with a slow tapering should be considered for switching to a longer-acting agent such as fluoxetine, which can then be tapered more easily (123). That the addition of other serotonergic medications such as fenfluramine or buspirone might alleviate SSRI withdrawal symptoms has been suggested but not yet tested. Additionally, patients should be reassured that, despite their unpleasantness, the symptoms are not dangerous and always disappear with time.

IV. BUPROPION

Bupropion, released in 1989, is structurally and biologically unique among the antidepressants. Its side-effect profile is consistent with its weak dopamine- inhibiting effect, its ability to enhance noradrenergic activity through a number of different mechanisms, and its lack of serotonergic activity (124). Given these biological properties, bupropion's side-effect profile does not resemble those of the other new antidepressants and is more like that of stimulants. The most common side effects associated with bupropion in clinical trials are agitation, dry mouth, insomnia, headache, nausea/vomiting, constipation, and tremor (9). The stimulating effects of bupropion may sometimes be helpful, especially with patients who show psychomotor retardation. Decreased appetite is also commonly seen with bupropion but is generally not very distressing for most patients. Approximately 10% of patients in the clinical trials discontinued bupropion because of side effects.

Because of its dopaminergic properties, bupropion has also been associated with new-onset psychotic symptoms or other neurotoxic reactions (125,126). Paradoxically, however, bupropion is thought to precipitate manic episodes less frequently than some other antidepressants. In one small study, it was associated with fewer manic switches than the tricyclic desipramine (127).

With its lack of serotonergic activity and its mild dopaminergic effects, bupropion (along with nefazodone) causes fewer sexual side effects than any other antidepressant (42). As with the other new antidepressants, overdoses with bupropion are generally benign in outcome. Seizures and hallucinations are relatively common in overdose (9).

The major concern about bupropion's side effects has been its propensity to cause seizures. In the most thorough review of the topic, Davidson estimated

the seizure risk to be 0.44% in patients receiving up to 450 mg daily, the maximum recommended dose (128). The seizure rate above this dose was 2.2%. By comparison, the seizure rate for tricyclics at therapeutic doses is 0.3 to 0.6%, while the rate for SSRIs is probably 0.2% (129).

In order to minimize the risk and the concern about seizures and to reduce the need for multiple (tid) dosing in order to obtain a daily dose of over 300 mg daily, sustained-release bupropion was introduced in late 1996. In doses up to 300 mg daily, the seizure risk for sustained-release bupropion is 0.1% (130). Presumably, this reflects the lower plasma (and brain) peak level of bupropion secondary to the more gradual absorption of the drug. However, the estimated seizure risk of the sustained-release compound at 400 mg daily has not yet been tested. Otherwise, side effects are similar for sustained- release bupropion and the immediate release form of this drug.

Stimulating side effects of bupropion can be managed by either lowering the dose or adding some type of tranquilizing medication. For daytime anxiety, low doses of a benzodiazepine—e.g., lorazepam 0.5 to 2 mg daily or clonazepam 0.5 to 1 mg daily—can be very effective. Occasionally, beta blockers such as propranolol 10 to 40 mg bid will be helpful. Insomnia can be treated by either a benzodiazepine or by adding a low dose of a sedating antidepressant such as trazodone 50 to 100 mg at bedtime.

To minimize the seizure risk, no more than 150 mg of bupropion should be taken at any one time, with the total daily dose not to exceed 450 mg. Bupropion in any form is contraindicated in patients with active eating disorders (either anorexia nervosa or bulimia nervosa) or those with a history of a seizure disorder. Bupropion should be prescribed with caution to those with other risk factors for seizures, such as recent withdrawal from alcohol or other anxiolytic drugs.

V. VENLAFAXINE

Venlafaxine, released in 1994, shares the powerful reuptake-blocking properties of the SSRIs while additionally blocking norepinephrine reuptake (131). Because of its powerful serotonergic effects, venlafaxine's side-effect profile is very similar to that of the SSRIs. Thus, the most common side effects reported in clinical trials are nausea, headache, dry mouth, insomnia, dizziness, somnolence, constipation, and nervousness (9). Although it has not been systematically studied, rates of sexual side effects are thought to be similar to those seen with SSRIs. Discontinuation for side effects due to venlafaxine was seen in 19% of patients in clinical trials, with nausea, somnolence, and

insomnia most commonly cited (9). Nausea seems to be more frequent in venlafaxine-treated patients than in those taking SSRIs (132).

As with other agents, tolerance to many of the side effects of venlafaxine (including nausea) develops over a few weeks. Also as with the SSRIs, serotonin syndrome may occur if venlafaxine is taken along with MAO inhibitors (133). Because of its short half-life, however, only 7 days washout time are required after venlafaxine discontinuation before an MAO inhibitor can be safely prescribed. Venlafaxine is relatively safe when taken in overdose, with sedation being the most common symptom.

Withdrawal reactions to venlafaxine, with identical symptoms to those noted above for SSRIs, are relatively common (134,135). Since venlafaxine's half-life is the shortest among the strongly serotonergic antidepressants, associated withdrawal reactions may be more common and more intense than those caused by SSRIs. Slow tapering and possibly switching to a longer-acting serotonergic agent may be helpful.

Alone among the newer antidepressants, venlafaxine is associated with hypertension in a dose-related manner. Sustained elevation of blood pressure (defined as a diastolic pressure of > 90 and 10 mm higher than baseline on at least three occasions) is seen in 2% of those taking < 100 mg of venlafaxine daily, 5% in the range of 101 to 200 mg, 6% in the range of 201 to 300 mg, and 13% in the group taking more than 300 mg (136). For approximately half the hypertensive patients, subsequent blood pressure readings diminished over time. It is assumed that the hypertensive effect of venlafaxine reflects its dose- related norepinephrine reuptake blockade.

Venlafaxine-induced side effects should be treated using the same approaches described for the side effects of SSRIs. since the biological mechanisms are identical. Cisapride at doses of 5 to 10 mg twice daily effectively treats the nausea associated with venlafaxine (137). If hypertension emerges, lowering the dose should be the first consideration. Patients who develop hypertension from venlafaxine but who have had excellent antidepressant responses may be treated with antihypertensive agents such as angiotensin-converting enzyme inhibitors or calcium channel blockers while continuing the antidepressant.

VI. NEFAZODONE

Nefazodone, an analog of trazodone, was released in 1995 and is structurally and biologically distinct from any of the other new antidepressants. The most common side effects seen in clinical trials with nefazodone were, in descend-

ing order, nausea, somnolence, dry mouth, dizziness, constipation, asthenia and light-headedness, and blurred vision (138). Some 12% of nefazodone- treated patients discontinued treatment, most often due to nausea, asthenia, dizziness, somnolence and light-headedness. Tolerance to nefazodone's side effects typically emerges over the first 6 weeks of treatment. In clinical trials comparing it to fluoxetine, nefazodone caused more dizziness and blurred vision and fewer stimulation effects such as agitation, anxiety, tremor and insomnia. Sexual side effects are unusual with nefazodone and, comparing across studies, are less common than with any other antidepressants (except bupropion and mirtazapine) (42,50). It is typically weight-neutral and, like other new antidepressants, is relatively safe in overdose. In comparison with trazodone, it has not yet been associated with a risk of priapism.

Open clinical experience, however, suggests that nefazodone's capacity to cause fatigue/sedation and dizziness is more problematic than might appear from the clinical trial data. As an example, in direct comparison studies with fluoxetine, nefazodone caused slightly lower rates of somnolence than the SSRI and similar rates of dizziness—observations that differ from the experience of most clinicians (138).

Since nefazodone does not possess anticholinergic activity, dry mouth and constipation are probably caused by alpha1-adrenergic blockade. Some of the dizziness may be similarly mediated, although there seems to be an additional nonorthostatic component to the side effect. The lack of sexual side effects seen with nefazodone is presumed to be due to the postsynaptic 5HT2 blockade reversing the serotonin reuptake blockade-induced sexual dysfunction.

Treatment of side effects caused by nefazodone is empirical. Although its manufacturer recommends a twice-daily dosing schedule, many clinicians prescribe nefazodone in a single nighttime dose to avoid excessive somnolence. Cisapride should probably not be given to treat nausea in nefazodone- treated patients because of a pharmacokinetic interaction that may lead to cardiotoxicity (9). Because the dizziness due to nefazodone is primarily not blood pressure related, its treatment is unknown.

VII. MIRTAZAPINE

The most recently released of the second-generation antidepressants, mirtazapine (Remeron) has been available only since mid-1996, thereby precluding the availability of information on side effects based on open clinical experience. In prerelease studies, the most common side effects were somnolence, occurring

Table 5 Management of Common Side Effects of Newer Antidepressantsa,b

Side Effect	Management Strategies
Stimulation/restlessness/ muscle tension	Slow dose increase, benzodiazepines, propranolol
Insomnia	A.M. dosing, benzodiazepines, zolpidem, trazodone
Nausea	Ingest with food, cisapride
Diarrhea	Acidophilus
Headaches	Sumatriptan (migraines): ?TCAs
Sexual dysfunction	Dopamine agonists, yohimbine, buspirone (see Table 3)
Somnolence	Stimulant
Anticholinergic effects	Sugar-free gum, cholinergic agents, bulk, bethanecol
Serotonin syndrome	? Cyproheptadine, methysergide, propranolol
Withdrawal symptoms	Slow taper, switch to fluoxetine

aWaiting for tolerance, switching agents, and lowering dose are universal general strategies.

bSide effects without specific remedies (i.e., weight gain, bleeding) are not listed here.

in more than half the patients treated; increased appetite and weight gain; and dizziness (139). Somnolence was typically maximal in the first week, with accommodation typically seen over the next month (140,141). Other side effects seen more frequently in mirtazapine-treated patients compared with those who were placebo-treated included dry mouth, nausea, and constipation. Discontinuation of mirtazapine in short-term studies (6 weeks) occurred in 16% of patients, primarily because of somnolence, with nausea the second most common cause. Sexual dysfunction is rare with mirtazapine.

Treatment of these common side effects is empirical and similar to the approach taken when they are caused by other antidepressants. Sedation should be treated by nighttime dosing and adjunctive daytime stimulating medications if needed. Patients should be warned about the potential weight gain and increased appetite with mirtazapine in advance, for preventive reasons.

A rare but serious side effect of mirtazapine—agranulocytosis—was seen in 3 of almost 3000 patients in prerelease studies. All patients recovered. Therefore, patients on mirtazapine should be told to inform their physician

in case of fever, sore throat, or other evidence of a low white cell count, which would necessitate drug discontinuation and close monitoring of the patient.

VII. SUMMARY

Overall, although generally accociated with fewer side effects than the older agents, the newer antidepressants cause adverse events that decrease patient acceptance of the medications. Table 5 summarizes the side effects associated with the newer antidepressants and lists specific management techniques if available. Proper attention to the management of these side effects will enhance compliance and thereby promote greater clinical effectiveness.

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6 Management of Adverse Effects Associated with Mood Stabilizers

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I. INTRODUCTION

Since the reintroduction of lithium in the late 1960s, the treatment of bipolar disorder has been revolutionized. The recent recognition of a wider spectrum of bipolar disorder subtypes (e.g., bipolar II, rapid cycling, mixed states), some of which are less responsive to this agent, as well as a substantial proportion of patients who cannot tolerate this agent, have led to a search for alternative therapies. The most productive line of inquiry has been the study of anticonvulsant-mood stabilizers, including valproate (VPA), carbamazepine (CBZ), and, most recently, lamotrigine and gabapentin. In addition, there is growing evidence that the newer generation of antipsychotics (e.g., clozapine, risperidone, olanzapine) may have distinct mood-stabilizing properties and benefit previously treatment-refractory patients. Finally, electroconvulsive therapy (ECT) is effective for both the manic and depressive phases of bipolar disorder.

As with any drug or somatic therapy, each of these approaches carries the risk of adverse effects, some potentially quite serious. Examples include:

• Thyroid dysregulation with lithium

• Teratogenicity with DVPX, CBZ, and lithium

• Hematotoxicity, such as agranulocytosis with clozapine

• Cognitive disruption with lithium and ECT

• Clinically relevant drug interactions, such as accelerated metabolism with CBZ

Thus, any potential strategy must carefully consider the risk-benefit ratio on an individualized basis, since a given patient may be particularly vulnerable to certain adverse event(s). This chapter considers the potential for adverse effects associated with mood stabilizers. The goal is to help clinicians develop strategies that minimize these risks.

II. LITHIUM—ADVERSE EFFECTS

A. General Description

Lithium has been the standard drug therapy for bipolar disorder over the last 25 years. It is an alkali metal that shares many properties with sodium and potassium as well as other elements of the same chemical group. Adverse effects involving multiple organ systems are common and require careful patient monitoring throughout treatment (1). Mild gastrointestinal upset, fine hand tremor, and muscle weakness may occur transiently during initial therapy, but they usually subside and are generally tolerated. Cognitive dulling and weight gain may be more problematic. Other adverse effects associated with chronic lithium treatment (e.g., thyroid and renal dysfunction, toxic serum levels) can be serious but are usually prevented by vigilant monitoring and appropriate intervention (see Tables 1 and 2).

Table 1 Effects of Lithium Toxicity

Mild Toxicity (1.5–2.0 mEq/L)	Moderate (2.0–2.5 niEq/L)	Severe (> 2.5 mEq/L)
Listlessness	Coarse tremors	Altered consciousness
Nausea	Confusion or delirium	Choreoathetosis
Diarrhea	Ataxia	Seizures
Slurred speech		Coma and death

Table 2 Lithium Drug Interactions

Drugs That May Increase Lithium Levels	Drugs That May Decrease Lithium Levels
NSAIDS: ibuprofen, indomethacin, naproxen	Calicum antagonists: verapamil
Thiazide diuretics: hydrochlorothiazide	Xanthines: caffeine, theophylline
Nonthiazide diuretics: indapamide	Osmotic diuretics: mannitol
Antibiotics: tetracycline	Carbonic anhydrase inhibitors: acetazolamide

B. Renal System

1. Frequency

While clinically significant nephrotoxicity is unlikely, the syndrome of polyuria-polydipsia has been reported to occur in up to 60% of lithium-treated patients. Diabetes insipidus occurs in 12 to 20% of patients treated with lithium and can cause 24-hr urine excretion volumes exceeding 3000 mL (2). Indeed, some patients' urine loss may exceed 7000 mL/day (3). Excessive urine loss of this magnitude may lead to dehydration, with the subsequent possibility of lithium toxicity. While this disorder is usually not serious, quality of life may be substantially compromised, often leading to noncompliance with treatment. Other agents that may be used concurrently and are implicated in this syndrome include interferon A, clomipramine, and risperidone.

2. Mechanism

Since lithium is eliminated by the kidneys, adequate renal functioning is required to avoid toxicity. Since most of the filtered load of lithium is reabsorbed in the proximal renal tubules, much like sodium, lithium retention is increased during states of sodium depletion. As a result, it is important for patients to be adequately hydrated prior to initiation of lithium therapy and throughout their treatment course. Lithium is also the most common cause of nephrogenic diabetes insipidus, which results from the drug's inhibitory effects on the cAMP-dependent action of antidiuretic hormone (ADH) on renal distal tubules (4).

The half-life of lithium is affected by a patient's age and renal function (as reflected by creatinine clearance). In the elderly or uremic patient, the half-

life may be as long as 36 hr, while it is normally 18 to 20 hr in young, healthy adults. Even though acute renal failure is a contraindication to the use of lithium, this agent may be used in stable and carefully monitored chronic renal failure. It is important to note that lithium at nontoxic levels, even administered over long periods, does not appear to result in significant renal dysfunction (5). Documented histopathological changes (such as sclerotic glomeruli and atrophic tubules) have been found in only a small percentage of lithium-treated patients, and most of these changes were associated with prior episodes of lithium toxicity (6).

3. Management

Lithium-induced diabetes insipidus does not respond to vasopressin, but several other treatment possibilities exist when this problem is significant. Potassium supplementation (10 to 20 mEq/L per day) may reduce polyuria. Hydrochlorothiazide (HCTZ) and other thiazide diuretics have been used successfully for many years, but they do not directly counter lithium's effects on ADH. The use of thiazide diuretics can also cause hypokalemia and impaired lithium excretion, which may result in the added risk of lithium toxicity and cardiac arrythmias. Lithium and potassium levels require regular monitoring with the use of these medications.

Amiloride, a potassium-sparing diuretic, interferes directly with lithium- induced ADH inhibition by blocking the entrance of lithium into ADH-sensitive cells. Hypokalemia is avoided and urine output usually diminishes within the first week of treatment (7). The dosage required is from 10 to 20 mg/ day, while higher doses appear to bring no added benefit (8). In patients not adequately responding to amiloride monotherapy, HCTZ may be added in a daily dose of 50 mg.

Indomethacin (e.g., 50 mg PO tid) and other prostaglandin inhibitors may also be used acutely to treat nephrogenic diabetes insipidus for immediate reduction of polyuria (9). Because of the adverse side effects associated with regular indomethacin use and because prostaglandin inhibitors can result in increased reabsorption of sodium and lithium in the kidney, this medication should only be used when other treatment modalities have failed. Finally, serum lithium levels <0.75 mEq/L are associated with less polyuria; and the use of the slightly lower levels when adequate to maintain the patient's mood may avoid the need for other medications.

Administration of lithium in a single daily dose, which allows renal structures a ‘‘recovery time’’ during trough serum levels, may minimize damage to renal structure and function. It is also advisable to reduce maintenance

lithium to the lowest effective dose and blood levels as well as to avoid concomitant use of antipsychotics. In summary:

• Renal complications are common but not usually serious.

• Polyuria/polydipsia may compromise quality of life and compliance.

• Amiloride and indomethacin are the most effective therapies for polyuria/polydipsia and SIADH, respectively.

C. Neurological System

1. Frequency

Possible central nervous system (CNS) adverse effects of lithium have not been well delineated, but one investigation reported that patients taken off lithium improved significantly in 9 out of 10 measures of cognition, creativity, and fine motor skills (10). In addition, tremors frequently occur; they may be present at rest or during movements and may be unrelated to serum drug concentration.

2. Mechanism

CNS adverse effects are often the result of toxic serum levels, which may result from accidental or intentional patient ingestion of lithium doses exceeding clinical needs (see Table 1). Patients with organic brain impairment are also at increased risk of neurotoxicity. Toxicity may also be caused by reduced clearance of lithium from the body, resulting from dehydration, sodium depletion, the concomitant use of diuretics and nonsteroidal anti- inflammatory drugs (NSAIDs), or renal disorders. An electroencephalogram (EEG) during toxic states may show diffuse slow waves in the range of 5 to 7 cps. The severity of acute lithium toxicity, (e.g., with an overdose) can be assessed by the level of neurological impairment (see Table 1). The basis for neurotoxicity when lithium was combined with such therapies as haloperidol, verapamil, and ECT is uncertain. Thus, it would be preferable to avoid such combinations; when necessary, however, the lowest effective dose of any agent should be utilized.

3. Management

Since no antidote is available, treatment is supportive. A patient's condition should be monitored closely, including fluid intake and output, mental status, and serum levels of lithium, creatinine (Cr), and electrolytes. Patients with

normal renal function should be able to clear lithium unassisted. If necessary, attempts should be made to remove excess lithium from the body by gastric lavage and emesis. Hemodialysis or peritoneal dialysis may be necessary when serum levels are > 2.5 mEq/L (11). Tremor can usually be controlled satisfactorily with beta blockers such as propranolol (120 to 240 mg/day in divided doses) or metoprolol (100 to 200 mg/day in divided doses) (12). Metoprolol may be preferred for patients with bronchospastic disease. In summary:

• Cognitive effects and tremor are common.

• Neurotoxicity occurs with excessive doses/levels.

• Treatment may involve supportive measures, dialysis, and beta blockers for tremors.

D. Gastrointestinal System

1. Frequency

Gastrointestinal upset-including nausea, vomiting, diarrhea and anorexiaoften occurs transiently early in the course of lithium therapy and may recur if toxic levels are experienced.

2. Management

Nausea usually appears shortly after dose ingestion and may be minimized by taking the medication with meals. Sustained-release preparations may also reduce nausea and vomiting but can result in diarrhea due to local irritation of the bowel wall by unabsorbed drug.

E. Endocrine System

1. Frequency

Clinical hypothyroidism develops in approximately 5% of lithium-treated patients, while 3% develop a benign, diffuse nontoxic goiter (13). Mild increases in TSH may be found in up to 23% of patients. Those at greater risk include:

• The elderly

• Females

• Those with a prior history of thyroid disease

• Patients taking other medications that may interfere with thyroid function

Other agents that may be taken concurrently and could interfere with thyroid function include CBZ, phenytoin, and ketoconazole.

2. Mechanism

Lithium has multiple antithyroid effects but acts primarily by preventing the release of thyroid hormones (such as thyroxine), inhibiting the uptake of iodine into the thyroid gland, and decreasing tyrosine iodination (14). The development of goiter appears to be more common in patients who have been on lithium for many years, and the risk is increased for those who smoke (15).

3. Management

Baseline thyroid function studies (including TSH, T3, and T4), should be obtained before initiation of lithium and on a regular basis every 6 to 12 months during maintenance therapy. The earliest indication of thyroid dysfunction may be mild increases in TSH. The immediate initiation of thyroid supplementation can prevent the subsequent development of significant hypothyroidism or goiter. Patients should also be monitored for clinical evidence of hypothyroidism such as recurrent, resistant mood instability; cold intolerance; weight gain; changes in hair texture and quantity; or constipation.

If lithium therapy must be continued in the presence of symptoms of hypothyroidism, supplementation should be initiated with T3 (liothyroxine, with a starting dose of 25 μg each day) or T4 (levothyroxine, with a starting dose of 50 μg each day). Doses may be gradually increased every few weeks until the patient is euthyroid. When necessary, stopping lithium and switching to another mood-stabilizing agent will usually result in prompt reversal of hypothyroidism. In summary:

• Thyroid dysfunction is common with lithium therapy.

• Routine monitoring of TFTs is necessary.

• Thyroid supplementation is appropriate if clinically significant complications occur.

Weight gain is also common with lithium. On average, patients will gain about 9 lb during therapy with this agent, but larger gains often occur, especially when this agent is combined with antidepressants and/or antipsychotics. Since this problem can occur with the three most commonly used mood stabilizers, an aggressive weight-management program should always be started at the initiation of treatment.

F. Cardiovascular System

1. Frequency

Lithium therapy seldom causes clinically significant adverse cardiovascular effects except when underlying cardiac disease is present. Common effects seen on the electrocardiogram (ECG) include t-wave flattening or inversion; u waves; and conduction delays such as first-degree AV block (16).

2. Mechanism

Since lithium affects sinus node function, bradycardia is also common. One study found that 78% of patients on lithium for more than 12 months had heart rates of less than 50 beats per minute (17). Although sinus node depression is generally mild, lithium is contraindicated in patients with sick sinus syndrome.

3. Management

Baseline ECGs should be obtained in the very young, the elderly, and those with pre-existing cardiac conditions. Special consideration should also be given to potential adverse drug interactions between lithium and concurrently prescribed cardiovascular medications. As noted earlier, certain diuretics may cause increased lithium reabsorption in the kidney, resulting in higher serum concentrations. Thus, more frequent monitoring of lithium levels and the use of lower doses will be required. Methyldopa and enalapril also tend to increase blood levels of lithium. Conversely, verapamil has been reported to lower serum lithium levels, and higher doses may be needed if regular monitoring reveals subtherapeutic plasma levels. In addition, as noted earlier, some cases of neurotoxicity have been reported with this combination (18). Since beta blockers do not interact with lithium, they may be the preferred treatment of hypertension in these patients.

G. Dermatological Effects

A variety of skin reactions have been reported, usually early in the course of lithium therapy. The most common problems are associated with exacerbations of psoriasis and acneiform eruptions. Possible mechanisms have included lithium's ability to decrease cAMP as well as to increase the number and activity of polymorphonuclear leukocytes. It appears that the patients most at risk for this complication are those with a predisposition to skin disorders. In addition, females are more likely than males to experience a dermatological reaction to lithium. These problems may clear spontaneously with lithium dose

reduction, with appropriate dermatological therapy, or only when lithium is discontinued.

H. Pregnancy

1. Frequency

Lithium crosses the placenta and has been associated with an increased incidence of fetal malformations, particularly involving the cardiovascular system. Cases of Ebstein's anomaly, a rare (i.e., 1 in 20,000) defect in which the tricuspid valve is displaced into the right ventricle, have been reported. A prospective study reported in 1992, however, found no overall difference in teratogenesis between pregnant bipolar women on lithium in the first trimester and a matched control group (19). The use of lithium near term may result in toxicity in newborns. Nursing may be a problem, because lithium appears in breast milk at levels one-third to two-thirds of the mother's serum levels, and the effects of lithium on infant development are unknown (20).

2. Management

The decision to maintain patients on this agent during pregnancy is complicated and must take into consideration the ravages of an exacerbation of bipolar disorder on both mother and fetus. Until the issue is resolved, it would be ideal to avoid lithium therapy, at least during the first trimester of pregnancy, when critical organogenesis is occurring; but this may not always be possible.

If lithium is continued during pregnancy, the serum level will need to be carefully monitored. The increase of 50 to 100% in glomerular filtration rate that normally occurs in the third trimester of pregnancy will proportionally increase lithium clearance, and the dosage may need to be increased to maintain desired therapeutic serum levels (21). Since the glomerular filtration rate (GFR) and lithium clearance quickly return to normal after delivery, it may be wise to stop lithium 2 or 3 days prior to delivery and restart a few days postpartum at a lower dose. In summary:

- Lithium carries a low-risk of teratogenicity.

- A woman's changing physiology during pregnancy may alter lithium levels.

- Breast-feeding should be avoided by patients taking lithium.

I. Drug Interactions

There are several clinically significant drug interactions with lithium (see Table 2). Mention has already been made of the possible cardiovascular and neurological effects of concomitant lithium use with various medications. Diuretics, such as thiazides, that act on the distal tubule do not affect lithium directly but increase sodium clearance, which, in turn, causes a compensatory increase in the proximal tubule's reabsorption of sodium and lithium. Anti- inflammatory agents, through inhibition of prostaglandin E2, also cause increased reabsorption of sodium and lithium. Since the most significant problems have been reported with indomethacin, this agent should be avoided. Acetaminophen and aspirin have little interaction with lithium and may be appropriate alternatives.

III. ANTICONVULSANTS—ADVERSE EFFECTS

A. General Description

Certain anticonvulsants have proven efficacious in the treatment of bipolar disorder. While these medications tend to share many common side effects, other adverse effects are drug-specific. Rarely, these side effects may be life- threatening, but all may contribute to patient noncompliance and treatment failure. Gastrointestinal discomfort, sedation, dizziness, and incoordination often occur with the initiation of therapy and may be minimized or avoided by starting at low doses and increasing them slowly. Other more serious side effects—such as hepatotoxicity, hematopoietic suppression, and severe skin reactions—may occur at any time and are more specifically linked to a particular medication. Before initiating therapy, baseline laboratory tests should be obtained, particularly a complete blood count with differential, electrolyte panels, and liver function tests. Results may help in choice of treatment agent and warn the physician of areas that may require more careful monitoring.

B. Valproate (VPA)

1. General Description

VPA is available in various formulations, including divalproex sodium (i.e., a compound comprising sodium valproate and valproic acid), dipropylacetic acid, and a closely related form, valpromide or dipropylacetamide. Reports on its benefit for the management of mood disorders date back to the mid-

1960s. Recently, the divalproex formulation became the first drug since lithium to receive FDA approval for the treatment of acute mania.

VPA's anticonvulsant and perhaps mood-stabilizing efficacy may be related to its putative ability to increase CNS levels of gamma-aminobutyric acid (GABA). Due to its rapid absorption, blood levels peak in 1 to 4 hr after oral administration, and the half-life ranges from 6 to 16 hr. It is metabolized primarily through the liver and is eliminated in the urine. Therapeutic concentrations for mood stabilization appear to be between 45 to 125 μg/mL (22). Adverse effects of most concern involve the hepatic system and there is a potential for teratogenicity.

2. Neurological System

a. Frequency. Sedation often occurs early in treatment but generally subsides over time. Hand tremor is common; it is present at rest and worsened by action or positioning. Tremor usually appears early (within the first month) in treatment and seems to be dose-related.

b. Management. Tremor may be prevented by using the lowest possible dose; the sprinkle formulation, which minimizes fluctuation between peak and trough serum levels; or adding a beta blocker such as propranolol or metoprolol (see also Chap. 11). The use of beta blockers reduces the amplitude of tremors without affecting their frequency. Unfortunately, only about 50 to 70% of patients will experience full symptomatic control, and prolonged use may cause significant side effects such as fatigue, weight gain, diarrhea, impotence, and depression (23). The average daily dose of propranolol needed to control symptoms is 120 to 240 mg in divided doses, although doses up to 320 mg/day have been required (24). Doses of 100 to 200 mg/day of metoprolol are generally needed. Although beta-blocker therapy is usually well tolerated, relative contraindications to their use include heart failure, second-or third-degree atrioventricular block, asthma, and insulin-dependent diabetes mellitus.

Alprazolam, a short-acting and minimally sedating benzodiazepine, has also been found to relieve tremor at doses of 0.75 to 3 mg/day (25). Because chronic use can lead to habituation or dependence, alprazolam is best used episodically for patients who require only intermittent tremor reduction to prevent social embarrassment or occupational interference. Methazolamide, a carbonic anhydrase inhibitor, has been reported to reduce hand tremor (at doses of 50 to 300 mg/day) in several open studies (26,27). A recent controlled trial, however, could not confirm the efficacy of this agent in the treatment of tremor

but did report that side effects such as paresthesias, sedation, headache, and gastrointestinal symptoms were common (28).

2. Hepatic System

a. Frequency. VPA is metabolized in the liver and may cause mild, transient elevations in serum transaminases and LDH. These usually appear early in therapy, are dose-dependent, and resolve spontaneously. Laboratory abnormalities may be noted in 20 to 40% of patients and do not predispose to the development of more serious hepatic injury. VPA can also interfere with the conversion of ammonia to urea and result in hyperammonemia in approximately 20% of patients. This is usually asymptomatic but infrequently causes lethargy (29).

Serious hepatotoxicity is possible but rare. Hepatic failure occurs in only 1 in 40,000 cases and appears to be an idiosyncratic reaction that is not dose- related. Children under the age of 2, especially those receiving anticonvulsant polypharmacy, who suffer from mental retardation and/or poor nutritional status have been shown to be at greatest risk (30,31). To our knowledge, no cases of hepatic failure have been reported in adults with bipolar disorder who were receiving VPA monotherapy, but liver failure has been reported in older children and in a mentally retarded adult with epilepsy taking valproate alone (32).

b. Management. The appearance of laboratory abnormalities does not require cessation of treatment; however, if enzyme levels do not stabilize or return to normal, VPA should be discontinued and an alternate mood-stabilizing agent such as lithium (or perhaps gabapentin) used in its place. Liver function tests should be monitored more often during the first several weeks of therapy and every 6 to 12 months afterwards. Routine liver function testing probably does not significantly prevent the occurrence of these unpredictable drug effects. Therefore, patients should be cautioned to immediately report symptoms of possible early hepatotoxicity such as easy bruising, decreased appetite, malaise, jaundice, and periorbital or dependent edema. In summary:

• Elevation of liver enzymes is common.

• Serious hepatotoxicity is rare.

• Patients should be educated about early symptoms so as to detect hepatotoxicity as quickly as possible.

3. Hematological System

Thrombocytopenia is common but rarely causes clinically significant complications (39).

4. Gastrointestinal System

a. Frequency. Nausea, appetite loss, and vomiting are less common with the enteric coated formulation (divalproex); when they do occur, they may be diminished by taking medication with food (33). Pancreatitis is rare but should be ruled out in patients complaining of unremitting abdominal pain and vomiting. Elevated serum amylase levels are usually diagnostic.

Weight gain, which may be substantial, has been reported variably in 7 to 57% of patients and may lead to noncompliance with therapy.

b. Management. Patients should be warned about this before starting VPA and, as with the other primary mood stabilizers, be advised to initiate a weight-management program at the beginning of treatment, since there are no specific remedies other than discontinuing the drug.

5. Dermatological System

Alopecia may occur in up to 4% of patients, is usually transient, and may be minimized by the use of vitamins containing selenium (50 µg/day) and zinc sulfate (50 mg/day).

6. Pregnancy

VPA is potentially teratogenic. Some 1 to 2% of fetuses exposed to this agent during the first trimester have developed neural tube defects and 1 % spina bifida.

a. Management. Women of childbearing years should use appropriate contraception if treatment with VPA is begun, as well as folate (1 mg/ day). If pregnancy does occur during treatment, this agent should be discontinued and ultrasonography utilized for monitoring of fetal development (34).

7. Toxicity

In an acute overdose, coma and death may occur. Hemodialysis, hemoperfusion, and naloxone may be used following attempts to remove any remaining tablets with gastric lavage (35,36).

8. Drug Interactions

a. Mechanism. Drug interactions involving VPA occur primarily through its effects on protein-binding capacity and on drug metabolism. VPA is more than 90% protein-bound and can compete for the same binding sites as other highly protein bound drugs such as aspirin and phenytoin. Free serum

concentrations of displaced drugs will be increased, and since the unbound fraction is pharmacologically active, drug toxicity may result even when total serum levels appear within the accepted range. Thus, when VPA is used concomitantly with other drugs (e.g., CBZ) that also have significant protein binding, it would be helpful to measure free drug levels and adjust dosages accordingly.

VPA is a nonspecific, weak inhibitor of CYP-450 enzymatic metabolism. Thus, serum levels of other hepatically metabolized drugs through this system may be increased because of their decreased clearance. In particular, concomitant use of VPA and diazepam, ethosuximide, and phenobarbital may result in increased serum levels of these drugs. VPA may also cause an elevation in serum levels of CBZ's active epoxide (and possibly toxic) metabolite by inhibiting its breakdown (37).

C. Carbamazepine (CBZ)

1. General Description

CBZ has a molecular structure similar to that of the tricyclic antidepressant imipramine and is primarily metabolized by the liver. Like lithium, it has a narrow therapeutic index and can cause toxicity at excessive serum levels. Unfortunately, the optimal level of CBZ for treatment of mania is unknown and careful titration of dose to clinical symptoms must be performed. In the treatment of epileptic seizures, the optimal range is between 4 to 12 μg/mL; levels greater than 15 μg/mL in children or 20 μg/mL in adults are considered toxic. Like most anticonvulsants, CBZ may cause adverse side effects involving multiple organ systems.

2. Neurological System

Various CNS adverse effects have reported with CBZ and include sedation, dizziness, ataxia/clumsiness, blurred vision/diplopia, and impaired task performance. Although uncommon, fatal CBZ toxicity does occur. CBZ overdose is characterized by neurological symptoms such as diplopia, dysarthria, ataxia, vertigo, nystagmus, and coma. Infrequently, cyclic coma with biphasic fluctuations of consciousness, seizures, respiratory depression, cardiac conduction defects, and the need for artificial ventilation may occur. Plasma levels are only moderately correlated to severity, but as noted earlier, over 15 μg/mL in children or 20 μg/mL in adults should be considered serious. Charcoal hemoperfusion, or gastric lavage with activated charcoal have been used in such cases, while benefit from plasmapheresis is controversial.

3. Hepatic System

a. Frequency. Carbamazepine commonly causes a mild, transient elevation of serum transaminases as well as alkaline phosphatase. These elevations rarely exceed 1.5 times normal levels and usually subside with continued treatment. They may, however, become problematic if liver function tests increase to more than two to three times normal levels. While significant hepatotoxicity seldom results even with prolonged CBZ therapy, a clinical syndrome resembling a mild viral hepatitis may occur; this usually improves after discontinuation of the medication.

b. Management. Because it is metabolized in the liver, carbamazepine is contraindicated in patients with hepatic dysfunction, and baseline liver function tests (LFTs) should be obtained prior to initiation of therapy. It is recommended that LFTs be monitored regularly every 6 to 12 months during treatment. Prolonged LFT abnormalities should lead to a withdrawal of CBZ.

4. Hematological System

a. Frequency. Leukopenia, defined as a white blood cell count less than 3000/mm3, occurs in up to 10% of patients treated with CBZ; it is usually benign and self-limited and tends to appear within the first month of treatment (38).

Serious hematopoietic suppression can occur, however, and CBZ is contraindicated in patients with a prior history of bone marrow suppression or adverse hematological reactions. Aplastic anemia may occur in 1 out of 125,000 cases with hypocellularity of the bone marrow and reduction of all formed blood elements. Agranulocytosis may also rarely occur. Of some comfort, Tohen et al. recently reported no serious hematological dyscrasias in over 2000 patients receiving either CBZ or VPA (39).

b. Management. These reactions usually appear during the first 6 months of therapy, but they may occur at any time and require regular monitoring of hematologic parameters. Patients without clinical evidence of impaired hematological function may safely tolerate moderate decreases in white blood cell (WBC) counts. Guidelines have been proposed that recommend discontinuation of CBZ when total WBC counts decrease below 3000/mm3 or the neutrophil count decreases below 1500/mm3 (40).

Since the onset of bone marrow suppression may be insidious, it is prudent to instruct patients to monitor themselves for the appearance of fever, malaise, sore throat, petechiae, or other evidence of possible hematological dysfunction rather than simply relying on laboratory surveillance. In cases

of suspected bone marrow involvement, medication should be discontinued immediately and medical intervention sought promptly. For these responses, we would discourage the combined use of CBZ and clozapine.

5. Dermatological System

a. Frequency. Rashes induced by CBZ are usually morbilliform, occur within the first 6 weeks of therapy, and may be accompanied by intense pruritus. Rashes occur in approximately 10% of patients and generally do not require cessation of therapy. The involvement of the mucous membranes or the appearance of fever or other constitutional symptoms may indicate the development of Stevens-Johnson or Lyell syndrome. These rare, but potentially life-threatening syndromes, occur in fewer than 1 out of 50,000 patients and require immediate cessation of carbamazepine and the appropriate level of medical intervention.

6. Cardiovascular System

a. Frequency. In rare instances, CBZ can result in depression of atrioventricular conduction and ventricular automaticity. This is caused by the innate membrane-depressant effects of CBZ, which are similar to those of quinidine and procainamide (41). Thus, patients with preexisting atrioventricular conduction disturbances should avoid therapy with CBZ when possible.

More commonly, CBZ may cause hyponatremia; it should therefore be used cautiously in patients who are on a salt-restricted diet (42). Hyponatremia is rarely significant unless sodium values are less than 125 mmol/L. Low sodium levels as well as concomitant diuretic use may also render patients more susceptible to the development of the syndrome of inappropriate antidiuretic hormone (SIADH). CBZ enhances the effects of antidiuretic hormone, and this may lead to impaired clearance of free water from the body. Again, older patients are at higher risk for this rare side effect and should be closely monitored.

b. Management. CBZ should be avoided by salt-restricted and elderly patients as well as those taking other medications that may predispose to development of hyponatremia, such as diuretics or lithium. Mild cases may be managed by reducing the dose of CBZ, while more severe cases require switching to another medication.

7. Pregnancy

CBZ has been linked to an increased development of craniofacial defects, spina bifida, and developmental delay in children whose mothers received this agent while pregnant.

a. Management. Due to the possibility of teratogenic effects, women of childbearing age should avoid use of CBZ. If that is not practical, contraception should be diligently used to avoid accidental pregnancy. It is also important to adjust the dose of oral contraceptive hormonal drugs since CBZ may increase their metabolism, thus compromising their effectiveness.

8. Toxicity

a. Description. Acute CBZ overdose can result in multiple neurological signs and symptoms. The appearance of diplopia may be a useful clinical indicator of developing toxicity. The severity of symptoms is not necessarily correlated with plasma drug levels, but life-threatening seizures and coma usually do not occur until blood levels exceed 20 to 25 μg/mL. Lower serum levels may be associated with drowsiness, ataxia, blurred vision, dysarthria, choreiform movements, or behavioral changes (43,44).

b. Management. Severe cases may require the use of gastric lavage, hemoperfusion, and plasmapheresis (45).

9. Drug Interactions

a. Mechanism. CBZ is a potent stimulator of CYP-450 microsomal enzymes and can cause decreased serum levels of other medications metabolized by this system. Since this may reduce their effectiveness, dosage levels of these medications may need to be increased accordingly (46). In turn, blood levels of carbamazepine may be influenced by other hepatically metabolized drugs. In particular, VPA, isonicotine hydrazine, and erythromycin may increase serum levels, while phenytoin and primidone can lower them. Table 3 summarizes interactions between CBZ and other medications that may be clinically significant.

Of particular clinical importance are CBZ-induced decreases in serum levels of oral contraceptives, theophylline, warfarin, and antipsychotics (47,48). As noted above, oral contraceptive (OC) failure may lead to accidental pregnancy and exposure of a developing fetus to the potentially teratogenic properties of CBZ (49).

Table 3 Carbamazepine Drug Interactions

Drugs Decreased by CBZ	Drugs Increasing CBZ	Drugs Decreasing CBZ
Haloperidol	Verapamil	Phenytoin
Oral contraceptives	Imipramine	Barbiturates
Theophylline	Erythromycin	Primidone
Warfarin	Fluoxetine	Folic acid
Folic acid	Isoniazid	
Doxycycline	Nicotinamide	
	Cimetidine	
	Diltiazem	

b. Management. OC levels should be closely monitored and patients should be warned to notify their physicians of spotting, which may indicate OC failure. Close monitoring of prothrombin time and the International Normalized Ratio (INR) is recommended when patients are using warfarin and carbamazepine concomitantly. Patients stabilized on haloperidol (or perhaps other antipsychotics) may demonstrate worsening of their symptoms when CBZ is added, necessitating an increase in the antipsychotic dose (50,51). Conversely, when CBZ is discontinued, the doses of these other agents may need to be lowered to avoid toxicity. In summary:

• CBZ is a potent inducer of the CYP-450 enzyme system.

• Other drugs that are substrates of this system should be monitored for the possibility of subtherapeutic levels.

• CBZ may also accelerate its own metabolism, so that dose adjustments may be required to compensate.

D. Newer Anticonvulsants

Preliminary reports indicate that gabapentin and lamotrigine may also possess mood-stabilizing properties, although this has not been confirmed. As with other anticonvulsants, these agents may cause gastric upset, drowsiness, and mild neurological symptoms. Rash may occur early in treatment with either agent, although the risk is greater with lamotrigine and is dose-related (52). Rare dermatological emergencies, such as the occurrence of Stevens-Johnson or Lyell's syndrome, are associated with the use of any anticonvulsant but are

more frequent in patients treated concurrently with lamotrigine and VPA (53). This is probably due to the inhibitory action of VPA on lamotrigine metabolism, but the exact mechanism is unknown. Therefore, this combination should usually be avoided.

All anticonvulsants should be considered potentially teratogenic and be used with caution in women of childbearing age, although gabapentin may be safer than the other agents. Neither gabapentin nor lamotrigine exhibit significant protein binding, nor do they affect hepatic metabolism, thus minimizing the potential of adverse drug interactions with other agents. Since gabapentin has 100% renal elimination, it should be avoided in patients with compromised renal function, but it may be appropriate for those with hepatic dysfunction.

IV. OTHER THERAPIES

A. Verapamil

Calcium channel blockers, used primarily in the treatment of cardiovascular disorders, have been proposed as a possible treatment for bipolar disorder because of certain biochemical properties they share with lithium (such as inhibition of TSH release, blocking of adenylate cyclase activity, and competition with calcium ions in neuromuscular cells). Their efficacy, however, has not yet been proven (54). The most common adverse effects are hypotension and bradycardia, which can usually be easily managed. Drug interactions, however, may be significant. In particular, increased blood levels of CBZ may result when it is used concomitantly with verapamil, and dosage must be adjusted accordingly. As noted earlier, the concurrent use of lithium and verapamil may increase the risk of neurotoxicity.

B. Atypical Antipsychotics

Conventional neuroleptics have frequently been used as adjuncts in the treatment of bipolar disorder and were the treatment of choice for acute mania prior to the introduction of lithium (1). Their nonspecific mood-stabilizing properties, undesirable side effects, and adverse drug interactions, however, limit their usefulness. Preliminary reports indicate that the new generation of novel antipsychotics (e.g. clozapine, risperidone, olanzapine) may possess mood-stabilizing properties separate and distinct from their antipsychotic effects (55,56). Their associated side effects and management are discussed in Chapter 2. While these agents are generally more benign than the conventional

neuroleptics, the life-threatening risk associated with clozapine-induced agranulocytosis must always be considered.

C. Electroconvulsive Therapy (ECT)

ECT has proven to be effective for both the manic and depressed phases of bipolar disorder (1). If a patient is in immediate danger, has previously responded to ECT, or there are medical contraindications to pharmacotherapy, this treatment may be the preferred choice. Complications of ECT can involve cognitive, cardiovascular, and a variety of other adverse events (e.g., prolonged seizures, headache, muscle aches).

1. Cognitive Effects

a. Frequency. Memory disturbances are common and typically include anterograde amnesia (i.e., the inability to recall newly learned material) and retrograde amnesia (i.e., the inability to recall previously learned material). Both types can present as deficits in either the dominant or nondominant cerebral hemispheres with verbal and nonverbal amnesias. These cognitive effects may be more severe with bitemporal electrode placement and could preclude an adequate trial. This is particularly true for older patients, who may develop an organic delirium. Overall, memory deficits are time-limited, rarely disabling, and outweighed by the benefits of treatment.

b. Management. Strategies to circumvent this problem include increasing time between treatments, switching from bilateral (BILAT) to unilateral, nondominant (UND) electrode placement (although there is some evidence that UND-ECT may not be effective for the manic phase), or adding low-dose, high-potency antipsychotics to manage organic delirium.

2. Cardiovascular System

a. Frequency. The mortality rate per course of ECT treatments is in the range of 3 deaths per 10,000 patients. Arrhythmias and cardiac arrest (usually due to asystole) may occur secondary to the combination of seizure activity and anesthetic agents (57). Transient rises in blood pressure and heart rate also occur with seizures and may be influenced by pretreatment of hypertension or tachycardia.

b. Management. Medical clearance should be obtained for high-risk patients. ECG at baseline and monitoring during treatment are required. Emergency equipment, including a defibrillator, is also necessary. In the event of

Table 4 Valproic Acid Drug Interactions

Drugs Increased by VPA	Drugs Increasing VPA	Drugs Decreasing VPA
Zidovudine	Phenytoin (free levels)	Phenobarbital
Diazepam	Aspirin	Rifampin
Ethosuximide	Felbamate	Carbamazepine
Lamotrigine		Phenytoin (total levels)
Phenobarbital		
Phenytoin (free levels)		
Tolbutamide		
Warfarin		

a serious arrhythmia or cardiac arrest, the attending anesthesiologist should direct the appropriate resuscitative procedures. In addition, ECT personnel should be trained in cardiopulmonary resuscitation techniques and the management of other cardiac emergencies. Electrolyte levels should be checked frequently, especially in patients on diuretics or digitalis (58).

3. Other Effects

Prolonged seizures, lasting more than 120 to 180 sec, may occur. This may require continued oxygenation, control of ventilation, and an intravenous bolus of the anesthetic agent or diazepam to abort the seizure. Patients may complain of headaches, muscle aches, and nausea, which are best treated symptomatically. Anxiolytics may be needed to control pretreatment anticipatory anxiety, but type and dose must be carefully chosen to avoid increasing the seizure threshold.

V. CONCLUSION

Adverse side effects are an important factor in the choice of any drug, including a mood stabilizer. Thus, treatment failure may result from patient noncompliance due to intolerance of these effects rather than from lack of medication efficacy. In addition, prior to initiating therapy with any agent, baseline laboratory tests such as hemogram, renal, thyroid, and hepatic panels should be obtained. The results of these tests should be taken into account in choosing a specific agent as well as in helping to focus on those systems that require closer monitoring during therapy. Many common, less serious side effects may

be minimized or avoided altogether by the simple strategy of initiating therapy with low doses, which are increased slowly as needed. Serious, life-threatening side effects are rare and are usually associated with the hepatic, hematopoetic, or thyroid systems or with pregnancy.

Although lithium has been the mainstay of therapy for bipolar disorder, it has numerous drawbacks. As a result, alternative treatments are currently available that may prove particularly beneficial in certain patient populations, including:

- Those who cannot tolerate lithium's side effects
- Those who have medical contraindications to lithium treatment (e.g., psoriasis, electrolyte imbalance, sick sinus syndrome, or preexisting renal disease)
- Those who experience an insufficient response to lithium therapy (e.g., rapid cyclers, patients with severe manic or mixed states, the elderly, or those with associated substance abuse).

VPA and CBZ have been the most utilized alternatives, but other anticonvulsants (e.g., lamotrigine, gabapentin) may also prove to be useful. While these new agents provide clinicians with a greatly expanded selection in the pharmacotherapy of bipolar disorder, they also necessitate a careful choice of the most appropriate agent for a given patient to minimize potential adverse effects or drug interactions.

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7 Management of Adverse Effects of Anxiolytics

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I. INTRODUCTION

The classes of psychopharmacological agents currently utilized in the treatment of anxiety disorders include tricyclic antidepressants (TCAs), serotonin- selective reuptake inhibitors (SSRIs), monamine oxidase inhibitors (MAOIs), benzodiazepines, and buspirone (Buspar). Although many of the newer agents used for the treatment of anxiety are associated with substantially fewer and less bothersome adverse effects than the older agents (TCAs, MAOIs), there are still unwanted effects associated with treatment. Assessment and treatment of the unwanted effects of the TCAs, SSRIs, and MAOIs are dealt with elsewhere in this volume. This chapter discusses clinical approaches to management of the side effects of the benzodiazepines and buspirone.

II. BENZODIAZEPINES

The benzodiazepines are widely used because of their effectiveness and relative safety. However, clinically significant adverse effects often occur in patients receiving these agents. The most significant of these side effects are sedation, impaired anterograde memory, slowed cognitive function, impaired motor performance, and behavioral disinhibition. In general, these adverse effects are not disabling, appear to be dose-dependent, and tend to diminish with long-term use. Tolerance appears to develop at different rates for different benzodiazepine-related side effects. For example, tolerance to the sedative and motor effects appears to develop most rapidly, often within a week or two (1), while tolerance to impairment in memory and cognitive function may never develop (2). Fortunately, tolerance to the anxiolytic effects of the benzodiazepines appears to occur very rarely; if it occurs at all, it develops very slowly.

A. Buspirone

Buspirone is a novel, nonbenzodiazepine anxiolytic that is not active at the gamma-aminobutyric acid (GABA)-benzodiazepine receptor complex and does not cross-react with the benzodiazepines. Buspirone does not cause sedation, amnesia, or cognitive impairment. The adverse side effects most often leading to discontinuation of buspirone treatment in clinical trials include dizziness, nervousness, nausea, and headache. Buspirone does not produce physical dependence and has no abuse potential. At present, it has received FDA approval for the treatment of generalized anxiety disorder (GAD). In addition, several case reports suggest that buspirone may also be useful in conjunction with the SSRIs to augment their antidepressant effects (3,4). Also, buspirone has been reported to be useful in reducing or reversing adverse sexual effects associated with the SSRIs.

Table 1 lists the reported adverse effects of the benzodiazepines and buspirone, including some that are very rarely observed. As mentioned above, drowsiness, fatigue, ataxia, and dizziness are the most commonly observed adverse effects of the benzodiazepines.

B. Management of Benzodiazepine Adverse Effects

The principal strategies for managing side effects of the benzodiazepines involve choosing the most appropriate agent and lowest effective dose. The

Table 1 Adverse Effects of the Benzodiazepines and Buspirone

Effect	Benzodiazepines	Buspirone
1. CNS effects		
Agitation	+	+
Amnesia	+	–
Anger attacks	+	+
Ataxia	+ +	+
Blurred vision	+	+
Confusion	+	+
Depression	+	+
Dizziness	+ +	+ +
Diplopia	+	–
Drowsiness	+++	–
Headache	+	+ +
Incoordination	+	–
Insomnia	+	+
Mania	+	+
Muscle spasms	+	+
Nightmares	+	+
Numbness	–	+
Paresthesias	–	+
Stuttering	+	–
Tinnitus	–	+
Tremor	+	+
Weakness	+	+
Vertigo	+	–
2. Cardiovascular effects		
Bradycardia	–	+
Congestive heart failure	–	+
3. Gastrointestinal effects		
Anorexia	+	+
Constipation	+	–
Diarrhea	–	+
Incontinence	+	–
Jaundice	+	–
Nausea	+	+ +
Sialorrhea	+	+
Weight gain	+	+

Table 1 Continued

Effect	Benzodiazepines	Buspirone
4. Sexual effects		
Decreased sex drive	+	+
Impotence	+	+
5. Renal effects		
Nocturia	–	+
Urinary frequency	+	+
6. Dermatological effects		
Alopecia	–	+
Edema	–	+
Pruritus	–	+
Rash	+	+

different benzodiazepines vary widely in rapidity of onset of action, their elimination half-lives, and their volumes of distribution, which allows the clinician to match pharmacokinetic profile to treatment situation. In fact, a working knowledge of these variables may be more important in using the benzodiazepines than any other class of psychotropic medication. The management of benzodiazepine adverse effects, as well as maximizing clinical efficacy, depends primarily on choosing the right drug and using it for the shortest possible time in the lowest effective amount.

Chronic benzodiazepine use may produce physiologic dependence, with a withdrawal syndrome that may follow abrupt discontinuation. In general, withdrawal symptoms are not severe, although in some cases they may be. This is especially true of the benzodiazepines with shorter half-lives. The issue of benzodiazepine dependence is discussed later in this chapter.

C. Benzodiazepines: Relative Potency

Table 2 lists the benzodiazepines currently approved for use in the United States. The relative potency is listed after each entry, with 1 mg of lorazepam (Ativan) being assigned the benchmark value of 1.0.

D. Benzodiazepines and Dependence

It is clear that benzodiazepine use can lead to physiological dependence, associated with a withdrawal syndrome that may appear when the drug is discon-

Table 2 Relative Potency of the Benzodiazepines

Name (Generic/Trade)	Relative Potency
Alprazolam (Xanax)	0.5
Chlordiazepoxide (Librium)	10.0
Clonazepam (Klonopin)	0.25
Clorazepate (Tranxene)	7.5
Diazepam (Valium)	5.0
Flurazepam (Dalmane)	30.0
Lorazepam (Ativan)	1.0
Oxazepam (Serax)	15.0
Quazepam (Doral)	15.0
Temazepam (Restoril)	30.0
Triazolam (Halcion)	0.25

Based on these parameters, benzodiazepines are described as either ‘‘high potency’’ or ‘‘low potency’’.

High Potency	Low Potency
Alprazolam (Xanax)	Chlordiazepoxide (Librium)
Clonazepam (Klonopin)	Clorazepate (Tranxene)
Lorazepam (Ativan)	Diazepam (Valium)
Triazolam (Halcion)	Flurazepam (Dalmane)
	Oxazepam (Serax)
	Quazepam (Doral)
	Temazepam (Restoril)

tinued. The term addiction is often used to describe this phenomenon, and it is important to distinguish dependence from addiction, because it is rare for the benzodiazepines to be abused in the compulsive and dysfunctional manner characterized as substance dependence in the fourth edition of the Diagnostic and Statistical Manual (DSM-IV) of the American Psychiatric Association. When true benzodiazepine abuse is observed, it nearly always occurs in conjunction with abuse of other substances. For this reason benzodiazepines should not be prescribed to patients with a history of substance abuse or dependence.

Although there is wide variability in presentation, common symptoms of benzodiazepine withdrawal include increasing anxiety, insomnia, psychomotor restlessness, and irritability. Because benzodiazepines are commonly

prescribed for anxiety and insomnia, the emergence of these withdrawal symptoms (“rebound” anxiety or insomnia) may be confused with the reemergence of the original symptoms for which the drugs were prescribed, although they are often more acute. These symptoms may be expected to clear relatively rapidly, usually within one to several days, and patients should be forewarned about what to expect. It is important to note that withdrawal symptoms with some drugs may first appear several days after discontinuation. Therefore, when the need for continued treatment is being evaluated by using a slow taper, a useful strategy is to stop tapering the medication when anxiety symptoms recur in order to help distinguish transient rebound symptoms from more long-lasting reemergent symptoms of the original disorder being treated. Withdrawal/abstinence symptoms are most often associated with the short- half-life, high-potency forms (alprazolam, triazolam, lorazepam), especially after abrupt withdrawal. However, gradual taper of short-half-life and long- half-life agents is tolerated well, with little difference noted between the two.

As mentioned above, the benzodiazepines vary markedly with regard to their pharmacokinetic properties (see Table 3). Onset of action, rate of distribution, and half-life should be considered when choosing a benzodiaze- pine. Drugs with a “rapid” onset of action can be expected to have effects within an hour; those with an ‘‘intermediate” onset of action usually begin working between 1 and 2 hr after oral administration; and those with “slow” onset of action take 2 to 3 hr to begin working. The rate of onset of action is primarily determined by rate of absorption from the gastrointestinal (GI) tract and not by rate of penetration to target tissues in the brain. Even though the benzodiazepines vary considerably in their lipophilicity, all the benzodiazepines move across the blood-brain barrier relatively rapidly after absorption. Some benzodiazepines are absorbed much more rapidly than others (6), and this difference in rates of absorption is reflected in the different rates of onset of action. In general the rate of absorption is increased if the drug is given on an empty stomach (7).

The rate of distribution of the drug (third column, Table 3) is generally referred to as the “alpha” phase of the drug's metabolism, while half-life (fourth column, Table 3) is referred to as the “beta” phase. When benzodiazepines are given on a one-time or intermittent basis, the rate of onset of action and the rate of distribution are the more important pharmacokinetic parameters. Diazepam (Valium), for example, has a rapid onset of action and also a rapid rate of distribution, so that although it will begin to work quickly, its effect will wear off quickly as the drug is rapidly distributed to peripheral tissues. A single dose of diazepam would be a good choice when rapid tranquilization for a very brief period is desirable.

Table 3 Pharmacokinetic Properties of the Benzodiazepines

Name	Onset of Action	Rate of Distribution	Half-Life (hours)a
Alprazolam (Xanax)b	Intermediate	Intermediate	Short (12–15)
Chlordiazepoxide (Librium)	Intermediate	Slow	Long (30–100)
Clonazepam (Klonopin)	Intermediate	Intermediate	Long(18–50)
Clorazepate (Tranxene)	Rapid	Rapid	Long (30–200)
Diazepam (Valium)	Rapid	Rapid	Long (30–100)
Flurazepam (Dalmane)	Rapid	Rapid	Long (50–150)
Lorazepam (Ativan)	Intermediate	Intermediate	Short (10–20)
Oxazepam (Serax)	Slow	Intermediate	Short (3–21)
Quazepam (Doral)	Intermediate	Intermediate	Long (50–150)
Temazepam (Restoril)	Slow	Rapid	Short (8–20)
Triazolam (Halcion)	Intermediate	Rapid	Short (1.5–5)

aParent compound plus active metabolites.

bBold print denotes high-potency benzodiazepine

Drug half-life (fourth column, Table 3) is often referred to as the "beta" phase of metabolism. For most of the benzodiazepines, this involves a two- step process of oxidation of the parent compound (often to an active metabolite) and conjugation (to inactive, water-soluble metabolites) with subsequent elimination. Lorazepam (Ativan), oxazepain (Serax), and temazepam (Restoril) are exceptions to this rule and are metabolized by conjugation only. With chronic administration, peripheral tissues become saturated and drug half-life (rather than rate of distribution) becomes the more important clinical consideration. Drugs with a relatively rapid onset of action and short half- life (i.e., lorazepam) are preferable in the management of acute or subacute conditions, such as agitation or insomnia. Benzodiazepines with a more gradual onset of action and longer half-life (i.e., chlordiazepoxide, clonazepam) are preferable in the treatment of chronic conditions, such as GAD.

E. Additional Pharmacokinetic Considerations

1. Drug-Drug Interactions (Benzodiazepines)

Drug-drug interactions may act to increase or decrease the clinical effect (and side effects) of the benzodiazepines through a variety of mechanisms, including effects on drug absorption, synergy or inhibition at the receptor site, and induction or inhibition of drug metabolism. A partial list of these drug-drug interactions is included in Table 4.

2. Impaired Hepatic Function

a. Benzodiazepines. The 3-hydroxy benzodiazepines (oxazepam, lorazepam, and temazepam) are metabolized by direct conjugation into inactive compounds with no active metabolites. The other benzodiazepines first undergo oxidation in the liver before conjugation, with the exception of clonazepam, which undergoes a reduction reaction rather than conjugation as its final metabolic step. In the diseased or failing liver, oxidation declines more rapidly than conjugation, so that benzodiazepines that are oxidized in the liver will have longer half-lives and tend to accumulate. In patients with significant hepatic disease, and especially in the case of patients with cirrhosis, the 3- hyroxy compounds are preferred, and dosage should be reduced and titrated against the emergence of possible side effects (lethargy, confusion, ataxia, etc.)

b. Buspirone. Buspirone is metabolized by oxidation in the liver, and one active metabolite is produced. The use of buspirone in patients with serious liver disease has not been studied, although a number of clinical trials

Table 4 Drug-Drug Interactions

Drug	Effect on Benzodiazepine Activity	Comment/Recommendation
1. Benzodiazepines		
Alcohol	Increases	May be lethal in combination, avoid use in alcoholics
Antacids	Decreases	Inhibited G1 asorption
Beta blockers	Increases	Oxazepam (38), diazepam (39)
Birth control pills	Decreases	Oxazepam, lorazepam (40)
	Increases	Chlordiazepoxide, diazepam (41), triazolam, temazepam, alprazolam (42), alprazolam (43)
Carbamazepine	Decreases	Alprazolam (43)
Cimetidine	Increases	Lorazepam, oxazepam (44), temazepam (45) do not interact
Clozapine	Increases	Report of respiratory arrest with iv lorazepam (46)
Digoxin	Increases	Reports of digoxin toxicity with digoxin diazepam (47), and alprazolam (48)
Disulfiram	Increases	Most benzodiazepines (49); alprazolam
		May not interact (50)
Erythromycin	Increases	Triazolam
Isoniazid	Increases	Report of valium (51) and triazolam (52) but not oxazepam (52) toxicity
Levodopa	Decreases	Reports of decreased levodopa effeet with chlordiazepoxide (53) and lorazepam (54)
Lithium	Increases	Report of hypothermia with diazepam (55) and neurotoxicity with clonazepam (56)
Loxapine	Increases	Report of hypotension, stupor with lorazepam (57)
MAOIs	Increases	Report of headache and flushing with clonazepam and phenelzine (58)

Table 4 Continued

Drug	Effect on Benzodiazepine Activity	Comment/Recommendation
Nefazodone	Increases	Triazolam (59) and alprazolam (60)
Omeprazole	Increases	Reports of toxicity with diazepam (61), triazolam and flurazepam (62)
Phenytoin	Decreases	Clonazepam (63) and oxazepam (64)
Probenecid	Increases	Lorazepam (65)
Rifampin	Decreases	Diazepam (66)
SSRIs	Increases	Some evidence for increased impairment of motor skills with diazepam (67) and alprazolam (68), but possibly not with donazepam (69) or triazolam (70)
Theophylline	Decreases	Diazepam (71)and alprazolam (72)
Valproic acid	Increases	Clonazepam, (73) diazepam (74), and midazolam (75)
Verapamil	Increases	Midazolam (76)
2. Buspirone		
Cimetidine	Increases	Minor effect
MAOIs	Unkown	May cause hytertensive reaction; do not use concurrently
SSRI's	Decreases	Fluoxetine, single case report (77)

have examined the efficacy of buspirone in treatment of alcoholic patients, without adverse effect (8).

3. Elderly Patients

Elderly patients metabolize benzodiazepines more slowly than younger patients, so that identical dosing strategies will result in significantly higher serum concentrations in older patients (9). Furthermore, the elderly show more sensitivity to the unwanted effects of the benzodiazepines, so that they become

more sedated and psychomotor-impaired than younger patients even when serum concentrations are similar (9). These effects are seen with both short- half-life and long half-life drugs, but are probably more significant with the longer-half-life benzodiazepines because of drug accumulation over time (9). It is important to remember that even single doses of a benzodiazepine can significantly impair some older individuals (10), and long-term use of benzodiazepines in the elderly should be avoided unless there are very compelling reasons for their use.

The use of buspirone in the elderly has not been extensively studied, although the limited data available suggest that it is sometimes effective and generally safe (11,12). Elderly patients appear to require approximately one- half of the usual adult dose for effectiveness.

F. General Treatment Recommendations to Minimize Side Effects

As noted in Section I above, all of the benzodiazepines produce a cluster of central nervous system (CNS) side effects including sedation, impaired memory and cognitive function, impaired motor performance, and behavioral disinhibition. There are no effective pharmacological treatments for the management of these side effects, and so the only viable method to minimize them is to choose the appropriate drug and adjust the dose appropriately. As a practical consideration, this involves matching an individual drug's pharmacokinetic profile to the specific clinical situation. In treating insomnia, for example, the ideal drug would have a rapid onset of action with a half-life long enough to help support sleep but short enough so that there would be a minimum of daytime sedation, motor impairment, and mental slowing. The ideal drug for treatment of chronic anxiety would allow once-a-day dosing with a long half- life to prevent breakthrough anxiety during the day and with a slow onset of action that might allow tolerance to develop to undesirable effects of the drug, including sedation and motor impairment. For this purpose the long-half-life benzodiazepines with a relatively slow onset of action are preferable for treating chronic anxiety. This is summarized in Table 5.

1. Benzodiazepine Dosing Strategies

Patients should be treated with the minimum effective benzodiazepine dosage and efforts made periodically to lower the dosage for all patients being treated for chronic disorders. These efforts should be recorded in the clinical records, accompanied by an ongoing analysis of the risk/benefit ratio to the patient as

Table 5 General Considerations in Choosing a Benzodiazepine

Clinical Situation	Preferred Pharmacokinetic Profile
1. Acute administration (e.g., agitation)	Onset: rapid or intermediate Distribution: slow or intermediate Half-life: short
2. Limited administration (e.g., insomnia, alcohol withdrawal)	Onset: rapid or intermediate Half-life: short or long (depending on situation)
3. Chronic administration (e.g., anxiety disorders)	Onset: intermediate of slow Half-life: long

part of the justification for chronic benzodiazepine therapy. Approximately five half-lives must pass before steady-state is achieved at any particular dose; therefore, for the benzodiazepines with relatively short half-lives, such as lorazepam (Ativan), a minimum of 4 days is necessary for steady-state to be achieved, and there is no pharmacokinetic rationale for altering dosage before this time has passed. For the long-half-life drugs such as clonazepam (Klonopin), 10 days or more will be required, so it is important to advise the patient that the true anxiolytic effects of the drug will not be apparent for more than a week.

Different clinical situations require different dosing strategies to optimize efficacy and limit adverse effects. When the clinician anticipates a short- term, situation-focused course of benzodiazepines, there is generally little need to start at a low dose and slowly advance up to the anticipated effective dose. For example, when pharmacological control of acute agitation is the goal, a short-acting, high-potency benzodiazepine such as lorazepam might be chosen, starting with the anticipated effective dose (1 mg tid or higher in a young, healthy patient). However, when it appears that the clinical situation will call for the chronic use of benzodiazepines, a different dosing strategy is logical. For example, if the clinician is going to treat GAD with a benzodiazepine, it would make sense to select a drug with a longer half-life to minimize interdose rebound of symptoms. In this case, speed of onset is a less critical factor and the presence of unwanted side effects is more important. Therefore, it makes sense to begin with a low dose and advance in a deliberate and planned manner to the anticipated therapeutic dose. For example, if clinical experience suggests that 30 mg/day of chlordiazepoxide is the likely effective dosage for treatment of GAD, it makes pharmacodynamic (as opposed to pharmacoki-

netic) sense to begin moving toward the target dose slowly to allow for target receptor adaptation (especially for adverse effects), with more rapid increases toward the target dosage coming later. This strategy is the mirror image of tapering a patient off a benzodiazepine or other psychotropic drug.

Once steady state has been achieved the longer-half-life drugs with slow onset of action such as chlordiazepoxide (Librium) or clonazepam (Klonopin) will show relatively little fluctuation in plasma levels and so can be given once a day, preferably at bedtime. Long-half-life drugs with rapid onset of action, such as diazepam (Valium), will always produce a rapid increase in serum levels after administration, even after steady state has been achieved; this rapid upswing in may be associated with a brief period of euphoria, a "rush." This may explain why diazepam has the greatest abuse potential among the benzodiazepines (13).

In considering target doses, it is important to consider the pharmacokinetic factors discussed above. Drug-drug interactions, relative volume of distribution (lean/fat ratio), and the patient's age are all important considerations.

G. Recommendations for Treatment of Specific Conditions or Populations

1. Treatment During Pregnancy

The use of benzodiazepines during pregnancy is controversial because of the possibility of increased risk for oral cleft and other anomalies. Altshuler and colleagues reviewed the available literature on this subject and concluded that ''while the increase in risk may be statistically significant, the absolute risk for oral cleft related to in utero drug exposure still remains small'' and "the possible increased risk for oral clefts associated with benzodiazepine exposure should not be considered an absolute contraindication to benzodiazepine use during pregnancy" (14). Nevertheless, benzodiazepines should be avoided, especially during the first trimester of pregnancy, whenever safer psychopharmacological and non-psychopharmacological options are available. For example, either behavioral therapy or an SSRI would be a reasonable and effective alternative for the treatment of panic disorder during pregnancy.

2. Treatment of the Elderly

As mentioned above, the elderly are more sensitive to both the pharmacokinetic and pharmacodynamic properties of the benzodiazepines, and there may be serious adverse consequences when these drugs are not used with the ut- most caution. One study looked at hospitalized patients over the age of 70

Table 6 Recommendations for Treatment of Elderly Patients

1. Avoid benzodiazepines if possible.
2. If benzodiazepines are necessary, avoid long-acting forms, and use instead short-acting, low-potency drugs without active metabolites, such as oxazepam (Serax).
3. Use the minimum effective dose, which will usually be 50% or less than that generally used in younger patients.
4. Use them for short periods of time (1 to 2 weeks) for prn indications and not to treat chronic conditions.

who suffered a fall while in the hospital and found that 70% of them had been receiving flurazepam as compared with only 19% of patients who did not suffer a fall (15). A number of general rules can be reasonably applied to the use of benzodiazepines in the elderly, these are outlined in Table 6.

3. Treatment of Insomnia

The treatment of insomnia is, of course, not only a topic to itself but almost an independent specialty. The recommendations that follow must assume that the patient's insomnia has been adequately evaluated, that nonpharmacological options have been exhausted, that confounding factors such as comorbid depression or substance abuse have been ruled out, and that a benzodiazepine has been selected as the agent of choice over, for example, a sedating antidepressant such as trazodone (Desyrel) or doxepin (Sinequan). Ideally, the choice of sedative should be tailored to shorten sleep latency in patients who have difficulty falling asleep and to maintain sleep in patients who are failing to sleep through the night or are waking up early. Diazepam (Valium) and flurazepam (Dalmane) have the most rapid onset on action and achieve maximum serum concentration in less than 1 hr. Triazolam (Halcion) and quazepam (Doral) act somewhat less rapidly (1 to 2 hr to peak concentration) and temazepam (Restoril) requires 3 hr to reach peak concentration. This would seem to suggest that diazepam and flurazepam are the drugs of choice for patients with delayed sleep onset. However, some problems are associated with the use of these drugs as sedative-hypnotics. First, their rapid rates of distribution tend to diminish their effectiveness in maintaining sleep integrity when used on a occasional prn basis. Second, they each have long half-life metabolites that accumulate when the drugs are used on a more chronic basis, and which may cause daytime lethargy and psychomotor slowing.

Triazolam (Halcion) and quazepam (Doral) have intermediate rates of onset of action. Triazolam is a high-potency compound with a very short half- life; is has been the subject of some controversy and, in fact, is no longer approved for use in Great Britain. Anecdotal reports indicate that triazolain is associated with the highest overall incidence of CNS adverse effects (16). Controlled studies have not uniformly confirmed this, and triazolam remains an effective hypnotic agent, especially for people with difficulty falling asleep. However, because it is a high-potency compound with a short half-life, it is particularly likely to produce rebound insomnia, which may be mistaken for a return of the original condition. Triazolam should probably be used only for very short term treatment of patients with difficulty falling asleep and should be tapered over a period of several days rather than abruptly discontinued. Quazepam is metabolized to the same active metabolite as is flurazepam and is essentially the same compound as flurazepam, with a somewhat slower onset of action.

It is likely that the best clinical compromise is to be found in the 3- hydroxy compounds (lorazepam, oxazepam, and temazepam). Although these drugs do not have a rapid onset of action, they have half-lives long enough to maintain sleep and do not have active metabolites that accumulate in the event that treatment becomes more extended. Timing and dosage may be adjusted in order to try to strike a balance between maintaining sleep and avoiding daytime psychomotor retardation or lethargy. Of these three, only lorazepam is a high-potency preparation, and the risk of rebound insomnia is probably greatest with lorazepam. As with the case of the other short-half- life, high-potency benzodiazepines, it is clinically wise to taper lorazepam rather than discontinuing it abruptly.

It is widely believed that tolerance develops rapidly to the sedating effects of the benzodiazepines, but this may not be true. One study found that normal volunteers did not habituate to the sedating effects of benzodiazepines after nine consecutive nights of administration (17).

Buspirone is nonsedating and is not effective for the treatment of insomnia.

4. Treatment of Panic Disorder

Current options for the treatment of panic disorder include behavioral therapy, the SSRIs, the TCAs, the MAOIs, and the benzodiazepines. Only the highpotency benzodiazepines alprazolam (Xanax), clonazepam (Klonopin), and lorazepam (Ativan) have been shown to be effective in treating panic disorder, although a study by Noyes suggests that diazepam (Valium) may be effective as well (18). The longer half-life of clonazepam reduces interdose rebound of

Table 7 Recommendations for Treatment of Insomnia

1. If a benzodiazepine is the sedative of choice, begin with either temazepam, oxazepam, or lorazepam and give instructions to the patient to take the dose at least 1 hr before bedtime (somewhat less for lorazepam). Adjust the timing of the dose depending upon clinical response: if the patient is not sleepy when bedtime arrives, take the dose a little earlier, and vice versa. If sleep is not maintained throughout the night, increase the dose, titrating it to maximize sleep maintenance and minimize daytime sedation.
2. If the patient has no problem maintaining sleep and is experiencing daytime lethargy of psychomotor retardation on even low doses of temazepam or oxazepam, then consider a change to triazolam. Triazolam should be tapered and not abruptly discontinued after treatment is complete.
3. Elderly patients should be treated with very low doses whenever a benzodiazepine is prescribed. In elderly patients, the best choice may be zolpidem (Ambien), a sedative that has shown early promise for treating this population.

panic symptoms, which may make it preferable for the treatment of panic disorder. It should be noted that clonazepam has been associated with the onset of depressive symptoms (19), although it has also been reported to have antidepressant effects (20). It may be possible to extend the effective half- life of alprazolam and thereby reduce interdose rebound by the addition of nefazodone, which inhibits the hepatic enzyme systems (CYP 3A3/4) responsible for the metabolism of alprazolam (21). Therefore, the combination of nefazodone and a triazolobenzodiazepine, alprazolam (Xanax) or triazolam (Halcion), requires a downward adjustment of dosages.

Table 8 Recommendations for Treatment of Panic Disorder

1. High-potency benzodiazepines may be useful for pm treatment of severe panic attacks while the patient is being started on a tricyclic, and SSRI, or an MAAOI. Lorazepam is probably the drug of choice for this purpose.
2. If a high-potency benzodiazepine is to be the primary pharmacological treatment, the clonazepam is a reasonable choice.
3. Buspirone has not been found to be effective in treatment of panic disorder (78).

5. Treatment of Generalized Anxiety Disorder

The treatment of generalized anxiety (GAD) has not been extensively studied. In fact, the validity of GAD as a diagnostic entity has been a subject of debate despite empirical study validating it as a category for DSM-IV (22). The role of psychopharmacology versus cognitive/behavioral treatment and the need for extended treatment (23) are all still matters requiring further study. Finally, it is not clear that the benzodiazepines are preferable to other psychotropics for the treatment of GAD (24). Given these caveats, the recommendations in Table 9 may be made.

6. Treatment of Situational Anxiety

Most situational anxiety related to stressful life events can be managed without the use of anxiolytics. In cases requiring their use, a high-potency preparation with a relatively short half-life such as lorazepam (Ativan) is preferable. The dosage should be targeted to the desired result: if a period of sedation is the goal, then a higher dose is preferable; while if mild anxiolysis with less sedation is the goal, then a lower dose given more frequently is the best strategy. As always, if the length of treatment extends for more than a few days, it will be necessary to taper the medication rather than abruptly discontinuing it.

Buspirone has not been studied in the treatment of situational anxiety, but the long period to onset of anxiolytic effect suggests that it would not be especially useful for treatment of this condition.

7. Treatment of Social Phobia

As in the case of panic disorder (see above), it is likely that the benzodiazepines are not the first pharmacological choice for treatment of social phobia. The monoamine oxidase inhibitors (MAOIs) are probably best studied in this respect (25), although the efficacy of both alprazolam (26) and clonazepam has been reported (27). There is growing evidence for the use of the serotonin selective reuptake inhibitors (SSRIs) for the treatment of social phobia. If the SSRIs prove to be as effective as or more effective than the benzodiazepines, it is likely that they will be considered the drugs of choice for patients who cannot tolerate MAOI dietary restrictions. Buspirone has shown some limited effectiveness in the treatment of social phobia (28,29).

8. Treatment of Obsessive-Compulsive Disorder

Clonazepam may have some place in the treatment of obsessive-compulsive disorder (30). It is speculated that the possible efficacy of clonazepam in treat

Table 9 Recommendations for Treatment of Generalized Anxiety Disorder

1. A reasonable treatment strategy is to begin treatment by prescribing both a short half-life, high-potency benzodiazepine (such as lorazepam) as well as an antidepressant with anxiolytic properties [such as imipramine or trazodone (79)]. After two weeks of treatment the benzodiazepine would be tapered and withdrawn, and antidepressant monotherapy would continue.

2. A second strategy would be to use a long-half-life benzodiazepine as monotherapy. Chlordiazepoxide and clonazepam have the best pharmacokinetic profiles when long-term use is being contemplated, because their long half-lives minimize interdose rebound and permit once- daily dosing. Their relatively slow onset of action makes them less likely to produce the brief euphoric "buzz" that reinforces use and possibly promotes abuse in a small number of patients. As mentioned above, it is a reasonable strategy to start at a low dose and advance up to the projected effective dose as tolerance to unwanted side effects develops.

3. Buspirone has been found to be as effective as benzodiazepines in controlled studies of treatment of GAD (GAD) (80), and because of its relatively benign side effect profile, may be a good clinical choice for patients with this condition. This is, of course, especially true for patients with a history of alcohol abuse or dependence.

Patients should be educated regarding the relatively slow onset of action of buspirone (1 to 2 weeks for first effects and 4 to 6 weeks for full effect). To minimize adverse effects buspirone should be started at 5 mg bid or tid for the first week, advancing by 5 mg increments every 2 to 4 days to a target dose of 15 to 30 mg/day. Individual patients may require up to 60 mg/day for control of their anxiety. Buspirone may be a particularly good choice for treatment of GAD in the elderly because of the hazards of the benzodiazepines for this population. In the elderly, buspirone should be started at 5 mg/day and advanced slowly, usually to no more than 15 mg/day. The principal adverse effect of concern in this group is orthostasis leading to falls, and this may be minimized by starting low, going slow, and urging the usual precautions: drink fluids, pause before getting out of bed, rise slowly, and pause before walking if necessary.

Table 10 Recommendations for Treatment of Social Phobia

1. For patients with social phobia, generalized type, SSRIs or MAOIs are usually indicated. Clonazepam or aprazolam may be reasonable choices in nondepressed patients. When there is comorbid depression antidepressants are indicated, with or without bexzodiazepine augmentation.
2. For patients with nongeneralized social phobia directed at specific social situations, consider the prn use of a high-potency, short-half-life preparation such as lorazepam in low dose, given approximately 30 min before the feared social situation. In these cases the usual warnings regarding operating motor vehicles or consuming CNS depressants such as alcohol must be especially emphasized, because many people with this type of social phobia are accustomed to taking alcohol to manage their phobia.
3. For patients with a history of substance abuse, and when the clinician wishes to avoid the use of benzodiazepines, a trial of buspirone is reasonable.

ing obsessive-compulsive disorder may be derived from its putative serotonergic properties.

9. Treatment of Behavioral Disinhibition Associated with Benzodiazepines

All benzodiazepines have been associated with paradoxical reactions, including increased agitation (31), disinhibition (32–35), and aggression (36). There is no treatment for these adverse effects other than to recognize the reaction and stop the medication when it occurs. These reactions may occur at any time but are more likely to be seen between 1 and 2 weeks after beginning treatment or following an increase in dose (37). Most case reports involving behavioral disinhibition implicate the short-acting benzodiazepines, but it has also be described with clonazepam. Again, the challenge to the clinician is to differentiate between a worsening of an underlying condition, which might require an increase in benzodiazepine dosage, against an adverse medication effect that would require decreasing or stopping the benzodiazepine.

III. CONCLUSIONS

The recognition of the high prevalence of anxiety disorders and the morbidity associated with untreated anxiety provides a clinical imperative for increased

detection and optimal treatment. Since long-term treatment is often indicated, clinicians should be aware of the most commonly occurring adverse effects and how to manage them appropriately. This chapter has highlighted the benzodazepines and azapirone anxiolytics and their management. As further advances in the pharmacotherapy of anxiety are realized, we will hopefully be able to offer patients even safer and more tolerable treatments. In the meantime, optimal use of the available agents is the goal for treating physicians; this chapter will hopefully assist in that effort.

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8 Management of Side Effects of Drugs Used in Treatment of Alcoholism and Drug Abuse

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I. INTRODUCTION

Since ancient times, physicians were held accountable for adverse effects resulting from their treatment. For example, Hammurabi's code in ancient Babylon decreed severe penalties for doctors who caused injuries as a result of their treatment (1). In modern psychopharmacology, side-effects profiles have assumed increasing importance as more classes of pharmacological agents with comparable effectiveness have been introduced.

Psychopharmacology for addictive disorders is a developing field. Although notable advances have been made with recent identification of potentially useful agents in decreasing harmful use, few classes of medications are currently available for the treatment of the different drug addictions.

A. DSM-IV Classification of Drug-Related Disorders

The classification system of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) recognizes 11 classes of substances that may be subject to abuse and may cause substance-related disorders. For each class of drug of abuse, there are 13 categories of substance-related disorders arranged into two broad groups; the substance-use disorders group, comprising substance abuse and substance dependence; and the substance-induced disorders group, which includes intoxication, withdrawal, and cognitive dysfunctions such as delirium, persisting dementia, and persisting amnestic disorders; psychotic, mood, and anxiety disorders; sexual dysfunction; and substance-induced sleep disorders (2).

While abstinence from substances may be sufficient to induce remission from most of these substance-related categories, pharmacotherapy still has an important role as an adjunct in the treatment of these disorders.

Of the above categories of substance-use disorders, however, pharmacotherapy is available only for opioid, alcohol, and nicotine dependence. Moreover, of the substance-induced disorders, pharmacological management is currently available only for withdrawal states from alcohol, other depressants, and opioids.

B. Classification of Adverse Drug Effects

Generally, medication side effects have been classified into two major types. The first, denominated type A, is defined as those reactions due to the expected effect of the drug at the usual therapeutic dose. These types of reactions may be due to an exaggerated effect of the intended therapeutic use or due to the effects of the drug on other receptor or organ systems that are not involved in the intended therapeutic use of the drug. These types of reactions are usually predictable, occur often, and cause increased morbidity but are associated with low mortality. Dose adjustment is usually sufficient to treat the symptoms (3). The second type of drug reactions, or type B reactions, are generally due to an idiosyncratic or unusual reaction to the medication. They are unpredictable and occur rarely but could be associated with high mortality. Treatment for these reactions is often discontinuation of the medication (3).

II. DRUGS USED IN THE TREATMENT OF ALCOHOLISM

Advances in pharmacological treatment for alcoholism is rapidly altering traditional treatment approaches in this field. Pharmacological agents are assum-

ing an important role as adjuncts to psychotherapeutic modalities, especially for those who are unable to maintain a state of abstinence. Naltrexone hydrochloride has recently been approved by the FDA as an adjunct in the treatment of alcoholism. Other medications, such as acamprosate, have also suggested efficacy in the treatment of alcoholism. For further information of potential pharmacological treatment for alcoholism, the reader is referred to several excellent reviews on the topic (4–6). In addition to these agents used to facilitate and maintain sobriety, pharmacological agents are also available for the treatment of alcohol withdrawal.

A. Benzodiazepines in the Treatment of Alcohol Withdrawal

A wide range of agents have been utilized to treat the alcohol withdrawal syndrome (7); however, benzodiazepines are currently considered by most as the agents of choice (8,9), although other sedative hypnotics, such as phenobarbital, have been used (10).

Of the benzodiazepines, long-acting compounds such as diazepam, and chlordiazepoxide, and intermediate-acting compounds such as lorazepam, oxazepam, and temazepam are the most frequently employed (11). Long-acting compounds are considered to have a more favorable pharmacokinetic profile, providing improved control over the withdrawal symptoms, especially when objective assessment procedures are utilized to guide drug dose administration (12). Several studies have found these compounds effective and safe in a variety of alcoholic subpopulations (12–14). Intermediate-acting benzodiazepines, especially those without active metabolites, are particularly useful in patients with compromised liver functions (11).

I. Benzodiazepines Side Effects

The different benzodiazepines used for alcohol detoxification share a common side effect profile. Differences among them are mostly determined by the pharmacokinetic properties of the individual drug.

Sedation and drowsiness occur most frequently but diminish with increased tolerance (15–20). Ataxia, dizziness, poor coordination, diplopia, and vertigo are also common (11). They appear to be dose-related and may result in falls and fractures, especially among the elderly and other frail patients (17,21). Impairments in motor performance has also been reported (11,21). Although the severity and clinical significance of such impairment is being debated (17), patients undergoing ambulatory detoxification should be cau-

tioned from operating complex machinery or performing tasks that require persistent attention, such as driving a vehicle. In certain cases, it may be necessary to solicit help from significant others or other sources of social support in transporting patients to treatment programs (22).

Long-acting benzodiazepines such as diazepam and chlordiazepoxide are more likely to produce these side effects by virtue of accumulation, which usually results from multiple dosing at short intervals. Side effects may develop gradually and progressively worsens if medication is continued without alteration in dosing schedule. Such effects are more likely to occur in patients with severe liver impairment, such as cirrhosis, and in the elderly. Therefore, it is important to tailor the dose to the presenting clinical situation. Smaller doses, less frequent dosing schedules, and close monitoring for developing signs of excessive sedation must be observed in high-risk patients. Conditions that impair oxidative metabolism of benzodiazepines—such as certain liver diseases, old age, and drug interactions—would also lead to accumulation of long-acting compounds (11,17,21).

On the other hand, intermediate-and short-acting benzodiazepines are more likely to produce side effects by virtue of single high doses and wide fluctuation in blood levels between doses. Episodes of severe agitation, hostility, and memory impairment have been reported (23–27). Fluctuating blood levels are also thought to be responsible for less than optimal withdrawal symptoms relief with these compounds. The intermediate-acting oxazepam, temazepam, and lorazepam do not have active metabolites. They are metabolized through glucuronization; thus their metabolism is less affected by liver impairments (11). These are therefore recommended for patients with severe liver impairment (7,11).

Benzodiazepines, however, are generally safer than other medications used for detoxification, such as phenobarbital. The benzodiazepines, as opposed barbiturates, have a high therapeutic index, with a wide margin of safety between the therapeutic dose and the toxic dose.

As with most side effects treatment, prevention of their occurrence should be emphasized as a primary goal. Tailoring the type of the medication and the dose to the characteristic of the patient—in addition to close monitoring of signs and symptoms of excessive benzodiazepines dose by frequent assessment of patients—is of primary importance in the prevention and management of adverse effects. The use of objective assessment scales to guide medication administration has been shown to decrease both overmedicating and undermedicating the patient (28). These detoxification procedures, such as the diazepam loading-dose method (12) implemented with the use of objective rating scale for the assessment of alcohol withdrawal (29), allow for frequent

assessment of the patient condition, thus preventing the development of side effects caused by excessive dose.

Problematic side effects with high potential for serious complications may also carry increased legal liability. These include ataxia and incoordination, which increase the risk of falls and fractures, especially in the elderly. Impairments of motor performance carry the risk of potential injury when operating complex machinery. Attention to patient characteristic and susceptibility, drug type, and dose are basic elements to consider in the management of alcohol detoxification and in preventing complications.

B. Alcohol Maintenance

Only two agents, disulfiram and naltrexone, are available to clinicians for influencing alcohol intake. Promising new agents, however, are rapidly expanding our armamentarium for alcoholism treatment.

I. Disulfiram

Disulfiram, an antioxidant originally used in the rubber industry, was discovered almost fifty years ago by two Danish physicians as a useful deterrent to the drinking of alcohol (30). Since then, disulfiram has been widely used throughout the world (31). The deterrent properties of disulfiram are due to its irreversible inhibition of the enzyme aldehyde dehydrogenase, responsible for the catalysis of acetaldehyde. This leads to the accumulation of acetaldehyde, which causes the acetaldehyde syndrome or disulfiram-ethanol reaction (DER) (30,31).

This syndrome develops shortly after ingestion of alcohol and varies in severity from causing mild discomfort to potentially fatal reactions. The symptoms of DER are thought to be entirely due to the accumulation of acetaldehyde in the body (32). Other factors have also been implicated in the DER reaction. Recovery occurs only after new enzyme molecules have been synthesized (31).

The major metabolite of disulfiram, diethylthiocarbamoyl, combines extensively with proteins and inhibits the activity of several enzymes including alcohol dehydrogenase, which may explain the increase in ethanol blood levels reported during treatment with disulfiram. Disulfiram also inhibits the enzyme dopamine beta-hydroxylase, which may result in reduction of norepinephrine synthesis and cause hypotension symptoms observed during DER. Other enzymes are also inhibited by disulfiram, such as sulfhydryl groups and hepatic

microsomal drug metabolizing enzymes. Consequently, disulfiram interferes with the metabolism of other drugs such as barbiturates (30).

a. Disulfiram Side Effects. Although the efficacy of this agent has been questioned, especially in high doses (33), there is evidence that disulfiram may be useful in certain subpopulation of alcoholic patients (33) or when used with psychotherapies directed at enhancing compliance (34,35). Adverse effects are reported to be limited when disulfiram is given in the lower dosage range (31). However, a number of potentially serious side effects may occur, especially with higher dosage ranges warranting caution and frequent monitoring (11). Careful patient observation and monitoring should include liver function tests (LFTs), patient education, and warnings regarding potential side effects.

Reported side effects from disulfiram include skin eruptions in the form of acne, skin allergic reactions such as urticaria, somnolence and fatigue, tremor, restlessness, headache, dizziness, metallic or garlic-like taste, mild gastrointestinal difficulties, and sexual dysfunction (36,37). Serious adverse reactions most frequently involve the liver, followed by neurological, skin, and psychiatric disturbances.

Death from disulfiram has been estimated at 1 per 25,000 treatment- years (38). Ethanol ingestion may also exacerbate disulfiram hepatic toxicity (39). Additionally, disulfiram, through its metabolite diethylthiocarbamoyl, appears to increase the absorption of certain metals such as nickel and lead (30), with potential accumulation of these metals in the brain. Consequently, patients should be warned regarding environmental exposure to these metals. Disulfiram should be avoided in pregnancy due to its teratogenic effects (40). Sexual dysfunctions such as reduced libido and erectile disturbances have also been reported (41,42).

Cardiovascular system effects, especially at the higher dose of 500 mg a day, may include increase in plasma noradrenaline, increase in systolic blood pressure, and increase in pulse rate, especially in a standing position. Although disulfiram does not cause clinically significant hypertension, hypertensive patients must be treated with caution and preferably using low doses.

A number of serious nervous system side effects have been described with disulfiram. Polyneuritis may develop very rapidly and may involve retrobulbar neuritis, which causes severe reduction in visual acuity as well as impaired color perception (44–47). Tobacco smoking has been implicated as a predisposing factor to this rare but serious adverse reaction. It is more likely to occur at doses of 500 mg/day and usually within the 2 to 6 months after the onset of the medication (45). Optic neuropathy has also been reported (44– 47).

Futhermore, disulfiram may cause severe psychopathological reactions. Studies have shown that these reactins are more frequent in those patients who had low plasma dopamine beta-hydroxylase levels (48,49). Severe schizophreniform reaction to the medication have been described (50). The neurological and psychiatric side effects from disulfiram are thought to be attributed to one of its metabolites, carbon disulfide (51). High doses of this metabolite may cause other toxic effects including parkinsonism, psychotic behavior, and encephalopathy. Also, inhibition of the enzyme dopamine beta-hydroxylase involved in the catabolism of dopamine is believed to increase susceptibility to psychotic reaction (50).

Liver toxicity is another serious side effect, which may be fatal. Although the cause of liver damage is uncertain or may be due to immunological mechanism, several studies indicate that disulfiram may cause serious liver reactions as well as severe hepatitis (52–58). Hepatic injury is reported to occur during the first few months of treatment (57). Higher doses are more likely to induce liver damage, although severe hepatitis has also been reported with lower doses of disulfiram (58). The usefulness of higher doses of disulfiram has been seriously questioned by a large, well-conducted clinical trial, which demonstrated that lower doses or even placebo doses of disulfiram were as effective as the higher doses (33). It is highly recommended, therefore, to monitor liver function prior to starting the medication and at regular intervals afterwards—more frequently during the first 2 months of treatment (54–56).

Disulfiram interacts with other medications and alcohol through its effect on liver metabolism, therefore causing prolongation of the effect of the medications normally metabolized in the liver, including benzodiazepines. Other medications can potentiate the DER; these include the tricyclics amitriptyline, vasodilators, beta-adrenergic antagonists, MAO inhibitors, and antipsychotic medications (55,11).

Contraindications to disulfiram include cardiovascular disorders, hepatic dysfunction, pregnancy, severe pulmonary dysfunction, as well as psychiatric disorders such as suicidal and impulsive behavior and a history of previous adverse event to disulfiram. The likelihood of developing psychiatric disturbances is increased in those with preexisting psychiatric conditions such as schizophrenia or depression. Higher doses of disulfiram are also more likely to induce psychotic adverse effects (11). Caution should be exercised in prescribing other medications whose metabolism is likely to be inhibited by disulfiram, such as phenytoin, warfarin, isoniazid, rifampin, diazepam, imipramine, and desipramine or other medications that are oxidatively metabolized (11).

Given the potential side effects and adverse reactions of disulfiram, stringent workup prior to initiating the medication and strict follow-up and moni-

toring procedures have been proposed (59). This includes a comprehensive medical and psychiatric examination, LFTs, hematology profiles, electrocardiography, and psychosocial assessments. Others have questioned the value of this stringent exam due to the likelihood of interfering with compliance (60). It is recommended, however, that close monitoring of LFTs be undertaken to prevent the development and progression of the potentially fatal disulfiram- induced hepatitis.

b. The Disulfiram Ethanol Reaction (DER). The DER develops within a few minutes of ingesting alcohol while on disulfiram maintenance. Symptoms usually range in severity according to the dose of disulfiram taken and the amount of alcohol ingested. In a mild DER reaction, patients may develop an increase in heart rate and blood pressure, chills, nausea, vomiting, hypertension, and shortness of breath. The symptoms may terminate in sedation and sleep (11,61). Mild DER has been treated with antihistamines (62, 63).

A moderate to severe DER is characterized by intense tachycardia and electrocardiogram changes. Severe complications such as myocardial infarction or cerebral vascular accident and cerebral hemorrhage may also develop. A hypotensive phase might follow, with bradycardia and possible cardiac arrest due to vagal stimulation. Vomiting, convulsions, congestive heart failure, and cardiovascular collapse may also ensue (61,62). Electrocardiogram changes have been documented during DER reactions, resulting from direct cardiac toxic effects (64,65). Severe delayed DER reactions have also been reported (66). Management of this syndrome includes supportive measures, such as modified Trendelenburg position for hypotension (67), cholinergic blockers for vagal induced bradycardia, ascorbic acid such as 1 mg intravenously for symptoms relief (68), and possibly 4 Methylbyrazol, which reportedly blocks acetaldehyde production by blocking alcohol metabolism and therefore reducing the symptoms of DER (69).

Other sources of alcohol, the so-called latent alcohol, may induce similar reaction. These include certain cough syrups, facial lotions, vinegar wine, sauces, and some candies (70,71). Patients should be warned and educated about such possibilities as well.

In summary, disulfiram may be a valuable and safe adjunctive medication in a subset of alcoholic patients, or when specific strategies are undertaken to ensure compliance (34). An effective and safe use of disulfiram, however, requires attention to patient selection, dose strength, frequent monitoring for hepatoxicity and other problematic adverse events, as well as screening for contraindications.

2. Naltrexone Hydrochloride

Naltrexone hydrochloride, a pure reversible opioid antagonist, is the first medication approved by the FDA for alcohol dependence in the 50 years since the introduction of disulfiram. Naltrexone appears to improve abstinence rates, reduces risk for alcohol relapse, and reduces craving to alcohol use among alcohol-dependent patients (72,73). This synthetic congener of oxymorphone blocks the subjective effects of intravenous opioids by competitive binding at the opioid receptor sites (74). A dose of 50 mg of naltrexone blocks the effects of 25 mg of intravenous heroin injection for up to 25 hr (74). Naltrexone does not produce tolerance, habituation, or withdrawal syndrome (75). However, it will precipitate an opioid withdrawal syndrome in opioid-dependent patients (75).

a. Naltrexone Side Effects. Experience with naltrexone for alcohol dependence has been relatively limited, given the recency of its approval for the treatment of alcoholism. Controlled trials and clinical reports indicate that naltrexone is a safe and well-tolerated medication with a limited side-effects profile and few adverse consequences. It appears to be better tolerated than disulfiram, with significantly less potential adverse reactions.

The most common side effects reported for naltrexone are nausea and headache (76). In a multisite safety study reporting on over 500 subjects, nausea was reported by 10% of the sample, followed by headache (7%), dizziness, nervousness, and fatigue (each at 4%), insomnia and vomiting (each at 3%), and anxiety and somnolence (at 2% each) (76). In O'Malley's study (72), three side effects were reported to occur more frequently than placebo. These included nausea (32.7% vs. 13.7%), weight loss (24.5 vs. 7.9%), and dizziness (34.7 vs. 17.7%). Side effects were experienced very early in treatment, after the first dose, and led three patients to withdraw from the study.

A potentially more serious side effect is the reported naltrexone-induced hepatotoxicity (77–79). Hepatotoxicity has not been observed at the 50-mg dose of naltrexone used in clinical trials. However, it has been reported for significantly higher doses (77). Hepatic effects are reportedly due to direct toxic effect and not to an idiosyncratic reaction (77). Liver function tests should therefore be performed prior to medication onset and at regular intervals thereafter. In clinical trials, an elevation of liver enzymes (AST and ALT) over three times the normal limit and an elevated bilirubin level constituted an exclusion criteria from prescribing naltrexone (72,73). Naltrexone is contraindicated in those with acute hepatitis or liver failure (74).

In studies of obese subjects, reversible liver cell damage was reported

with daily doses of 300 mg (77,78). Elevated LFTs (transaminase) developed within 3 to 8 weeks of onset of naltrexone in 5 of 26 subjects. Of 60 patients in another study, 6 developed LFT abnormalities (79). In these studies, nausea and vomiting developed within the first 24 hr of treatment and responded to reduction in dose. Furthermore, depression, anxiety, change in mental acuity, and loss of energy were noted in others, but these improved after discontinuation (80,81). Other reported side effects include gastrointestinal irritation, clinically insignificant increase in blood pressure, fatigue, decreased food intake, anorexia, and weight loss (80–82). Most side effects tend to improve within days, however (69).

Naltrexone is contraindicated in patients who are opiate-dependent, on opiate therapy, or in opioid withdrawal. Naltrexone will precipitate an acute opiate withdrawal syndrome, signs of which may appear 5 min after ingestion of the medication and which lasts for up to 48 hr. Mental confusion, somnolence, and visual hallucinations may occur. Significant fluid loss due to vomiting and diarrhea may require fluid administration. Close monitoring and treatment with nonopioid medication is also required (74).

b. The Naloxone Challenge Test. If opiate dependence is suspected, a naloxone (Narcan) challenge test should be performed to ensure absence of an opiate-dependence syndrome. This test should not be undertaken, however, if urine screen is positive for opioids or in patients with symptoms of opiate withdrawal. Naloxone, a short-acting opiate antagonist, may precipitate opioid withdrwal signs and symptoms of short duration. In the naloxone challenge test, an 0.8-mg dose of naloxone may be administered either intravascularly or subcutaneously. As per manufacturer's recommendation (74) for the intravenous challenge, a dose of 0.8 mg of naloxone is drawn into a sterile syringe. A dose of 0.2 mg is injected intravenously and the patient observed for 30 sec while the needle is still in the vein. If there are no signs or symptoms of opioid withdrawal, then the remaining 0.6 mg is injected. The patient should be observed for additional 20 min for opioid withdrawal. If the subcutaneous route is selected, then a dose of 0.8 mg is injected subcutaneously and the patient observed for 20 min. Vital signs as well as signs and symptoms of opiod withdrawal should be monitored during the 20-min observation period. Symptoms of opioid withdrawal may include a feeling of temperature change; muscle, joint, or bone pain; abdominal pain (cramps); and skin paresthesia. Withdrawal signs may include runny nose, stuffiness, lacrimation, yawning, sweating, tremors, piloerection, and/or vomiting. Patients who develop signs and symptoms of opioid withdrawal in response to the test are at high risk for developing withdrawal syndrome if naltrexone is administered; therefore naltrexone should not be used. If the results of the challenge test are equivocal,

the naloxone challenge may be repeated in 24 hr. If no signs or symptoms are present during the observation period, then naltrexone may be initiated. Naltrexone should be initiated only if naloxone challenge test is negative. Typically, this may be so after 5 to 7 days from last use of a short-acting opiate such as heroin or 7 to 10 days after a long-acting opiate such as methadone (74). Naltrexone may be started cautiously at 25 mg and then increased to 50 mg if no signs or symptoms of withdrawal occur.

Attempts to use opioids to overcome naltrexone blockade carry a serious risk of opioid overdose (74). Naltrexone may block the effects of opioid analgesics. Therefore alternative pain-management strategies need to be instituted, such as regional anesthesia, benzodiazepines, nonopioid analgesics, and/or general anesthesia (74). When opioids are used, dose should be individualized, using a rapid-acting opioid analgesic and monitoring the patient closely in a setting where cardiopulmonary resuscitation is available.

Interaction of naltrexone with alcohol may increase the likelihood of side effects of naltrexone, such as nausea and vomiting (82). On the other hand, naltrexone is reported to decrease the stimulating effects of alcohol and to augment its sedative effects (82).

Experience with naltrexone for alcoholic patients indicates that it is a safe and well-tolerated medication and free of serious adverse reactions (72,75,76). The side effect of nausea might improve upon decreasing the dose. Another strategy is to start on half the recommended dose (e.g., 25 mg) and then increase the medication when tolerated. Patient education is also very important in terms of ability to cope with incipient side effects. Most current studies support the use of naltrexone for up to 12 weeks as an adjunct of psychosocial interventions for the treatment of alcoholism. Long-term administration of naltrexone may be required for a substantial number of alcoholics. Limited information is available, however, regarding the long-term safety of naltrexone in alcoholics. Although prolonged administration of naltrexone may reportedly cause increased density of opioid receptors in the brain, with a potential subsequent exaggerated response to an opiate agonist (83).

Overall, naltrexone offers several advantages over disulfiram in terms of ease of use, side-effects profile, and the lack of serious adverse reactions.

3. Acamprosate

Acamprosate, or calcium acetyl-homotaurinate, is a relatively novel drug for the treatment of alcoholism introduced in France during the past decade (84). It is still not available in the United States, however. Acamprosate is a synthetic derivative of homotaurinate, a naturally occurring structural analogue of gamma-aminobutyric acid (GABA) (85). Several clinical trials in Europe have

reported effectiveness for acamprosate in decreasing alcohol use and decreasing relapse (84). This medication appears to be safe, well tolerated, and without addictive potential (86).

Although its exact mechanism of action is still unknown, acamprosate is thought to influence craving associated with conditioned withdrawal (84). Acamprosate reduces the severity and frequency of relapses (84). Acamprosate does not have an aversive action such as that to disulfiram, nor is it similar to naltrexone in blocking the rewarding effect of alcohol. There is also no evidence of acute interaction between acamprosate and alcohol (86,87). Therefore acamprosate does not block or potentiate the effects of alcohol. It is not a sedative or an anxiolytic (85), nor does it have an addictive potential (88). It is hypothesized that acamprosate reduces craving in a unique way (84). Since its introduction in France in 1989, it has gained wide acceptance in several European countries.

Mild transient side effects have been reported for acamprosate. The most frequent of these involve the gastrointestinal system and the skin. Diarrhea is the most frequent side effect, with a frequency of up to 10%. This side effect seems to be dose-related (89). Less frequently, nausea, vomiting, and abdominal pain may occur.

The most common dermatological side effect is pruritus (90). Sexual side effects have been reported to include decreased as well as increased libido and impotence or frigidity. These side effects tended to be transient. Vertigo was also reported to occur more than placebo (90).

In a long-term study of acamprosate, adverse effects were usually reported within the first 4 weeks. Diarrhea and headache were the most frequent side effects reported by both the medication and the placebo groups (91).

II. DRUGS USED IN THE TREATMENT OF OPIOID DEPENDENCE

A. Opiate Withdrawal

Except for clonidine hydrochloride, medications used for opiate withdrawal— such as methadone, naltrexone hydrochloride, and buprenorphine—are also used in maintenance treatment. This section discusses clonidine hydrochloride, and the other drugs are discussed in the section that follow.

1. Clonidine Hydrochloride

For decades, clinicians have attempted to treat the opiate withdrawal syndrome symptomatically using short courses of various nonopiate sedatives and anxio-

lytics. Perhaps the most commonly used nonopiate alternative to methadone for opiate withdrawal is the alpha adrenergic agonist clonidine. This medication is primarily used in the treatment of hypertension. It stimulates the alpha2- adrenergic receptors, especially in the locus ceruleus, resulting in an inhibition of norepinephrine release (92). Consequently, clonidine suppresses the autonomic symptoms of withdrawal, such as restlessness, tachycardia, hypertension, lacrimation, rhinorrhea, and sweating (93–96). However, clonidine does little to alleviate the subjective symptoms of opiate withdrawal, such as muscle aches, back pain, insomnia, and craving for opioids (97). Consequently, this treatment modality is sometimes not well accepted by patients (97). Compliance with detoxification with clonidine has been shown to be better, and dropout rates lower, in inpatient rather than outpatient programs (97).

Double-blind, placebo-controlled studies have generally shown clonidine to be safe and effective in opiate detoxification when blood pressure is carefully monitored (95,96). The detoxification period with clonidine is generally shorter than that with methadone, and this is a major advantage (98–100).

a. Clonidine Side Effects. Clonidine is usually given orally in doses from 0.1 to 0.3 mg every 6 hr (102). However, transdermal clonidine patches have also been utilized, which deliver clonidine at an approximately constant rate for 7 days, permitting once-a-week dosing (103). The most common adverse reactions to clonidine are dry mouth, drowsiness, dizziness, constipation, and sedation. Cardiovascular side effects include orthostasis, palpitations, bradycardia, and tachycardia. Rare cardiovascular adverse reactions include congestive heart failure, Raynaud's phenomenon, conduction disturbances, and arthythmias. Other side effects include nausea and vomiting, abnormal LFTS, mental depression, headaches, and rash (104). When present, these adverse effects can generally be treated by lowering the dose, though discontinuation of the medication may be necessary for more persistent or severe effects.

Clonidine has not been approved by the FDA for use in opiate detoxification; nonetheless, this treatment regimen has been used so widely for so many years, that it is generally considered an acceptable alternative to methadone (101).

B. Opioid Maintenance Treatment

1. Agonist Substitution Therapy

The aims of agonist maintenance treatment are to provide an adequate dose to stabilize the patient and reduce craving for opiates in addition to enhancing engagement in treatment programs, maximizing chances of recovery, and pre-

venting the use of other illicit drugs (105). Maintenance therapy with opiate agonist drugs is indicated in patients with over 1 year of chronic relapsing opioid dependence who also show evidence of physiological dependence (106).

Approved agonist substitution drugs include methadone and L-alphaacetyl-methadol (LAAM). Methadone is the first, most widely used, and most thoroughly studied medication. LAAM is a longer-acting opioid agonist that has recently been approved by the FDA. Buprenorphine, a partial opioid agonist/antagonist, is still being studied as a useful drug in maintenance treatment for opiate dependence (106).

a. Methadone Maintenance. Methadone maintenance treatment for heroin dependence was introduced by Dole and Nyswander (107) over thirty years ago. Since then it has gained broad acceptance and its usefulness has been amply demonstrated (108,109). Methadone maintenance is effective in decreasing morbidity, mortality, and criminal behavior (108,109). It has also been shown to be effective in AIDS prevention strategies (110,111) and in reducing the risk of HIV infection (110,111).

Higher doses are associated with better outcome (105). However, there is substantial variability in blood levels even at high doses. Blood level monitoring may be useful in certain cases to ensure an adequate dose. Methadone appears to normalize abnormalities in physiological processes such as reproductive functioning and production of stress hormones in heroin abusers (112).

Methadone is a long-acting mu-receptor opioid agonist with subjective and physiological effects similar to those of morphine and other mu-receptor opioid agonists (113). It therefore blocks the effects of street heroin by its cross-tolerance property with other opiates. Methadone inhibits gastrointestinal motility and causes biliary tract spasms. However, it does not affect the pregnant uterus. It depresses the respiratory center and has antitussive action. It also produces hypothermia and mild hyperglycemia. Other physiological abnormalities include decrease in plasma levels of reproduction related-hormones, such as follicle-stimulating hormone and luteinizing hormone. These abnormalities were noted to remit, however, after 2 to 10 months of treatment (114). Male reproductive difficulties were also noted (115). Other physiological abnormalities and side effects induced by methadone include excessive sweating, lymphocytosis, and increased prolactin, albumin, and globulin levels in the plasma (79).

Tolerance develops to the adverse reactions of methadone and most of them disappear within several weeks of the onset of treatment. Tolerance develops with chronic use, especially to the anorectic, miotic, sedative, respiratory depressant, and cardiovascular effects. However, studies of long-term

treatment with methadone indicate that constipation and sweating appear to persist with chronic use (79). Although constipation may be severe at times, occasionally resulting in fecal impaction and intestinal obstruction, it is usually easily managed with fluids and a stool softener (116).

Side effects usually appearing during the stabilization phase include constipation, sweating, a skin rash—which may be transient, weight gain, and water retention (79). During the early phases of treatment, methadone's side effects may include euphoria, drowsiness, and somnolence. Sedation is a common side effect, specially at higher doses (117). Patients may also complain of decreased libido and sexual dysfunction such as inability to sustain erection. Other side effects may include transient ankle edema at onset of treatment, especially in women, which generally improves with time. However, dose reduction may be required to improve symptoms. Severe edema and edema occurring after years of treatment have been reported (117). Also, dizziness, nausea, vomiting, and hypotension have been reported in ambulatory patients (79). Biliary tract pressure is increased by opiate agonists, which may result in biliary spasm or colic, especially in the sphincter of Oddi, leading to increased amylase and lipase plasma levels. Urinary retention and oliguria may also occur. On rare occasions, secondary adrenocortical hypofunction or adrenal hypertrophy associated with hyperplasia of the reticular zone have been induced by chronic opiate agonist therapy. Cases of reversible thrombocytopenia in patients with chronic hepatitis and a case of choreic movement have also been reported. Hepatic and renal dysfunction may also cause prolongation and a greater cumulative effect of the opiate agonist (79).

Chronic effects of methadone may include tolerance as well as psychological and physical dependence. The abstinence syndrome from methadone is less intense but more prolonged than that from other opiate agonists with shorter half-lives. Peak symptoms of withdrawal may occur at day 6, including weakness, anxiety, anorexia, insomnia, abdominal discomfort, headache, sweating, and hot and cold flashes. These symptoms may remit after 14 days, although lethargy and anorexia have been described to last longer (116).

Certain drugs, such as rifampin and phenytoin, may enhance the metabolism of methadone and induce withdrawal symptoms (116). Methadone is reportedly safe in pregnant women, with mild effects on the offspring. Offspring may, however, develop neonatal abstinence syndrome after delivery (118).

b. Levo-alpha-acetylmethadol or levomethadyl acetate hydrochloride (LAAM). LAAM (levo-alpha-acetylmethadol or levomethadyl acetate hydrochloride) is a long-acting opiate agonist that was recently approved by the FDA for opioid maintenance treatment in opiate-dependent patients. LAAM is a synthetic opiate agonist with action similar to morphine. Its therapeutic

effects are similar to those of methadone. It blocks the opiate withdrawal symptoms and reduces craving. It also increases tolerance to the opiate and therefore blocks the ''high'' effects of abused opiates. The main advantage of LAAM is its long-acting property (up to 92 hr, as opposed to 24 hr with methadone) which allows dispensation of medication three times per week instead of the daily doses currently employed with methadone. This may eliminate the problem of drug diversion related to take-home dosing. It will also provide for a less disruptive schedule, facilitating integration at work or within the community (106). Although retention of patients in treatment is reported to be lower than with high-dose methadone, improved outcomes have been documented for those who received longer treatment with LAAM (119).

Adverse effects of LAAM are similar to those of other mu-receptor agonists. Therefore these may be adverse events related to the development of dependence, tolerance, and withdrawal, risks of overdose, and side effects related to the physiological effects of LAAM (113).

A particular risk of this medication is that of overdose while the dose is being adjusted. The dosing schedule of three times per week should be strictly observed. Daily dosing may lead to fatal overdose, and the single dose should be individualized (120). The two active metabolites of LAAM, noracetylmethadol and di-noracetylmethadol, are more potent than those of the parent compound and have long half lives (2 to 3 days) (121). Therefore, they can rapidly accumulate to toxic levels. Dose increase and adjustment must be cautiously undertaken and tailored to the tolerance developed to the medication. Usually, 2 weeks are needed to achieve a plateau after adjustment of dose. Dose reduction is recommended in patients who report signs and symptoms of excessive dose, such as complaints of poor concentration, drowsiness, and dizziness on standing (120). Precautions must be undertaken in prescribing LAAM because its full effect is not felt for several days.

During the first 72 hr of treatment LAAM does not fully suppress opiate withdrawal symptoms (122). In patients who exhibit signs or symptoms of opiate withdrawal, supportive care rather than symptom suppression with LAAM should be implemented. Patients should be warned against opiate abuse during this period, which may lead to toxic overdose (121).

Overdose on LAAM usually results from its combined use with other drugs, although overdose has also resulted from LAAM alone because of too frequent dosing (120). A nontolerant individual may suffer serious overdose at doses above 40 mg. Overdose on LAAM is a medical emergency and must be treated accordingly. Side effects of LAAM must be differentiated from heroin or methadone withdrawal symptoms. Aggressive dose increases of

LAAM to suppress withdrawal symptoms are not recommended and may result in overdose.

Caution should exercised when converting from a known daily dose of methadone to LAAM. An equivalent LAAM dose is equal to 1.2 to 1.3 times the methadone dose (120). However, the total single dose of LAAM should not exceed 120 mg. Increases are recommended at 5 to 10 mg every second or third dose. To convert from LAAM to methadone, methadone should start 48 hr after the last dose of LAAM. If needed, supplemental doses of methadone may be given at 72-hr intervals (120).

Like other opioid agonists, LAAM produces drug dependence with abuse potential and risk for diversion and illicit use. The withdrawal syndrome has a slow onset and prolonged duration, with less severe symptoms. It usually appears 72 hr after the last dose. Symptoms may include nasal congestion, abdominal symptoms, diarrhea, muscle aches, and anxiety (120).

On the other hand, large studies have shown that LAAM did not differ from methadone in terms of adverse reactions, and no serious adverse reactions were reported (119). Adverse reactions reported on a stable dose within the second and third months of treatment include nausea and delayed-onset sedation (123–125).

Furthermore, the Physicians' Desk Reference (120) suggests that ambulatory patients be cautioned because LAAM may also impair mental or physical abilities. It must be used with extreme caution in head-injured patients; patients with respiratory ailments such as asthma, chronic obstructive pulmonary disease or other respiratory conditions; in the elderly or debilitated, and in those with hepatic or renal dysfunctions, Addison's disease, prostatic hypertrophy, or urethral stricture. Patients with conduction defects should also be carefully monitored. Furthermore, LAAM may obscure acute abdomen. This medication is not recommended in pregnancy. Monthly pregnancy test are required by regulation. Those who become pregnant are recommended to be switched to methadone.

Drug interactions such as polydrug and alcohol may produce serious overdose. Medication interactions, as with methadone, may significantly alter LAAM blood levels. Rifampin is known to decrease methadone blood levels by 50%. Other drugs such as carbamazepine, phenobarbital, and phenytoin, also decrease methadone blood levels. On the other hand, drugs that slow the metabolism of opiates include erythromycin and cimetidine. The antifungal ketoconazole may increase LAAM blood levels and side effects (120).

LAAM, however, is one of the most exhaustively investigated agents. It has an adverse-effects profile similar to that of methadone but a pharmaco-

logical profile that enhances flexibility in the clinical care of these patients. Increased vigilance and monitoring of drug effects during dose adjustment are advised; if other medications are used, such vigilance should help to prevent problems related to iatrogenic overdose.

c. Buprenorphine Hydrochloride. Buprenorphine is a synthetic opiate analgesic. It also has partial agonist activity, acting at mu opiate receptors in the central and peripheral nervous systems. It has a prolonged duration of analgesia as well as limited potential for physical dependence. Its opiate-related activities appear to be dose-related. At lower doses, buprenorphine has analgesic and opiate agonist effects. However, at higher doses, its opiate antagonist activity predominates (106). Buprenorphine, therefore, may precipitate mild to moderate withdrawal in some patients who are physically dependent on opiates (126–128). Buprenorphine may produce psychological dependence and limited physical dependence. However, tolerance to its agonist activity rarely develops. Buprenorphine produces effects similar to those of opiate agonists such as morphine as well as side effects similar to those of the partial opiate agonists (129).

Buprenorphine has been used successfully in methadone withdrawal (130). It is also proposed to be used for maintenance in opiate-dependent patients (131). It appears that in low to moderate doses, buprenorphine does not precipitate opiate withdrawal in heroin addicts. Withdrawal symptoms from buprenorphine appears to be minimal, even when it is abruptly discontinued (128). Given its antagonistic properties at higher doses, it appears to limit the possibility of accidental overdose (132).

The major disadvantage of buprenorphine is its poor oral bioavailability; it is therefore given sublingually. Its abuse potential also limits its dispensing to home (132). On the other hand, it is safe on overdose, with a reduced possibility of respiratory depression (132). The most common side effects include sedation or drowsiness, nausea, vomiting, dizziness, and headache, hypotension, miosis, and diaphoresis (129). These side effects were reported more frequently in ambulatory patients.

Prolonged administration of buprenorphine, 1 to 2 months, produced a reversible decrease in hematological indices. The drug should be used with caution in patients with pulmonary impairment or compromised respiratory function as well as in patients with hypothyroidism, adrenocortical insufficiency, or severe renal impairment.

Chronically, patients may develop psychological dependence on the opiate agonist activity of buprenorphine; however, the reinforcing property of buprenorphine is less than that of pure opiate agonists. Infrequently, a limited physical dependence may also occur. Signs of acute withdrawal from bupren-

orphine are similar but less intense than those of morphine or methadone. Drug interactions may include potentiation of central nervous system depressants such as benzodiazepines, monoamine oxidase inhibitors, other opiate agonists, general anesthetics and tranquilizers, as well as sedative-hypnotics and alcohol (129).

2. Opiate Antagonist Treatment

Naltrexone hydrochloride is an alternative to methadone maintenance treatment. The goal of this treatment is to block the effects of the usual street doses of opiates, thereby discouraging use and facilitating extinction of classically conditioned drug craving. Because of its long duration of action (24 to 72 hr), naltrexone can be administered three times a week (100 mg on Monday and Wednesday and 150 mg on Friday). This medication has no abuse potential. Studies have shown that although naltrexone is effective in blocking the street opiate's "high" effects, it is not well accepted by patients and compliance with this medication has been generally poor (133–134). Side effects are similar to those described for treatment of alcohol use. However, in opiate addiction, reported side effects of naltrexone may have been related to precipitation of the opiate withdrawal syndrome (132). Other reported side effects have included sexual dysfunctions such as increased libido; changes in appetite, weight loss, and depressive symptoms were also reported. However, several studies did not confirm mood changes (135). The higher dose range used with this population might increase the risk of liver toxicity attributed to naltrexone (77,78). Studies have shown that liver damage among this population is usually due to other liver diseases resulting from drug use such as hepatitis (132).

III. DRUGS USED IN THE TREATMENT OF TOBACCO DEPENDENCE

Clinically available pharmacological approaches to tobacco dependence include nicotine replacement therapy (gums or patches) and symptomatic treatment of nicotine withdrawal.

A. Nicotine Replacement Therapy

The goal of nicotine replacement therapy is to aid in initiating abstinence from cigarette smoking so that effective relapse-prevention strategies may be developed. Nicotine replacement facilitates smoking cessation by reducing

withdrawal symptoms, thus decreasing craving and the acute reinforcing effects of cigarettes. It also provides a safer delivery system of nicotine, since these nicotine replacement products lack the toxic substances associated with smoking, such as tar. Furthermore, these products have low abuse potential because they do not cause the dramatic increase in nicotine blood levels associated with cigarette smoking (136). Nicotine replacement may also have secondary beneficial effects on mood, attentional states, and coping abilities (137).

Several forms of nicotine replacement therapy exist. The oldest and most tested and used forms include the nicotine gum products and the more recent transdermal nicotine "patch" form. Newly available nicotine delivery products include nicotine nasal spray and a nicotine inhaler. For a comprehensive review of smoking cessation therapy, the reader is referred to the excellent NIH Guideline for Smoking Cessation (138).

Several metanalyses of studies of the efficacy of the "nicotine gum" and "nicotine patches" have supported the efficacy of both of these as compared with placebo. (138) The patch, however, appears to be more acceptable to patients, as side effects and poor compliance were more frequently reported with the use of nicotine gum. Nicotine replacement is effective, especially for the long term, if it is administered in conjunction with behavioral therapies (139).

The side effects of nicotine gum include systemic effects and local effects related to chewing the gum. The latter are usually mild and transient and are easily corrected by education about the correct chewing technique. Mechanical effects from chewing may include irritation and tingling of the tongue and mouth and traumatic injury to the oral mucosa and teeth. Jaw and muscle ache, traumatic or aphtous ulcers, unpleasant taste, and mouth or throat soreness may also occur. These effects are usually transient and last for only a few days (140). However, they may lead to poor compliance, especially in nonmotivated patients.

Other side effects may include gastrointestinal distress, especially during the first week of treatment. These most frequently consist of indigestion and nausea. Vomiting may also occur. Excessive chewing with resulting rapid release of nicotine from the gum, along with excessive salivation, may cause or exacerbate these gastrointestinal effects. Modification of chewing techniques should help in alleviating these symptoms. Other side effects may include dizziness, light-headedness, headache, insomnia, irritability, and heart palpitation. Dose-related hiccups are reported to occur in up to 23% of patients, especially when the higher dosage of 4 mg is used. Palpitation, tachycardia, and arrhythmia have also been reported (140).

To minimize side effects related to incorrect techniques of chewing the gum, patients should be given instructions on nicotine gum use. These may include warning against rapid and excessive chewing. Correct chewing technique involves alternating between chewing slowly and parking the gum for at least 20 to 30 min. Also, patients should be instructed to limit or eliminate acidic beverages or fluid intake while chewing. Furthermore, the maximum daily dose of 30 gums for the 2-mg or 20 gums for the 4-mg gum should not be exceeded.

Side effects reported for the nicotine patch include topical reaction, dry mouth, gastrointestinal symptoms such as diarrhea and dyspepsia, nervousness, and sweating.

Nicotine replacement is contraindicated in patient with unstable coronary artery disease, history of life-threatening arrhythmia, skin disorders for the patch, and mandibular joint disease for the gum.

B. Other Medications

Clonidine and bupropion are clinically available to be used in smoking cessation. Side effects of both of these medications are discussed elsewhere in this book. Clonidine has been found to decrease nicotine withdrawal symptoms in heavy smokers, such as anxiety, irritability, restlessness, and craving (141). A differential effect of gender was reported, where females were significantly more likely than males to cease smoking (141). Side effects of clonidine may be an impediment to its use, however. As discussed earlier in this chapter, these side effects most frequently include drowsiness, orthostasis, and rebound hypertension with abrupt discontinuation.

Bupropion has recently been approved by the FDA to be used in smoking cessation. Side effects of bupropion are detailed in Chapter 5 of this book.

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9 Managing Side Effects of Psychostimulants

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I. INTRODUCTION

In managing the side effects of stimulants in children and adolescents, the following principles may apply—as they would to the rational management of any class of pvsychopharmacological agents. Green (1) suggests starting at a low dosage (e.g., for methylphenidate, a 5-mg test dose followed by 5-mg increments), since pharmacokinetics may vary not only between the various age groups but between individuals of the same age. For these and other reasons, some children may be responders at low doses that are ineffective for other children. He warns that behavioral toxicity (worsening of target symptoms) may occur at higher initial doses before the emergence of other side effects, particularly in younger children.

There are no absolute contraindications to stimulant use. Relative con-

traindications are psychosis, pregnancy, history of substance abuse in the patient or in the family, tic disorder, adverse effects, height-growth retardation, cardiac and blood pressure anomalies, impaired liver functioning (especially with pemoline), anxiety disorders, hypertension, hyperthyroidism, glaucoma, use of monoamine oxidase inhibitors, and perhaps seizure disorders. Overall, stimulants are safe medications, but their increased use, especially over the last 5 to 10 years [over 500% increase in use of methylphenidate from 1990 to 1995 (2)], will probably result in an increased need to monitor side effects by the physician, assuming that the need for the medication has been properly established.

Clinicians who treat many children with attention deficit hyperactivity disorder (ADHD) will often need to combine more than one medication for effective symptom control or for children with comorbid disorders. The purpose of combined pharmacotherapy is to maximize therapeutic effects and broaden the therapeutic range while minimizing side effects. For example, side effects can be minimized and even improved by certain combinations of drugs (e.g., the addition of an antidepressant to methylphenidate may improve the dysphoria associated in some cases with stimulants) or the addition of a second drug may lead to a decrease in the dosage of the first drug (the addition of clonidine to stimulants may lead to a decrease in the dosage of stimulant). However, it is doubtful that ‘‘cocktails,’’ the word euphemistically used for drug combinations of three or above, offer any significant therapeutic advantage.

II. PREVALENCE RATES AND EPIDEMIOLOGY

Community-based studies confirm that ADHD is one of the most prevalent psychiatric disorders in childhood and adolescence, with estimates of 3 to 5% in the elementary school population in North America. Over 750,000 children are treated with psychostimulants per year for ADHD symptoms and 25% of children in special education programs (3). However there is a wide discrepancy between geographical areas, varying from 0.04% in Suffolk County (4) and up to 7% of elementary school children in Baltimore County (5). In terms of the usage of stimulants, methylphenidate is the most widely prescribed, accounting for over 90% of prescriptions (3). In other countries (France, for example), there is disagreement on the diagnosis and the use of medication, specifically stimulants, to treat ADHD.

III. PHARMACOKINETICS

The amphetamines are well absorbed orally, achieve peak plasma levels in 2 to 3 hr, and have a half-life of 4 to 6 hr, but they display large interindividual variation. They are potent releasers of dopamine as well as serotonin, dopamine and norepinephrine reuptake blockers. They are mainly metabolized via oxidative deamination to benzoic and hippuric acid, which are inactive. Given an acid urine and normal renal function, about one-third to one-half of the drug is excreted unchanged (6).

Methylphenidate (MPH) is similar to amphetamines, though its mode of action is different (6). It does not release dopamine in the absence of nerve impulses but is an effective blocker of catecholamine reuptake, with stronger effects on dopamine than on norepinephrine. In children, it is easily absorbed, reaches peak plasma levels in 1 to 2 hr, and has a half-life of 2 to 3 hr. It is chiefly deesterified to ritalinic acid, which accounts for 80% of the dose. Essentially none of the drug appears unchanged in the urine.

Magnesium pemoline is also believed to block dopamine reuptake, like methylphenidate, though it has minimal sympathomimetic effects and its structure is dissimilar to that of other stimulants. It reaches peak serum levels in 2 to 4 hr and its half-life is 8 to 12 hr. Pemoline has a longer half-life than MPH, allowing once-a-day dosing, but the therapeutic effect may not appear for 3 weeks. This is due in part to the weekly titration of 18.75-mg increments, where 75 mg would be reached only after 3 weeks. If dosing is increased at 3-day intervals, therapeutic effects may appear sooner (7).

MPH-SR (sustained release) uses a wax-matrix vehicle to release MPH slowly and peaks about 1 hr later than the standard preparation, with the maximum concentration in blood occurring about 180 min after oral dosing and peak plasma levels lower than those with an equivalent dose of regular methylphenidate. Some authors have suggested that it may not be as effective as the standard methylphenidate equivalent dosage (8), but other studies have disputed this, showing equal efficacy of long-acting preparations (9). Dextroamphetamine spansules display peak serum levels for between 8 and 10 hr. The sustained-release (SR) preparations show shallower pharmacokinetic curves, with some children showing a prolonged response while in others the SR preparation is released similarly to the regular preparations. Adverse reactions to medication may appear unpredictably during different phases of the drug's absorption or metabolic phases (7).

In summary, methylphenidate's short half-life prevents steady-state concentration, leading to the necessity for multiple dosing. The usual administration times are in the morning (after breakfast) and after lunch (afternoon)

supplemented, by a mid-to late-afternoon dose if necessary for homework or socialization. Since pemoline and dextroamphetamine have longer half-lives, they can be given once daily. Methylphenidate may produce behavioral instability as a result of rapidly changing peak and trough drug levels. The implication of pharmacokinetics in terms of management alerts the clinician to inquire about what phase of drug administration is problematic, leading to a decision to alter the timing, change the dosage, change the medication, or choose between a regular or sustained-release preparation.

IV. ADVERSE EFFECTS OF STIMULANTS

A. Baseline Evaluation

After the proper diagnosis is established, it is imperative that the clinician perform a thorough baseline evaluation of signs and symptoms that may predate any treatment, since many of the adverse effects of medication are similar to the symptoms being treated. These include general health factors (eating and sleeping), medical history (seizure disorder, hepatic or renal disease, asthma), a neurological exam to document presence of tics or other adventitious movements, medication history (previous use of neuroleptics, other sympathomimetics), developmental history (language or learning disability), family history (presence of psychiatric symptoms in the parents or sibs), and the child's personality (noting any crankiness, irritability, or other nervous habits). Height and weight should be obtained and plotted on a standardized growth curve.

The usual laboratory tests ordered are complete blood count (CBC), electrolytes, blood urea nitrogen (BUN), urinalysis, serum creatinine, and liver function tests if pemoline is contemplated. Some centers now screen for thyroid anomalies; if this is done, usually a thyroid-stimulating hormone (TSH) test is sufficient to detect thyroid-related abnormalities. A rating scale such as the Stimulant Drug Side Effect Rating Scale (10) may be used by the clinician to objectively document the potential adverse effects before and after treatment. For abnormal involuntary movements, the use of a standardized scale such as the Abnormal Involuntary Movement Scale (AIMS) (Ref. 1, p. 30) is recommended, especially if the child will be on a combination of stimulant and neuroleptic.

Many side effects can be managed by starting at low dosages, especially in special populations (i.e., preschoolers) or readjusting the dosage either by decreasing it or giving it at different times of the day. In terms of child characteristics and side effects, Barkley (11) found that preschoolers treated with

methylphenidate exhibited significantly more side effects than did older children and adolescents. Highly anxious children with a history of somatic complaints may also be more prone to reporting more side effects or not be willing to tolerate side effects, but this applies to their reactions to other categories of medications as well.

In general, adverse effects are less frequent and less severe with methylphenidate than with dextroamphetamine. Gross and Wilson (12) noted that the side effects were infrequently severe enough to discontinue medication (1.1% of 377 patients for methylphenidate and 4.3% of 371 patients for dextroamphetamine). DuPaul and Barkley (13) found that less than 4% of patients had to be taken off the stimulants because of adverse side effects. Adverse effects can be broken down into how frequent they are and whether they are short-or long-term. Frequent short-term side effects include insomnia, decreased appetite, minor weight loss, headache, heart rate elevations at rest, minor increases in systolic blood pressure, and increased crying. Less frequent side effects are tics, physiological rebound, behavioral and cognitive toxicity, and psychosis. Long-term and infrequent side effects are slowed growth, liver toxicity associated with pemoline, drug dependence and abuse, negative self- attribution and possible cardiovascular effects (14).

In terms of short-term adverse effects, Barkley et al. (15) found that over half their sample exhibited decreased appetite, insomnia, anxiousness, irritability, or proneness to crying on both doses of MPH (0.3 mg/kg and 0.5 mg/kg), but many of these conditions were present during the placebo condition and may represent characteristics associated with the disorder rather than the treatment. Stomach aches and headaches were reported in about one-third of cases. Nail biting, irritability, sadness, and staring were about equal in frequency in the drug and placebo groups. The severity of the side effects was quite mild and declined with the drug trial. The authors suggest also that more side effects seemed related to the “washout phase” rather than the peak phase of drug treatment.

Fine (16), in a double-blind placebo-controlled trial of methylphenidate at dosages of 0.3 and 0.6 mg bid for 3 weeks, found that only 3 (biting nails, trouble sleeping, and decreased appetite) out of 16 side effects were more frequent than with placebo. He concluded that the similarity between ADHD symptoms and methylphenidate side effects may make some patients or parents unnecessarily stop taking the medication. The implication for the clinician is to take a thorough pre-medication history since parents may often confuse characteristics of the child with the effects of treatment. Specific management strategies for individual adverse effects are reviewed below.

B. Insomnia

Insomnia is the most common side effect observed with stimulant use, as high as 68% on doses of 0.5 mg/kg (15) compared with 40% in the placebo group. Usually the effect is transient and disappears after the first 2 to 3 weeks after starting treatment. A careful history must be taken prior to starting medication, as a large percentage of ADHD children are poor sleepers and the mothers often describe these children as having had sleep problems as infants. The clinician should correlate the sleep problem with the rest of the personality. Children who have extremely high activity levels often report that they do not need a lot of sleep. Other children with ADHD need a "wind-down" period of 1 to 2 hr; some ADHD children may be more exhausted whereas others are more stimulated by physical activity prior to bedtime. On the other hand, children with comorbid anxiety as a trait or a disorder have sleep problems that may be exacerbated by stimulants (by producing insomnia directly or an increase in their worry thoughts). During treatment, some parents have reported an increase in nightmares with the use of stimulants. Insomnia may be more of a problem with pemoline and dextroamphetamine.

The clinician must keep in mind the differential diagnosis of insomnia if it does not appear related to the stimulant use. Insomnia may be one of the first signs of a depressive disorder that may be comorbid with ADHD or be the primary diagnosis. In this instance, insomnia may be manifest either as a sleep onset problem, nighttime awakening, or early morning awakening. In teenagers, insomnia coupled with a lack of need for sleep may be one of the first signs of a manic-depressive illness. Children or teens with an incipient psychosis may be kept awake by auditory hallucinations. Teens who abuse drugs may have sleep disturbances as well. Prescription and over-the-counter drugs, especially diet pills, may cause insomnia, and the clinician should inquire about this as well as caffeine and cola intake.

In addition to sleep-onset problems, the clinician should inquire about other symptoms that may be indicative of parasomnias, such as obstructive sleep apnea, narcolepsy, night terrors, sleepwalking, and restless-leg syndrome (RLS) (see Ref. 17 for review). In narcolepsy, patients experience vivid and frightening imagery upon falling asleep or waking, paralysis upon awakening, sleep attacks (sudden onset of rapid-eye-movement sleep during the day), cataplexy, and excessive daytime sleepiness. Several children with narcolepsy present with bizarre psychiatric symptomatology and some have been diagnosed as having ADHD (18). One case study of a child with RLS had a decrease in her hyperactivity when this condition was treated (19).

Treatment of stimulant-induced insomnia consists of timing the last dose such that it does not interfere with sleep, discontinuing the late-afternoon dose, or decreasing the overall daily dosage. Wilens and Biederman (20) suggest changing to shorter-acting preparations. In some instances where the child experiences physiological rebound in the late afternoon, this may be associated with increased hyperactivity and inability to settle at bedtime. General measures of sleep hygiene should be attempted first. Providing the child with soft music or reading materials with which to relax is a good idea, whereas playing computer games or watching television tends to be more stimulating. As mentioned, some hyperactive children need a "winding-down" period, whereas others seem to settle better if they are exhausted from physical activity. Either way, a bedtime routine is necessary throughout the week, as this activity often becomes the focus for an escalating power struggle between child and parent. Poor sleep often leads to irritability the next day. Soothing drinks, warm milk, and fruits high in tryptophan (bananas, raisins) may be tried.

The last resort is to add another psychotropic agent that may help with the sleep problem. This is usually a sedating antidepressant such as trazadone or the alpha2-adrenergic agonist clonidine. We have had good success with trazadone (21) in dosages from 25 to 100 mg taken 1 hr before bedtime. Male patients must be warned about priapism, a prolonged and at times painful erection, which is usually but not always reversible after discontinuation of the drug (it should not pose a problem in the dosages we recommend).

Clonidine may help to alleviate insomnia when given 1 hr before bedtime. In addition, it can be given throughout the day to help control hyperactive behavior, although its effectiveness in this regard has been questioned recently. The initial clonidine dosage is 0.025 to 0.050 mg at bedtime with additional doses throughout the day as required to counteract adverse effects or rebound. Older children may require slightly higher dosages, up to 0.3 mg/ day in divided doses. Excessive sedation and hypotension are the major side effects. Blood pressure and pulse must be monitored initially and after each dose increase. The clinician must inquire about a previous history of cardiac problems, which would then require close monitoring of the cardiovascular effects of clonidine, including an electrocardiogram (ECG). According to Cantwell and colleagues (22), there are two patterns of clonidine-induced cardiovascular problems—one presenting with decreased pulse, decreased blood pressure, ECG changes and complaints of fatigue and sedation, whereas the other presents with tachycardia, tachypnea, fever, anxiety, and mental status changes. Children with preexisting heart disease, conduction problems, or bradycardia may be more susceptible to the first pattern of side effects whereas

the second pattern may be due to fluctuating clonidine levels associated with withdrawal and/or clonidine-stimulant noradrenergic overarousal. Nightmares have been associated with the use of clonidine.

We do not recommend the use of chloral hydrate, antihistamines, or benzodiazepines in the treatment of stimulant-induced insomnia. The use of benzodiazepines is contraindicated because they may produce paradoxical effects such as behavioral disinhibition. Antihistamines and chloral hydrate, if they are effective, lose their efficacy over time, and the dosage has to be increased; they may also have a daytime carryover effect. At effective dosages, antihistamines may have limiting side effects (such as dry mouth or urinary retention for sedating antihistamines). Zolpidem has been used as a hypnotic with the adult population, but we are unaware of any use in children. The use of traditional sedating tricyclics such as amitriptyline and imipramine is limited by their anticholinergic side effects even at lower dosages.

In summary, insomnia is a common but transitory side effect with stimulants. It is managed by decreasing or changing the timing of the dosage. If another medication is needed, we recommend trazadone or clonidine.

C. Anorexia

According to Greenhill (7), children with ADHD who take psychostimulants routinely show appetite suppression when starting treatment. This effect is transient and abates after 6 weeks of treatment, but it may be long-standing. Appetite usually returns in the evening. Dextroamphetamine's effect on appetite is greater than that of methylphenidate or pemoline. Parents should not be rigid about when the child chooses to eat, since the child may be hungrier in the late afternoon or evening. To counteract the anorexia, the dosing should be timed after breakfast or lunch. There are different opinions about giving the medication before, during, or after meals (before meals, since absorption is better in an acidic medium); however, if giving the medication with meals increases compliance and helps the parent remember, then this should be done. Again, it is worth bearing in mind that many ADHD children are poor or picky eaters prior to starting the medication. The child should also be asked whether he or she does not want to eat because of stomach aches or simply does not have any appetite. Persistent stomach aches can be treated with ant- acids.

In terms of a differential diagnosis of anorexia, a mood disorder should be considered as well as anorexia nervosa in adolescents. The clinician should exclude any possible underlying organic cause such as a malignancy. In addition to the above strategies, not giving the medication on the weekend or

during holidays may increase overall caloric intake. If there are persistent anorexic effects that do not respond to a decrease in the medication, the clinician can consider adding a small dose of a neuroleptic such as thioridazine (5 to 10 mg), which stimulates appetite; but this is not routinely recommended.

D. Growth Effects

Height and weight effects have been reported for both methylphenidate and dextroamphetamine. Mattes and Gittelman (23) reported significant decreases in height and weight percentiles over a 4-year period in prepubertal children on dosages of 40 to 50 mg/day of methylphenidate. In many instances, medication was discontinued during the summer. Height percentiles dropped from the first to the fourth year of the study: 1.4 percentile points in the first year (not significant), 8.1 percentile after the second year, 13 points after the third, and 18 after the fourth. In general 1 to 3 cm of height and 1 to 3 kg of weight were not gained over several years of treatment. Overall suppression of linear growth was proportional to the age and to the child's initial height, so that taller children lost more height. It appears, however, that an accelerated rate of growth or rebound occurred once the stimulant was discontinued and that there was no significant compromise of ultimate height attained. Dextroamphetamine appears to suppress growth more than methylphenidate or pemoline, and this effect is most often seen during the first year of treatment.

Psychostimulants may continue to suppress growth in late versus early adolescence. Vincent et al. reported no significant deviations from expected height and weight growth velocities in 31 adolescents who had received methylphenidate continuously since age 12, from 6 months to 6 years after their twelfth birthday (24). However with epiphyseal closing of the long bones between 17 and 21 years of age, psychostimulants in some cases may cause permanent stunting of growth in late adolescence (25). Spencer et al. (26) present data indicating that the height effect may be more due to the condition of ADHD itself than to the treatment.

In terms of a differential diagnosis of height and weight loss, organic conditions must be ruled out, such as food allergies or sensitivities, gastrointestinal tract diseases (ulcers, malabsorption syndromes), endocrine problems (growth hormone or thyroid hormone), and malignancies. Psychosocial causes must be considered, ranging from malnutrition, failure to thrive, and child abuse.

The risk of compromised weight and height, especially in late adolescence, can be minimized by choosing an alternative medicine, or, if a stimulant is necessary, monitoring the height and weight carefully and stopping the

stimulant if any significant delay is noted. The use of a drug holiday (summer vacation and school holidays) is recommended, as is using the minimum required dose necessary to improve behavior. Alternative medications range from the tricyclic antidepressants (although imipramine and desipramine have fallen into disrepute because of reports of sudden death), buproprion, and the alpha2 agonists. Neuroleptics should be tried as a very last resort because of the extrapyramidal side-effect risk (see Section VI, on tics, for alternatives to stimulants).

E. Abdominal Pain

This adverse effect usually disappears over time. When using pemoline, liver function tests (LFTs) must be drawn in order to rule out a chemical hepatitis, which may present as gastrointestinal (GI) upset. The medication should be given after breakfast or lunch. If these measures fail to relieve the GI upset, then antacids can be prescribed or a trial of sustained-release methylphenidate or dextroamphetamine, which are absorbed more slowly, can be tried. The clinician should rule out gastric pain, which may be related to peptic ulcers.

F. Physiological Rebound Effect

This usually occurs at the end of the afternoon when drug plasma levels are decreasing. Children may present with irritability, overtalkativeness, noncompliance, excitability, motor hyperactivity, and insomnia starting up to 5 hr after the last dose. In other words, the child's rebound behavior may be as bad as or worse than his or her original symtomatology. One possible alternative is to add a small afternoon dose, such as 2.5 or 5 mg of MPH. Another possibility is to switch to slow-release preparations. They have a greater delay in the onset of action and, for some, their effect may not last as long as a second dose of the medication. The clinician may elect to combine the short- and long-acting preparation of either MPH or dextroamphetamine. For example the child could receive the short- and long-acting preparations in the morning supplemented by another short-acting preparation at lunch.

Children should be warned not to chew the sustained-release MPH tablet, as unpredictably high concentrations of the drug in the blood may occur, with resulting toxic effects (27). The amphetamine spansule does not present this problem. As mentioned previously, clonidine may be used for treating both insomnia and/or behavioral rebound. If clonidine is given precisely for this purpose, it should be timed so that it is effective while the stimulant level

is falling. Alternatively, if the child's overall behavior seems out of control, the clinician may need to readjust the dosage or try a different medication.

G. Decreased Cognitive Ability or Cognitive Constriction

Psychostimulants may cause cognitive constriction in tasks that call for changes in mental set, or what has been termed divergent thinking. It has been speculated that high doses of stimulants may cause overfocusing or perseverative responding to situations requiring flexibility in problem solving. This usually only occurs at doses higher than 1 mg/kg per day and is usually not seen at 0.3 to 0.69 mg/kg per day (28) The effect, however, has not been demonstrated in controlled studies looking for it (29). Rapport (30) has shown that some children are quieted down by the medication but show no gain in cognitive ability. The clinician should review his or her assessment and rule out any other cause of decreased cognitive ability, such as a learning disability or a mood, anxiety, and psychotic disorder. Many ADHD children with learning disabilities try to hide their deficits by appearing as class clowns or setting up situations where their acting out leads to removal from the classroom. ADHD children may appear to be falling behind academically as expectations rise with successive school years.

H. Behavioral Toxicity

There is some question as to whether higher dosages of stimulants not only increase focus and decrease negative oppositional behavior but also actually inhibit prosocial behavior (10). Parents will especially notice that the child is no longer his or herself, is too serious, or is not spontaneous. Behavioral toxicity has also been interpreted as meaning that the medication's effects mimic symptoms it was originally supposed to control. In both situations, the treatment is to reduce the dosage—or, if the effect persists, to change or to stop the medication.

I. Mood Effects

Important differences have emerged between children's and adults' reactions to the effects of dextro-amphetamine on mood. While amphetamine had a consistent euphoriant effect on adults, it produced dysphoria, irritability, and crankiness in both normal and hyperactive children (31). This age-related dif-

ference in response is consistent with recent case reports of adverse behavioral side effects including dysphoria, anxiety, and hallucinations in some children given ordinary doses of other potent, centrally active sympathomimetic agents such as the nasal decongestant oxymetazoline (Dristan) and pseudoephedrine (Actifed and others) (32,33). It is also believed that steroids produce euphoria much less frequently in children than in adults (34).

As a first step, the dose should be reduced or the medication changed to a long-acting preparation. In adding a second agent, the lowest dose should be given—in the case of fluoxetine, 5 to 10 mg/day. Wilens and Biederman (20) recommend considering a comorbid mood disorder. In an open trial, Gammon and Brown (35) have added fluoxetine to stimulant treatment in ADHD children and found improvement, especially in children who had more prominent mood symptoms.

J. Impaired Liver Function

Impaired liver function has been observed only with the use of pemoline. Hepatitis with elevated liver function tests (LFTs) is observed in nearly 3% of children receiving this drug. Unfortunately this complication does not always remit upon discontinuation of this drug. If the baseline LFTs are abnormal, then pemoline should not be prescribed. Nehra et al. (36) reported a review of 100 cases of hepatitis due to the administration of pemoline and stated that the reaction appeared as early as 1 week or as late as 1 year after having taken the drug. In their discussion, they stated that pemoline-induced hepatic injury appeared to be hepatocellular, that the mechanism of injury was clearly idiosyncratic rather than inherent toxicity of the drug, and that a group of adolescent patients appear to be susceptible to other hepatotoxins; this may present a clinical dilemma to the physician. Patterson (37), in a letter to the editor of the Southern Medical Journal, suggests predrug serum baseline level for SGOT, SGPT, LDH, and alkaline phosphatase. He suggests that LFTs be measured every 2 weeks for the first 6 weeks and then every 2 months. The hepatocellular damage appears to be reversible after discontinuation of the drug in most cases.

However, some cases of hepatotoxicity have proven fatal. In a letter issued by the company itself (January 13, 1997), representatives for Abbott Laboratories (38) state that the association between pemoline and life-threatening hepatic failure should make physicians consider other agents than pemoline as first-line agents for the treatment of ADHD. They go on to state that since its marketing in 1975, 13 cases of acute hepatic failure have been re-

ported to the FDA. Of these 13 cases, 11 resulted in death or liver transplantation, usually within 4 weeks of the signs of liver failure. The earliest onset occurred 6 months after pemoline therapy, and some cases were accompanied by a prodrome (dark urine, anorexia, malaise, gastrointestinal symptoms), while in other cases there was no identifiable prodrome before the onset of jaundice. In reviewing these cases, it was not clear whether the recommended baseline and follow-up LFTs were predictive of acute liver failure. In other words, even with conscientious monitoring of LFTs liver problems can develop suddenly and unpredictably.

Because of these limitations, pemoline is no longer recommended as a first-line treatment for ADHD, and parents should be informed of the hepatotoxicity danger. If there is a risk that the patient or the parents may not comply with regular follow-up, the drug should not be prescribed.

K. Cardiac and Blood Pressure Anomalies

Stimulants should not be prescribed to children with baseline tachycardia and hypertension (39). When tachycardia and hypertension are present after the initiation of therapy, the effects on heart rate and blood pressure are usually not clinically significant and often do not require that the medication be discontinued. Increases in blood pressure and pulse are an effect of these agents and are present in virtually all of the medicated children. Blood pressure and pulse monitoring should be checked at each visit, especially when the dosage is increased. An ECG is usually not necessary at baseline but should be done if there are prominent cardiac symptoms such as palpitations, irregular pulse, shortness of breath, syncope, and dizziness. A cardiology consultation should be sought if symptoms persist.

L. Seizures

There is no increase frequency of seizures with the use of stimulants (40). Careful monitoring is required when stimulants and anticonvulsants are coadministered, as stimulants tend to increase the blood levels of these medications.

M. Overdose

Overdosing with stimulants results in hyperactivity secondary to their sympathomimetic effects, with resulting tachycardia, hyperthermia, and hypertension. Psychosis and delirium may occur. An overdose may result in death

because of hypertensive, hyperthermic, cardiovascular, or epileptic complications.

Such cases are medical emergencies and require urgent treatment. Paranoid psychosis is best treated with chlorpromazine 50 mg PO or IM four times a day, since it blocks both dopamine and alpha-adrenergic receptors, thereby serving as both an antipsychotic and antihypertensive agent. Severe hypertension and tachycardia are treated with propranolol 1 mg intravenously every 5 min up to a maximum of 8 mg (41). When the hypertension is mild, haloperidol, 5 mg bid, is probably a better choice, since it is less sedating and less anticholinergic. On the other hand, if extra sedation is necessary because of agitation, then the benzodiazepines are a safe alternative, such as lorazepam 1 to 2 mg PO/IM. It is the only benzodiazepine that can be given IM. Seizures can be treated with lorazepam or diazepam.

N. Drug-Induced Psychosis

Overall, this adverse event is rare, with fewer than thirty childhood cases having been reported (42). This reaction may occur de novo or in individuals predisposed to psychosis. High doses of amphetamines regularly induce brief paranoid psychoses in adults. Psychosis is a contraindication for stimulants. The psychosis may be iatrogenically induced when the disorganization resulting from the drug's effect is interpreted by the clinician as a worsening of the presenting symptom and more medication is given, resulting in more prominent psychotomimetic effect (1).

Ney (43) first reported the occurrence of psychotic phenomena, including auditory, visual, and tactile hallucinations, in an 8-year-old child receiving therapeutic doses of dextroamphetamine. Lucas and Weiss (44) cited a case of a 15-year-old girl who had been on 40 mg/day of methylphenidate for over 5 years; she developed visual and olfactory hallucinations, culminating in catatonic withdrawal. Medication termination promptly relieved the symptoms. A 10-year-old boy with severe behavioral difficulties and dyslexia also developed visual hallucinations and became physically abusive after three doses of 10 mg of methylphenidate. A case of MPH-induced mania has also been reported (45).

The best treatment for such complications is careful exclusion of children with a personal or family history suggestive of psychosis and regular monitoring of patients on high and long-term doses of stimulants. There is controversy as to whether children with pervasive developmental disorders are more vulnerable to the psychotomimetic effects of stimulants.

O. Drug Abuse

When psychostimulants are taken in therapeutic doses, tolerance does not develop in children other than the adjustments required in some individuals for increased metabolism as they grow older. Individuals who abuse stimulants for their euphorigenic effect become tolerant of high doses that could harm or kill persons without that tolerance. They may develop physical and psychological dependence on these substances. Tolerance to the euphorigenic effect develops quickly. When these drugs are taken in large, nontherapeutic quantities, the following signs and symptoms may appear:

1. Sympathomimetic overload, including dry mouth, pupillary dilation, and bruxism

2. Stereotyped behavior

3. Irritability/emotional lability

4. Paranoia/formication

The clinical picture of chronic abuse may resemble schizophrenia, including psychosis; auditory, visual, and tactile hallucinations; and ideas of reference. Psychological withdrawal after chronic abuse is common, although physical withdrawal does not occur. Careful monitoring for a resulting dysphoria and/or major depressive disorder with feelings of hopelessness and suicidal ideation is important (46).

In terms of the different stimulants, dextroamphetamine is the most euphorigenic, MPH is less so, and pemoline not at all (14). Although euphoria is thought to be rare in prepubertal children, at least one case has been reported in an 11-year-old boy taking MPH (47).

There was an epidemic of stimulant abuse in Sweden in 1971, which prompted the FDA to reclassify MPH as a schedule II drug (abuse potential). Pemoline is not classified as a class II drug. Physicians are now obligated to obtain a Drug Enforcement Agency (DEA) registration number, particularly in those states with multiple-prescriptions programs. This monitoring by state authorities makes it possible to expose illicit distribution of psychostimulants.

Adolescents and adults who are already abusing other drugs may experiment with stimulants alone or in combination with other street drugs. In a memo to the American Pharmaceutical Association, editors Hincle and Winckler reported that one of the recent trends in drug abuse is snorting MPH (48). Students are among the highest users, and they do it to ‘‘study harder,’’ ‘‘party harder,’’ or just for the buzz. Hincle and Winckler feel that the drug is addictive and, especially if snorted, can result in tremors, seizures, hyperten-

sion, psychosis, and stroke. Its abuse potential is enhanced by its low cost on the street, its wide availability, and the misconception that since it is a "legal" or "prescribed" drug, it must be safe. Physicians must be careful not to minimize these problems in prescribing stimulants. There have been reports of intravenous drug abusers crushing MPH tablets and suspending the particles in liquid, then injecting the liquid as a way of prolonging a cocaine "high." Intravenous amphetamine may lead to necrotizing angiitis of the brain.

Of equal concern is whether the child with ADHD has a substance- abusing parent who takes stimulants. The parent may either experiment with the child's medication him or herself or sell it on the street to support a drug habit. The parent may call the physician and claim that the medication was lost or that the child flushed it down the toilet. Adolescents who control their own medication may face similar problems. Concurrently there has been pressure from different groups, especially parent groups, who want to loosen restriction on the production and prescription of MPH. Physicians must play a vital role in public policy regarding the psychopharmacological treatment of ADHD.

P. Negative Self-Attributions

We mention this as a side effect but it is an essential part of the therapeutic relationship, as the clinician must be aware that his young patients may feel socially ostracized for taking medication or may develop the belief that they cannot function without the medication. Often the physician may be in the middle of a conflict between the parents and the child or between the school and the family. In such instances physicians must remind themselves that their role is to serve the best interests of the child.

Q. Other Rare Side Effects

These are mentioned in the Physicians Desk Reference and include alopecia and leukocytosis. A complete blood count should be included once a year as part of the general physical examination.

V. LEGAL ASPECTS OF PRESCRIBING PSYCHOSTIMULANTS

With respect to MPH, the Compendium of Pharmaceuticals and Specialists (CPS) of the Canadian Pharmaceutical Association states that the safety and

efficacy of MPH have not been established in the under-6 age group and that dextroamphetamine is not recommended for the under-3 age group. In actual clinical practice, MPH is frequently used in the under-6 age group and appears to be preferred by clinicians over dextroamphetamine. We do not think that a physician would get into trouble with the law for prescribing MPH in children under age 6, bearing in mind the usual standard of prudence in clinical practice.

Concerning the addiction and abuse potential of dextroamphetamine and possibly methylphenidate, we speculate that the physician may be liable if the usual standard of vigilance is not exercised in terms of a proper assessment that rules out potential drug abuse (more problematic in the case of adolescents and children with substance-abusing parents) and of adequate follow-up at regular intervals. The physician must use his or her judgement as to what constitutes adequate follow-up.

Another potential legal issue is whether the school has a right to insist that a student be medicated. As far as we know, at least in Canada, even minors cannot be forced to receive treatment. However schools usually find a way around this by using different tactics (i.e., they will keep suspending a child until the parents do something).

Can a parent insist that his or her child be medicated? This depends on a lot of factors. The age of consent varies across different countries and states. In the case of an older child (say 12 or 13) who is asked for consent and refuses it, the legal argument could be made that ADHD is not a life-threatening condition and that therefore treatment is not compulsory. No matter what the age group, a power struggle over the medication is not a good situation for anyone involved.

VI. STIMULANTS AND TICS

A. What Is the Pathophysiology of Tics?

Sympathomimetic agents increase stereotypical behavior in primates. In fact, one of the measures of dopamine-blocking agents is the extent to which such behaviors can be reduced in animals whose stereotyped behavior has been induced by stimulants. The accepted theory has been that since tics are the result of excessive dopaminergic activity, dopamine agonists such as the stimulants should exacerbate tics and dopamine-receptor blockers should ameliorate them.

B. Do Stimulants Induce Tic Disorder?

It is not surprising that some individuals exposed to stimulants may exhibit an increase in stereotypical behavior, including tics. The relationship between psychostimulants and tics has been known for some time, but the major concern now is that possibly the susceptibility to a tic disorder or Tourette's syndrome (TS) may not only be increased but can be made permanent by the use of stimulants. Initially it was thought that stimulants could cause irreversible TS. What appears more certain is that stimulants exacerbate TS. This has been interpreted to mean that stimulants may not directly cause tics by themselves but might unmask an underlying susceptibility to TS.

C. What Is the Prevalence of Tic Disorder in Children Treated with Stimulants?

There is a great overlap between TS and ADHD (in one study as many as 48% of TS patients received a diagnosis of ADHD before a diagnosis of TS) (49). The prevalence of TS is approximately between 1 and 6 cases per 1000 boys (50). One of the definitive studies done by Denckla et al. (51) reported that 1.3% of a large population of patients (1520) with minimal brain dysfunction treated with MPH developed transient tics. Of the 20 cases identified, 14 developed new onset of motor tics and 6 experienced an exacerbation of their preexisting tics during MPH administration, showing that methylphenidate treatment in children with minimal brain dysfunction (MBD) only rarely elicits tics. It has been estimated that less than 1% of ADHD children treated with stimulants will develop a tic disorder and that in 13% of these cases MPH may exacerbate preexisting tics (52).

Erenberg et al. (53) reviewed the records of 2000 TS patients; 48 had been treated with stimulants (42 with MPH, 13 with pemoline, and 5 with amphetamine). Among 39 patients with preexisting tics, stimulants increased tic severity in 11, produced no change in 26, and decreased tics in 2. Tics could occur with any of the commonly used stimulants (MPH, dextroamphetamine, and pemoline).

D. Does Prior Exposure to a Neuroleptic Predispose a Child to the Development of Tics?

There are a few case reports that suggest such a relationship. Mitchell and Mathews (54) reported a 10-year-old who had been treated with thioridazine (no previous movement disorder reported) for hyperactivity who was started

on pemoline and developed motor tics. When pemoline was stopped the tics disappeared, and when the child was rechallenged with pemoline, the tics recurred. Sleator (55) reported a 6-year-old child with TS, also treated previously with thioridazine, who developed exacerbation of tics when pemoline was introduced. The child had the same response to MPH. Feeney and Klykylo (56) report a case of a 14-year-old girl on MPH and fluoxetine who developed tardive dyskinesia after treatment with risperidone.

E. Does Switching to Another Psychostimulant Help or Worsen the Predisposition to Tics?

There are limited data, but there is at least one report showing that switching from methylphenidate to pemoline worsened the tic disorder (57).

F. Are Stimulants More Prone to Induce Motor or Vocal Tics?

Stimulant medication may induce both motor and vocal tics, but motor tics may be more easily detected and hence reported more often.

G. Are There Any Other Possible Movement or Behavior Disorders Associated with Stimulant Use?

If we include in this category stereotypical or self-directed behavior such as lip licking, lip smacking, and picking of the fingertips, this—as well as choreiform and choreoathetoid movements—has been reported by Sallee (58,59) for pemoline. Psychostimulants may not only lead to compulsive self-administration of the drug but are well known to elicit repetitive behavior with no obvious goal or reinforcer in normal humans and animals. In animals, repetitive chewing, lip smacking, licking, and grooming can be elicited by a single or chronic doses of amphetamines. In humans, the stereotypical behavior can be more complex, such as disassembling watches and dismantling objects that are in perfect working order. Other repetitive behaviors include bruxism, nail biting, compulsive nail polishing, continuous dressing and undressing, sorting of objects in a handbag, and obsessive housecleaning. These stimulant-induced behaviors resemble to some degree the compulsive, repetitive behavior and movements characteristic of TS, a similarity strong enough to suggest that both phenomena share a common dopaminergic mechanism (60).

H. What Is the Management?

In terms of management of tics, there are different opinions. Barkley et al. (10) suggest that the medication be stopped immediately if there is a new onset of tics in a child with no previous personal or family history of TS. The tics usually subside within 7 to 10 days. The stimulant may be resumed at a lower dosage if the child's behavior deteriorates. Gadow (61), however, is more in favor of continuing the stimulant, since the tics may diminish on their own. Theoretically, if stimulants unmask TS or cause appearance de novo of tics, there should be a dose relationship (i.e., the incidence of this side effect should increase with dosage). Only well-designed double-blind studies employing multiple dosage levels can answer this question, but there are only a few well-designed studies that address it. Recent data from Gadow (61) suggest that a substantial majority of those children with preexisting tics have no exacerbation of tic severity when given up to 0.5 mg/kg per day of MPH.

The parents and child should be informed that simple tics such as the "bunny rabbit nose,'' buccal/lingual tics, and simple picking behavior may be transient and nonproblematic. Most authorities recommend that stimulants be immediately and permanently discontinued when TS is observed or multiple motor tics occur (46). Therefore the most up-to-date recommendation in light of Gadow's recent data is that stimulants can be used or continued with mild tics or TS but should be stopped if there is a significant increase in the severity or frequency or if multiple tics appear.

Some clinicians have suggested combining a neuroleptic and a stimulant for these patients, but this has not been widely endorsed. Alternatively, clonidine may be added if there is a need to keep the child on a stimulant, or it can be tried on its own. It should be borne in mind that clonidine can cause depression in 5% of cases (62). Guanfacine (Tenex) is a newer alpha2a adrenergic agonist that is less sedating and hypotensive than clonidine (50). If the child must be taken off the stimulants and clonidine is not effective to control ADHD, one of the antidepressants may be used, such as imipramine (between 2.5 and 5.0 mg/kg per day), desipramine (same dosage), nortryptiline (50 to 150 mg/day) and buproprion (between 100 and 250 mg/day or 3 to 7 mg/kg per day). Desipramine has a more favorable side-effect profile but has been associated with lethal cardiotoxicity; therefore ECG monitoring is essential. Among the neuroleptics, pimozide (1 to 2 mg/day up to 10 mg maximum) and haloperidol (0.05 to 0.15 mg/kg per day) have been recommended for TS, whereas chlorpromazine (0.25 mg/kg tid to qid) and thioridazine (0.5 mg/kg divided bid to tid up to a maximum of 3.0 mg/kg per day) are sometimes

used for management of ADHD (46). Neuroleptics for the treatment of ADHD should be considered as a last resort.

VII. SPECIAL POPULATIONS

A. Mental Retardation

Gadow and Poling (63) reviewed the literature on the use of stimulants in this population and concluded that the stimulants were highly effective in reducing symptoms of hyperactivity and conduct disorder in some individuals regardless of the degree of mental retardation (MR). ADHD children who are also mentally retarded may benefit if their mental age is over 5 and their IQ is over 55. Patients with more severe retardation have a lower response rate and a higher rate of side effects (64). Handen and colleagues (65) demonstrated that MR children with ADHD may be at a significantly greater risk of developing side effects from stimulant use than 7nonretarded children. Methylphenidate significantly decreased the rates of hyperactivity, irritability, moodiness, and anxiety, but 22% of the children needed to have their medication discontinued owing to the appearance of intolerable side effects, including motor tics and severe social withdrawal.

Stimulants can help children with ADHD who also have fragile-X syndrome, the second most common known cause of MR (66), as well as children with head trauma and organic brain disease (46). These patients are not at any greater risk for seizures secondary to the stimulant use.

B. Medically Compromised Children

Stimulants can be quite helpful in children who are medically compromised and have significant behavior problems secondary to ADHD. For example, stimulants are used in children with kidney problems; however, the dosage must be adjusted according to the amount of kidney function remaining. Although the manufacturer's insert cautions that stimulants may lower seizure threshold in children with epilepsy, McBride et al. (67) treated 23 children who had seizure disorders of various types, 15 of whom received concomitant anticonvulsant medication; no increase in seizures was found. Stimulants are considered safe in children with seizure disorders as long as the clinician monitors them closely for any increase in seizure frequency or severity.

C. Autism

Birmaher and colleagues (68) treated nine hyperactive, autistic children with MPH and found good results and no adverse side effects. Strayhorn et al. (69) treated two autistic children with MPH and found improvements in some ADHD symptoms but also an increase in sadness and temper tantrums. Realmuto et al. (70) treated two autistic children; one regressed while the other showed no change. In summary, stimulants are not absolutely contraindicated in autistic children with ADHD features, as they were once thought to be, but each case must be judged individually.

VIII. SIDE EFFECTS OF OTHER CNS STIMULANTS (CAFFEINE, THEOPHYLLINE, THEOBROMINE, AND OTHER SYMPATHOMIMETICS)

For the clinician, knowledge of the various stimulants implies taking a rigorous history of the use of caffeine-containing products, weight reduction agents, and cold preparations that may have interactive or additive effects when combined with other stimulants. Adolescents and adults who are taking psychostimulants for attentional difficulties may not be aware of the total amounts of stimulants they are ingesting.

Caffeine, theophylline, and theobromine are three chemically related compounds known as methylxanthines. The major sources of caffeine are coffee, tea, soda, and over-the-counter medications, while chocolate, cocoa, and chocolate milk are the main sources of theobromine. In addition, both theophylline and theobromine are found as metabolites of caffeine consumed in foods and beverages. Theophylline and caffeine are potent stimulants of the CNS; theobromine is virtually inactive in this respect. Traditionally, caffeine has been considered the most potent of the methylxanthines; however, theophylline produces more profound and more dangerous CNS stimulation than does caffeine (71).

The three main actions of methylxanthines on the CNS are intracellular mobilization of calcium, inhibition of phosphodiesterases, and antagonism of adenosine receptors (72). The action thought most likely to account for the behavioral effects in humans is the antagonism of adenosine receptors. Adenosine acts presynaptically to inhibit neuronal release of acetylcholine, norepinephrine, dopamine, gamma aminobutyric acid, and serotonin.

Adults ingesting caffeine usually experience less drowsiness, less fatigue, and a more rapid and clearer flow of thought. Comparable salutary ef-

fects of low doses of theophylline have not been investigated. As the dose of caffeine or theophylline is increased, signs of progressive CNS stimulation are produced, including nervousness or anxiety, restlessness, insomnia, tremors, and hyperesthesia. At still higher doses, focal and generalized convulsions are produced; theophylline is clearly more potent than caffeine in this regard. Finally, patients with panic disorders may be sensitive to the effects of methylxanthines (73).

In terms of the subjective effects of caffeine on children, caffeine (5 mg/ kg bid) produced negative subjective effects such as nervousness, jitteriness, stomach ache, and nausea in children who consumed little caffeine as well as in children exposed to higher dosages (74,75). The performance-enhancing effects of caffeine in children with ADHD appear to be less robust and caffeine does not consistently improve observer ratings of ADHD. Firestone et al. (76) found that caffeine in doses of 300 and 500 mg/day were not as effective in reducing ADHD as MPH. He found the side effects of both caffeine and methylphenidate to be minimal. Symptoms of caffeine intoxication in children are similar to those in adults. In addition, it was found that the ability of asthmatic children to perform repetitive tasks requiring concentration declines during periods of medication with theophylline (77).

There have been frequent reports of the effects of methylxanthines on the metabolism of other drugs through hepatic and renal interactions. Systemic agents used to treat asthma, such as theophylline, can produce agitation, weakness, palpitations, and dizziness when given with stimulants. Greenhill (3) suggests referral of these children to a pediatrician or allergist, to switch from the oral preparation to an inhalant, as a way of avoiding the additive sympathomimetic effects. Concerning a possible lithium interaction, there is some evidence that methylxanthines increase renal lithium clearance (78). Jefferson (79) recommended stopping coffee in two of his patients with lithium-induced hand tremor who drank large amounts of coffee, but their tremor worsened upon coffee cessation, possibly through the mechanism of increased blood lithium levels, since caffeine increases renal lithium clearance.

Looking at inhibitors of the cytochrome P450 hepatic enzyme system, it has been noted that the selective serotonin reuptake inhibitor fluvoxamine is a potent inhibitor of this system, especially the P450 CYP1A2. Since theophylline is metabolized by this system, when both drugs are given together, toxic elevations of theophylline may be caused, as in asthmatic children (80). It has also been reported that concurrent fluvoxamine and caffeine intake leads to decreased clearance and increased half-life of caffeine, which could lead to caffeine intoxication in some patients who continue the same level of coffee or cola ingestion (81). Theophylline's pharmacokinetics may not be affected

by paroxetine, since paroxetine has been shown to inhibit the P450 CYP2D6 but not the CYP1A2 or CYP3A families of enzymes.

In terms of other sympathomimetics, adverse behavioral side effects including dysphoria, anxiety, and hallucinations may occur in some children on ordinary doses of potent centrally active sympathomimetic agents such as the nasal decongestants oxymetazoline (Dristan) and pseudoephedrine (Actifed) (32,33). In adults, adverse effects related to the use of ephedrine and associated alkaloids (pseudoephedrine, norephedrine, and N-methylephedrine) as dietary supplements ranged from headache to death (82). Children and adults who are on stimulants should therefore not use these compounds, as certain additive effects may occur.

IX. SIDE EFFECTS OF NICOTINE AS CNS STIMULANT

A recent report (1994) of the U.S. Department of Health and Human Services (83) estimates that more than 3 million adolescents use nicotine through tobacco smoking and that 25% of 17- to 18-year-olds are current smokers.

The effects of nicotine on the central nervous system appear to be more complex than originally thought; the mechanisms of action have not been fully clarified but may involve sites of action at the cholinergic, serotonergic, noradrenergic, and dopaminergic receptors (84). To date, however, it has been demonstrated that a significant component of CNS activity is through receptors usually responsive to the neurotransmitter acetylcholine (85). Nicotine-induced acetylcholine release results in desynchronization of the cortical ECG. The most consistent finding of nicotine effects on human cognition is the improvement of sustained attention (i.e., vigilance) under continuous rapid information-processing conditions. The neuroanatomical site for these electrophysiological effects is most likely the hippocampus where nicotinic receptors are activated (86).

In terms of interaction with other drugs, smoking induces liver microsomal enzymes and therefore could theoretically cause decreased levels of drugs to be metabolized by the liver. For example, it has been shown that smoking decreases levels of clozapine and haloperidol by 38% (87). The mechanism may be through the effect of benzopyrenes and related compounds on the P450 system. Smoking increases the metabolism of caffeine; therefore smoking cessation increases caffeine levels by 50 to 60% (88). Conversely it has been reported that amphetamines may act as behavioral stimulants to in-

crease cigarette smoking (89), either through the mechanism of increased subject-rated satisfaction or an increase in general learned or stereotypical behavior. An uncontrolled trial suggested that MPH decreased tobacco withdrawal (90).

The practical value for the clinician rests on inquiring, through a thorough history about the extent of smoking in an adolescent or adult and determining the effect on possible interactive mechanisms (i.e., through hepatic microsomal enzyme inhibition or induction) with other psychostimulants or sympathomimetics.

X. DRUG INTERACTIONS

The issue of drug interactions is becoming increasingly important because of the extended use of stimulants not only in children but among adults as well. In addition, the question of treating children with comorbidities or those who show only a partial response is forcing many clinicians to treat children with multiple medications. This section deals with possible pharmacokinetic and pharmacodynamic interactions. The best way to deal with side effects is to prevent them; therefore a good knowledge base is the physician's best tool. Most of the following interactions have been reported through a Medline search through Micromedex from 1974 to 1996.

In general stimulants inhibit the metabolism of anticoagulants such as warfarin and coumadin, anticonvulsants, phenylbutazone, and heterocyclic antidepressants. Stimulants also decrease the hypotensive effect of guanethidine. They potentiate the effects of all sympathomimetics and recreational stimulants.

Concerning antidepressants, stimulants should not be administered with monoamine oxidase inhibitors (MAOIs such as pargyline, selegiline, phenelzine, procarbazine, tranylcypromine, clorgyline, and isocarboxazid) or wait till 14 days after stopping the MAOI in order to avoid a hypertensive crisis due to release of excessive norepinephrine. This should not be a problem with moclobemide, a reversible MAOI antidepressant.

In combinations with tricyclic antidepressants, the action of both drugs may be enhanced, due either to enhanced release of norepinephrine (amphetamine) or inhibition of the hepatic metabolic pathway (MPH). This interaction has been reported for amitryptiline, imipramine, desipramine, amoxapine, dothiepin, doxepin, nortriptyline, trimipramine, clomipramine, and protriptyline. In combination with imipramine, stimulants may cause confusion, mood lability, aggression, and psychosis. In addition, it has been reported that methylphe-

nidate can counteract the hypotensive effect of antidepressants and raise blood pressure as high as 170/120. However, Pataki and Carlson (91) have reported that the combination of desipramine and MPH is well tolerated.

In particular MPH elevates the concentration of the serotonin reuptake blocker fluoxetine, greatly enhancing the ability of both compounds to produce agitation (42, p. 434). It has been our experience that fluvoxamine, which inhibits the P450 system more than any other selective serotonin reuptake inhibitor, may cause extreme agitation on its own or in combination with MPH in certain cases, but it can be well tolerated in other cases (92). Gammon and Brown (35) have used fluoxetine as an add-on treatment to treat ADHD in children with secondary mood disorders and found that the combination was well tolerated.

Additive effects between psychostimulants and the systemic agents used to treat asthma, such as theophylline, can produce feelings of dizziness, tachycardia, palpitation, weakness, and agitation. Stimulants may counteract the effects of antihistamines and benzodiazepines. Concerning the interaction with neuroleptics, these comprise a broad category of agents; therefore there are a variety of mechanisms of interaction. Phenothiazines (chlorpromazine, chlorprothixene, fluphenazine, mesoridazine, perphenazine, pipotiazine, prochlorphenazine, thioridazine, trifluoperazine, triflupromazine, and thiethylperazine), act by inhibiting the uptake of neurotransmitters into the adrenergic neuron, which could result in the inhibition of the central effects of sympathomimetics. In addition, amphetamines may inhibit the antipsychotic effect of chlorpromazine, and chlorpromazine may reverse the anorectic effect of amphetamines.

Concomitant haloperidol therapy may result in a decreased CNS effect of amphetamine, and this interaction may be useful in the treatment of amphetamine abuse. The antagonism of sympathomimetics by blocking the uptake of neurotransmitters into the adrenergic neuron with antipsychotics seems counterintuitive to their combined use with stimulants in the treatment of ADHD. This fact has not prevented clinicians from simultaneous prescription of antipsychotics and stimulants, but the pharmacological basis of the combined use is not clear.

Amphetamine may act synergistically with phenytoin or phenobarbital to increase anticonvulsant activity. It also slows the intestinal absorption of phenytoin, phenobarbital, and ethosoximide. In terms of interactions with alpha- and beta-adrenergic agonists and antagonists, concomitant administration of clonidine (an alpha-adrenergic agonist) with amphetamine resulted in an increased duration of action. Dextroamphetamine blocks the action of some beta-adrenergic antagonists, such as propranolol. Lithium may inhibit the stim-

ulatory effect of amphetamines. The renal clearance of dextroamphetamine is enhanced by urine-acidifying drugs and decreased by urine-alkalinizing drugs (thiazides). The intestinal absorption is lowered by gastrointestinal acidifying drugs and increased by gastrointestinal alkalinizing drugs (46).

XI. CONCLUSION

In conclusion, stimulants are safe medications and are usually well tolerated. Knowledge of side-effect management becomes more important as more children are prescribed these compounds and they are on them for longer periods of time. Combined pharmacotherapy is indicated for treatment-resistant cases, partial responders, and children with other comorbid conditions. Careful monitoring of side effects ensures greater compliance and reassures parents. Frequent follow-up visits are necessary to judge the need for continuing treatment and effectiveness of the medication and to deal with any emerging side effects. The clinician must remember that pharmacotherapy is only one part of the treatment in a multimodal, comprehensive approach to helping the child with behavioral difficulties.

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10 Management of Side Effects of Psychotropic Drugs in Special Populations

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I. INTRODUCTION

Previous chapters in this book cover the recognition and management of side effects related to the major classes of psychotropic agents. It is important to recognize that in the clinical practice of psychiatry, there are groups of patients who may be particularly vulnerable to certain side effects or for whom typical side effects are more problematic. This chapter covers several such groups, discussing which side effects are more likely to occur or may present in a more severe form and what is known about the mechanisms of action. General guidelines are also provided, but more details about management of particular side effects can be found elsewhere in this volume.

II. GERIATRIC-AGE PATIENTS

Adults over age 65 are the fastest-growing segment of the population. Currently one in every eight Americans is over age 65; it is projected that this will change to one in every five during the first part of the twenty-first century. The elderly, because of their increasing burden of physical illness, are a highly medicated group. Psychotropic medications make up a significant portion of prescription drugs used by the elderly; only cardiovascular and analgesic medications are used more frequently than sedatives and hypnotics in this group (1). It is therefore of utmost importance for clinicians to be aware of the unique concerns in medicating older patients.

Before dealing with the practical aspects of prescribing psychotropic medications and assessing and managing side effects in the elderly, basic pharmacokinetic and pharmacodynamic principles are reviewed. The term pharmacokinetics refers to the processes of absorption, distribution, biotransformation, and elimination of the drug from the body. Pharmacodynamics, on the other hand, refers to the physiological and neurobehavioral effects of the drug. The aging process can affect both pharmacokinetics and pharmacodynamics in profound ways (2).

In the absence of gastrointestinal pathology, the absorption of psychotropic medications is not significantly affected by aging. However, many drugs taken by elderly patients for other illnesses (e.g., anticholinergics, antacids) can decrease gastric motility or alter ionization. Distribution of the drug, however, is significantly changed with aging. Most psychotropic agents (with the exception of lithium) are very fat-soluble. As people age, lean muscle mass and total body water decrease, while total body fat tends to increase. Therefore, a given dose of a drug in an older person is diluted or distributed more extensively in the peripheral tissues than in a younger person. The clinical implications of this are that elimination of the drug from the body may be delayed and the drug's effect may last longer than in younger people. Another factor increasing the potential for toxicity is protein binding. Most psychotropics are highly protein-bound and only the free fraction is active. Because plasma albumin tends to decrease with age, it is more likely that a higher percentage of drug will be unbound and therefore active. This could be associated with an increase in toxicity.

Most psychotropics go through hepatic metabolism. There are age-related changes in hepatic blood flow, and the process of oxidation by which the drug is metabolized may also be impaired. Both of these lead to slower metabolism, resulting in a longer half-life of the drug and its active metabolites. Decreases in kidney function as a result of aging or because of concomi-

tant disease (e.g., congestive heart failure, hypertension) can also contribute to decreased clearance of medication.

The elderly display greater sensitivity than younger people to the effects of medications even at the same concentration. This is thought to be a result of pharmacodynamic sensitivity—e.g., the receptor itself is more sensitized to the medication. In aggregate, for these pharmacokinetic and pharmacodynamic reasons, the elderly display a greater number and severity of side effects, often at doses typically considered ''too low'' to cause these side effects (2).

The side effects described for each class of drugs in the preceding chapters apply to the elderly as well. In some instances, these side effects may be magnified in intensity and be potentially more dangerous in the elderly. A brief description of these side effects for each class of medications is given below.

A. Antipsychotic Medications

The major side effects of antipsychotic drugs in the elderly are sedation, orthostatic hypotension, those due to anticholinergic properties, and movement disorders. The less potent neuroleptic medications (e.g., chlorpromazine, thioridazine) can cause significant sedation. Although this property may be clinically helpful (i.e., decreasing agitation and inducing sleep), there is a danger of the neuroleptic accumulating, with resulting increasing sedation over days and weeks. This can lead to confusion and exacerbate cognitive symptoms, particularly in patients with dementia or delirium. Orthostatic hypotension can lead to dizziness and falls. This is particularly troublesome in the elderly, who may already have lower cardiac output and are more prone to bone and hip fractures. The mechanism leading to orthostatic hypotension is thought to be blockage of alpha-adrenergic receptors. In general, the low-potency drugs also have high alpha-adrenergic-blocker properties. For these reasons, in most circumstances, the higher-potency drugs (e.g., haloperidol, fluphenazine) are preferable in the elderly.

The elderly are especially susceptible to anticholinergic side effects. This is a problem with certain neuroleptics and tricyclic antidepressants. The typical symptoms of dry mouth, constipation, urinary retention, tachycardia, and blurry vision all have increased significance in the elderly. Men with prostatic hypertrophy can be quite vulnerable to these medications, leading to acute states of urinary retention. Glaucoma can be precipitated as well. In addition, the elderly are more vulnerable to the central nervous system (CNS) side effects of anticholinergic medications. Disorientation, confusion, impaired

memory, visual hallucinations, and worsening of irritability and agitation can all occur. These symptoms are more likely to occur when older patients are taking a combination of neuroleptic and anticholinergic medications and/or nonpsychiatric medications with anticholinergic properties. To lessen the possibility of these side effects, efforts should be made to avoid these medications or combinations. If this cannot be done, lowering of the dose is an option. Finally, the addition of cholinergic compounds (e.g., bethanechol) might help in certain situations like urinary retention. In severe emergencies, physostigmine, a cholinesterase inhibitor, has been used. This should be done in a controlled setting with cardiac monitoring.

Movement disorders secondary to neuroleptics may be divided into those occurring early in treatment (e.g., dystonias, akinesia, akathisia, parkinsonian symptoms) and those that occur late in treatment (e.g., tardive dyskinesia). As opposed to the symptoms described above, it is the higher-potency neuroleptic drugs that are more likely to cause movement disorders, particularly the early-onset ones. The incidence of akathisia increases with age (3). This symptom can be troublesome for the elderly, and it may appear as if the patient is agitated. However, increasing the neuroleptic dose will make these symptoms worse. Like akathisia, neuroleptic-induced parkinsonism is more frequent in the elderly; it is estimated that 75% of elderly on chronic neuroleptic treatment experience this problem (4). Treatment of these side effects is best begun with a lowering of the neuroleptic dose. If this is not successful or cannot be accomplished because of an increase in psychosis or agitation, low dose antiparkinsonian agents may be administered. However, this must be done with care because of the increased risk of anticholinergic toxicity. Alternatively, one may choose low-dose benzodiazepines, beta blockers, or amantadine, though each of these has its own side-effects profile as well. In contrast to akathisia and parkinsonism, acute dystonic reactions occur less frequently in older patients; older patients may display the Pisa syndrome, where the trunk is flexed to one side.

Tardive dyskinesia (TD) is a later-appearing side effect in people exposed to neuroleptics. It must be distinguished from a number of late-appearing dyskinetic movements that have been described in elderly who have never had exposure to neuroleptic drugs. Risk factors for TD are advanced age, female gender, length of exposure to and amount of neuroleptic medication, concomitant medical illness, and presence of mood disorders (5). Obviously many of these risk factors make the elderly more vulnerable to develop TD. Because treatment of TD often is unsuccessful, every effort should be made to prevent its occurrence. Initial treatments include decreasing the dose of neuroleptic medication, eliminating use of anticholinergic medications, and

eliminating any stimulant medication that the patient may be taking. Benzodiazepines and propranolol may have some usefulness in decreasing movements.

Other less common but possible side effects include neuroleptic-induced catatonia, neuroleptic malignant syndrome, grand mal seizures, the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), and temperature dysregulations.

Although experience with novel or atypical antipsychotics in the elderly is limited, they may offer potential advantages in having a more benign side- effects profile (6). Medications such as risperidone, olanzapine, and clozapine offer advantages in decreasing the potential of movement disorders, though clozapine and olanzapine can be sedating and can cause orthostatic hypotension. Whether these new agents lessen the risk of developing TD in the elderly is not yet established.

B. Antidepressants

With the advent of newer agents to treat depression, clinicians now have a wider range of medications, many of which cause less disruptive side effects when treating the elderly. The tricyclic antidepressants (TCA), despite their well-known effectiveness, are prone to cause troublesome side effects in older people. Many of these side effects are similar to those discussed with antipsychotic agents, e.g., anticholinergic problems, orthostatic hypotension, and sedation. This is particularly true for tertiary amine TCAs (e.g., amitriptyline, imipramine, doxepin) but less so for secondary amines (e.g., desipramine, nortriptyline). Caution must be taken in using TCA and heterocyclic medications in patients with pre-existing cardiac conduction defects. Bundle branch blocks and partial or complete atrioventricular blocks have been reported, although not with trazodone (7).

The selective serotonin reuptake inhibitors (SSRIs) have a more favorable side-effects profile when used in older patients (8,9). These drugs have relatively low anticholinergic and hypotensive effects, although they may cause gastrointestinal symptoms, headache, dizziness, agitation, insomnia, sexual dysfunction, and, in some cases, sedation. Fluoxetine has the longest half-life of this group of medications, and this may be quite prolonged in older patients. Other new antidepressants with favorable side-effects profiles include buproprion, venlafaxine, and nefazodone (6). Although not specific to the elderly, drug interactions have been reported when some SSRIs are taken in combination with TCAs.

There may be a place for the use of monoamine oxidase inhibitors (MAOIs) in the treatment of geriatric depression (10). The side-effects profile

and concerns regarding dietary restrictions and use of concomitant medications are the same as in younger patients. Orthostatic hypotension may be particularly troublesome, and other potential side effects include peripheral neuropathy, weight gain, and exacerbation of cognitive problems.

Psychostimulants have been used in the treatment of depressed elderly, including frail and medically ill elderly (11,12). Their side-effects profile is relatively benign. There can be tachycardia, mild increases in blood pressure, agitation, and restlessness, but most of these are quite manageable. It is not clear whether or to what degree tolerance develops in this setting.

C. Mood Stabilizers

Although it is relatively rare for mania to present for the first time in an older patient, there are significant numbers of older patients who have had long- standing bipolar illness and are on mood stabilizers. In most cases, the mood stabilizer is lithium; there are few data on using more recently introduced mood stabilizers (e.g., carbamazepine, divalproex) in the elderly.

The side-effects profile of lithium in the elderly is the same as that in younger patients. Because of pharmacokinetic variables (e.g., decreased volume of distribution, decreased renal blood flow and clearance), these side effects may be seen at lower plasma levels than in younger patients. Certain side effects may occur with more frequency or be more serious in the elderly because of the consequences of the side effect and/or coexisting conditions. Confusion may occur at relatively modest blood levels; it is more likely to be seen when patients are taking other medications such as diuretics and non- steroidal anti-inflammatory drugs. Dizziness and ataxia may be problematic, leading to falls. Although cardiac toxicity is not usually a problem with lithium, this may be a more serious concern with older patients. Lithium's effect upon the kidney are well known. Because the elderly already may have reduced renal function, these effects may be more pronounced and conditions like diabetes insipidus or serious electrolyte imbalances may be seen. Careful following of electrolytes and lithium plasma levels should be done if the patient remains on lithium. Monitoring should also include being alert to changes in behavior, gait, and water drinking habits.

D. Anxiolytics and Sedative/Hypnotics

There is a large literature on the problems and controversies associated with benzodiazepine use in the elderly (13–18). The same pharmacokinetic and

pharmacodynamic variables leading to more side effects in other classes of drugs are involved in the use of benzodiazepines as well. The metabolism of the long-acting benzodiazepines (e.g., diazepam, chlordiazepoxide, clonazepam, flurazepam) leads to several active metabolites (e.g., desmethyldiazepam), which can increase the severity of side effects and/or prolong them. In some cases, the half-life of the parent drug and its active metabolites may be as long as 1 week (16). This causes increasing levels of side effects; moreover, after a long-acting benzodiazepine is stopped, side effects may persist for days while the drug and its metabolites are excreted. Intermediate and short-half-life benzodiazepines (e.g., lorazepam, alprazolam, oxazepam, triazolam) undergo less complex hepatic metabolism and have no active metabolites. Although withdrawal symptoms may be more pronounced with these shorter-half-life medications, they generally have a more favorable side-effects profile in the elderly (15,17,18).

The most significant side effects of benzodiazepines in the elderly are sedation, cognitive and psychomotor impairment, and cerebellar dysfunction. All may be seen at lower doses than would be expected to cause these side effects in younger patients. Sedation may be seen soon after taking the medication, but it may also persist; there can be significant hangover effects if a longer-acting agent is taken as a hypnotic. If a patient already has cognitive impairment, benzodiazepine use may make this impairment more serious, and disorientation and severe confusional states are not uncommon. Sedation in combination with ataxia and unsteadiness may make the elderly more prone to falls or other signs of motor incoordination. Psychomotor slowing, decreased reaction times, and reduced eye-hand coordination may all occur as side effects. The effects upon performance tasks such as driving skills could be problematic. Finally, there are concerns about dependence and withdrawal reactions, although there are no data indicating that these problems are more severe in the elderly.

Because of the concerns regarding benzodiazepines, the use of nonbenzodiazepine anxiolytic medications may be considered in elderly patients. Older drugs, such as meprobamate and barbiturates, have potentially serious toxic effects in the elderly, including being lethal in overdose; their use cannot be recommended. On the other hand, buspirone, an azapirone anxiolytic, has been shown to have efficacy in the treatment of the anxious older patients (19,20). It has a favorable side-effects profile and no particular problems in elderly patients are reported. As with younger patients, there are no data suggesting efficacy in panic disorder, and there is a lag time of up to several weeks before efficacy is seen.

Nonbenzodiazepine hypnotics like zolpidem may cause less side effects than benzodiazepines, though long-term use should be discouraged. However, tolerance and withdrawal reactions have been reported in the elderly (21).

E. General Guidelines

The adage "start low, go slow" applies to drug prescribing practices for the elderly. For almost all psychotropics, the starting dose should be approximately one-third to one-half of what would be considered a normal starting dose in a young person. Before prescribing psychotropics, extreme care should be taken in obtaining a medical history and a listing of other medications, including over-the-counter and home remedies. Drug interactions are a major source of side effects in the elderly; considering the large number of medications that elderly patients may be taking, drug interactions are exceedingly common. Whenever possible, decrease the number of drugs prescribed; this must often be done in concert with the primary care provider. Minimizing the use of drugs with significant anticholinergic properties is important, as is monitoring blood pressures, asking about changes in bowel and bladder function, inquiring about falls, and noting any behavioral changes. In addition, when the patient is on a neuroleptic, frequent examination for extrapyramidal symptoms (EPS) is indicated, as is some monitoring of temperature.

III. MEDICALLY ILL PATIENTS

Many of the considerations relevant to side effects in the geriatric-age patient hold true for the medically ill patient as well. Specific considerations include the nature of the comorbid medical disease and its effects upon behavior; how the medical illness may affect the metabolism and disposition of psychotropic medications; drug interactions; and how the side effects of psychotropic agents may affect the comorbid medical illness. Reviews of this broad topic, including lists of potential drug interactions, have recently been published (22–24). What follows is a brief discussion of major side effects by class of psychotropic in specific medical conditions.

A. Antipsychotic Medications

As with the elderly, the major side effects from antipsychotic agents in the medically ill relate to their anticholinergic, hypotensive, cardiac, sedative, and

movement disorder-inducing properties. Care must be taken in patients with preexisting cardiac conduction defects, particularly if they are on other medications affecting cardiac conduction. Delirious patients may be made worse with strongly anticholinergic antipsychotic agents. Debilitated patients may be more susceptible to neuroleptic malignant syndrome or neuroleptic-induced catatonia. Patients with Parkinson's disease may become worse with neuroleptics that cause extrapyramidal side effects. The newer antipsychotics, with their lower propensity to cause this problem, may be preferable in this setting (25).

B. Antidepressants

The most problematic side effects of antidepressants in the medically ill stem from the anticholinergic, alpha-blocker, and antihistaminic properties of these drugs. As noted above, this is mostly true for the tricyclics and less so or nonexistent with SSRIs and newer agents. In patients with preexisting cardiac conduction defects, TCAs can worsen this condition by prolonging the refractory period of the action potential of the cardiac conduction system. Thus, patients with second-degree heart block, sick sinus syndrome, bifascicular heart block, and prolonged QT intervals on their electrocardiograms (ECGs) are more at risk (26). Antidepressants can be used safely in the post-myocardial infarction period; however, because of the potential for arrhythmias, orthostatic hypotension, and so on, TCAs should probably be avoided. As noted above, glaucoma and prostatic hypertrophy are conditions where anticholinergic medications should be avoided. Rare reports of the serotonin syndrome have been linked to use of SSRIs in combination either with other psychotropic medications (e.g., MAOIs) or with opiate analgesics (e.g., meperidine). MAOIs should be used cautiously in hypertensive patients and those on pressor-like medications for other reasons.

C. Mood Stabilizers

Patients with renal disease are at risk for side effects when treated with lithium. As opposed to most other psychotropics, lithium is not fat-soluble, and its metabolism is not through the liver but through the kidneys. The use of traditional diuretics and other states leading to dehydration and volume depletion can raise lithium levels into the toxic range. Lithium has been given to patients undergoing renal dialysis, but the lithium is not excreted between dialysis

treatments; therefore dose adjustments and schedules need to be altered (27). Although lithium can cause hypothyroidism in a significant number of patients who take it, those with pretreatment elevations of thyroid-stimulating hormone (TSH) may be at increased risk.

Carbamazepine can cause a wide array of side effects. The most prominent ones involve the hepatic and hematological systems. Care must be taken in giving carbamazepine to patients with lowered white blood cell counts and those who have preexisting liver disease. Hyponatremia can also be seen in patients taking carbamazepine and in those medically ill patients with electrolyte disturbances (e.g., those taking diuretics, having congestive heart failure, etc.). Carbamazepine is associated with a large number of drug interactions owing to its metabolism through the hepatic cytochrome P450 system (see below). Because it can induce the metabolism of many other drugs, the available plasma levels of these other drugs (e.g., TCAs, neuroleptics, quinidine, propranolol) may be reduced when they are taken concomitantly. Alternatively, other drugs may inhibit the metabolism of carbamazepine, leading to toxic reactions. Examples of these drugs are verapamil, dilatazem, propoxyphene, and erythromycin.

D. Anxiolytics and Sedative/Hypnotics

Again, much of what has been said regarding problems of sedation and confusion with use of benzodiazepines applies to the medically ill patient. In addition, patients with severe respiratory problems may be vulnerable. Those who retain CO2 are at greatest risk, with the possibility of the benzodiazepine reducing their hypoxic response to ventilation. Benzodiazepines also should be used cautiously or not at all in patients with sleep apnea syndrome. Buspirone is a good alternative to benzodiazepines in the medically ill but is not useful for the immediate relief of anxiety. Some of the antidepressants, particularly those that are more sedating, may be useful to treat anxiety in the medically ill.

E. Patients with Central Nervous System Disease

Patients whose primary medical illness affects the CNS may be particularly vulnerable to side effects of medications that affect brain function. This holds true for disorders such as traumatic brain injury, stroke, and Parkinson's disease. Although many of the concerns discussed above apply equally well to these patients, it is important to highlight them regarding this group, be-

cause—as a result of their brain disorder—they often exhibit abnormal behaviors and are therefore frequently given psychotropic medication; the sites of their lesions may be the same as the sites of action of the drug, leading to idiosyncratic responses.

Unfortunately, there have been few controlled studies of the use of psychotropic medication in patients with traumatic brain injury. Finding the optimal dose can be more difficult, as these patients are often more sensitive to changes in dose than are others. Titrating upward slowly after beginning with low doses is the most prudent course. The use of antidepressants in patients with brain injury can lead to excess sedation, worsening of cognition due to anticholinergic side effects, and, at least theoretically, to a lowering of the seizure threshold. There have been a number of reports describing the use of antidepressants in poststroke depression. Although they are effective in this condition, there is an increased risk of side effects (e.g., delirium), particularly when using the older antidepressants that have higher anticholinergic side effects (28).

The use of antipsychotic agents in brain-injured patients may lead to a greater incidence of EPS. Neuroleptic malignant syndrome and tardive dyskinesia also may be more common in this population (29). Benzodiazepines can lead to worsening of balance, ataxia, and coordination—conditions likely to already be present in brain injured patients. In those brain-injured patients who are already confused and disoriented, sedating anxiolytics like the benzodiazepines may make these conditions worse. There have been reports of paradoxical violence in patients with brain injury who have taken benzodiazepines, but this is not a consistent finding.

Although some studies report no increase in seizures, at least one study (30) noted a marked increase during antidepressant treatment even in brain- injured patients who were concomitantly on anticonvulsant medications. The severity of the injury and the dose and timing of drug increases may be important variables related to the onset of seizures. There may also be interactions between antidepressants and anticonvulsive medications. Concomitant use of phenytoin, carbamazepine, and phenobarbital may lead to a lowering of the plasma level of antidepressants by inducing their enzymatic metabolism, while some of the SSRIs may increase plasma levels of phenytoin, valproate, and carbamazepine.

Treating patients with CNS manifestations of HIV disease is a challenge. As for other patients with brain injury, debilitation, and cognitive impairment, they are at risk for more and more severe side effects from the whole range of psychotropic agents (31).

IV. PREGNANT AND BREAST-FEEDING WOMEN

Much needed and serious attention has recently been given to the unique concerns regarding women who are pregnant or breast-feeding and who must be on psychotropic medications. Comprehensive reviews on this subjects have been written (32–36) and only a brief discussion regarding side effects is presented here. The concerns regarding the use of medication during this period relate to risks to the fetus (teratogenicity and neonatal exposures) when drugs are taken during pregnancy and side effects to the newborn from medication passed during breast-feeding.

Altshuler et al. (32) performed a comprehensive review of the literature regarding the major classes of psychotropics and their effect upon the fetus. They found a slightly higher rate of congenital malformations with the mother's first-trimester exposure to low-potency neuroleptics. There were less data but no evidence for this association with haloperidol and no available data on the novel antipsychotics. Although earlier reports noted an association of birth defects with TCAs, the more recent and methodologically rigorous studies do not support this. Major structural abnormalities were not found in infants of mothers taking SSRIs (32). One recent report noted that minor anomalies and perinatal birth complications were found to be more frequent in women taking fluoxetine during the third trimester (37), but another reported no problems in IQ, language development, or behavioral development in preschool children whose mothers had taken fluoxetine or tricyclic antidepressants during pregnancy (38). A higher-than-normal rate of congenital anomalies has been reported in a small sample of infants exposed to MAOIs in utero (32).

Early reports regarding exposure to lithium during pregnancy revealed a higher risk of congenital malformations, particularly related to the cardiac system; more recent reports corroborate this finding but indicate that the risk is much lower than was previously thought (39). Reports using alternative mood stabilizers (carbamazepine and valproic acid) indicate a higher risk of spina bifida with both medications in infants exposed in utero (32). First-trimester exposure to benzodiazepines may place infants at risk for cleft palate (32), although this is an inconsistent finding (40). Use of benzodiazepines or other CNS depressants late in the third trimester may lead to perinatal problems such as hypotonicity, failure to feed, and low Apgar scores.

Most psychotropic medications are excreted in breast milk, but in concentrations low enough not to cause significant problems. When these drugs must be utilized, paying attention to half-life and pharmacokinetics in relation

to the timing of breast-feeding can further decrease the concentration of drug delivered to the fetus (41).

V. PATIENTS FROM ETHNIC MINORITY GROUPS

The importance of considering the effects that culture and ethnicity have in health care is increasingly apparent considering the diversification of the population in all metropolitan areas. Ethnicity and culture exert powerful influences on the effects of a wide array of medications, including the majority of psychotropics (42,43). Numerous reports in the past four decades have indicated that substantial cross-ethnic differences exist in the dosage requirements and side-effects profiles of various psychotropic medications. Advances in the fields of pharmacokinetics, pharmacodynamics, and pharmacogenetics have begun to shed light on some of the mechanisms that may be responsible for these differences (42–47).

Although the clinical applications of this work are just beginning to be understood, it is useful to review the knowledge about the mechanisms underlying possible interethnic differences in side-effects profiles. Despite the fact that side effects unique to psychotropics have not been demonstrated in patients of a particular ethnic group, increased vulnerability to side effects and drug interactions may be seen, and clinicians need to be aware of this.

Metabolism has been identified as the most likely pharmacokinetic variable contributing to interindividual and cross-ethnic variations (43,44). Drugs and other foreign substances are metabolized by a number of enzymes whose activities vary substantially across individuals and ethnic groups. In recent years, a large number of drug-metabolizing enzymes as well as the genes responsible for encoding these enzymes have been identified and characterized. Many of these enzymes and their genes are present in two or more distinct forms within a given population, a condition known as polymorphism. Often, multiple forms of mutations lead to the inactivation or reduction of the activity of the enzymes (48). Substantial ethnic variations exist in the frequency of these gene mutations (genotypes) and the enzyme activity (phenotypes) of many of these polymorphic drug-metabolizing enzymes. Since these enzymes are responsible for the metabolism of many of the medications commonly used in clinical settings, variations in their activity will be reflected in significant differences in the pharmacokinetics of the drug, possibly resulting in variations in therapeutic dose ranges and side-effects profiles.

From a historical perspective, there are striking examples highlighting

the interplay of genetics and drug response. The development of severe hemolytic anemia in soldiers of African-American descent who were given the drug primaquine for the prevention of malaria led to the discovery in these men of an inborn deficiency of the enzyme glucose-6-phosphate dehydrogenase (43,48). Different side-effects profiles among Caucasian and Asians in response to isoniazid, the first antituberculosis medication, led to the finding of a differential rate of acetylation, a step in the elimination of isoniazid, between members of these ethnic groups. Subsequently, specific genetic loci of point mutations among subjects from different ethnic groups have been identified that are responsible for slow acetylation (49). A third example is the ''flushing response'' in a large number of Asians when exposed to alcohol (50,51). The mechanisms underlying this clinical observation are that in the metabolism of alcohol, a genetically determined deficiency of the enzyme aldehyde dehydrogenase results in the rapid accumulation of acetaldehyde, which is highly toxic and capable of inducing the symptoms of the flushing response.

As these examples show, the contribution that genetics makes to a large number of drug-metabolizing enzymes is well established. The activities of many of these enzymes show substantial cross-ethnic differences. Among these, the cytochrome P450 enzyme system has received the most attention, particularly because this system clearly relates to clinical issues and the use of psychotropic medications (52–55).

The metabolism and detoxification of the majority of modern chemotherapeutic agents, as well as a large number of foreign substances, is usually first achieved through oxidation by a group of isozymes belonging to the cytochrome P450 system (56,57). It is estimated that more than twenty P450 isozymes (grouped into families) exist in human beings, with each enzyme being encoded by a specific gene. As in the case of the examples described above, the phenotypes (the activities of the enzymes) and genotypes (the structure of the encoding genes) of some of these P450 enzymes manifest distinct interindividual as well as cross-ethnic variations. Such diversity is most clearly seen in two extensively studied P450 isozymes, namely, the CYP2D6 (debrisoquine hydroxylase) and the CYP2C19 (mephenytoin hydroxylase). In any given population, these isozymes have been found to be bimodally distributed. A certain proportion of people, deficient in the activity of these enzymes, are classified as poor metabolizers (PMs). In contrast, those without such deficiencies are classified as extensive metabolizers (EMs).

It has been demonstrated that the bimodal distribution of the activities of these important enzymes is genetically controlled and can be traced to mutations in the nucleic acid sequence in the DNA, leading to alterations in the amino acid structure and subsequent activity of the enzymes. Many labora-

tories have shown that different alleles are responsible for the changes in metabolism. These alleles have previously been labelled CYP2D6A, CYP2D6B, CYP2D6D, CYP2D6E, and CYP2D6T. A more recent proposal has been made to rename these alleles using a combination numerical and letter system:e.g., CYP2D6*1A and CYP2D6*1B would share common key mutations but differ with respect to specific base changes in the DNA (58). Even more rare alleles have been found, which also have been associated with decreased activity.

Substantial cross-ethnic differences in the frequency of the PM phenotype exist with these enzymes (43,44,46,48,59). For example, the PM rate for CYP2D6 ranges from less than 1% in some studies of Asians to more than 19% in Sans bushmen, while the PM rate for CYP2C19 is 0 in Cuna Amerindians and 22% in Japanese. As this is studied further, the situation becomes more complex, with intermediate rates of metabolism and "supermetabolizers" discovered as well. For example, although the prevalence of PMs of CYP2D6 in Asians is low, over 30% of Asians exhibit a metabolic capacity significantly lower than Caucasian EMs, representing a group of slow metabolizers (SMs). Genetic sequencing of these subjects revealed an abnormality in a large gene fragment of the enzyme. Although Caucasian EM subjects also have mutations in the genetic sequence of this enzyme, in this case it is a point mutation rather than a gene insertion (60). Investigations have shown that there are differing rates of mutations among ethnic groups. For example, the CYP2D6B (CYP2D6*4), associated with decreased activity, is found in approximately 23% of Caucasians, 8% of Mexican Americans, but only 2% of African blacks and 1% of East Asians. In contrast, CYP2D6J (CYP2D6*10), also associated with decreased activity, is found in about 47% of East Asians but only 5% of Caucasians. The specific pathway through which a particular medication is metabolized will determine the activity of the metabolism, hence the blood level of the medication and perhaps the severity of the side effects.

With the exception of benzodiazepines (which are metabolized by other P450 isozymes) and lithium, CYP2D6 is involved in the metabolism of practically all medications commonly used in psychiatry, including most neuroleptics and antidepressants. Many studies have demonstrated that CYP2D6 activity correlates highly with the pharmacokinetics and clinical effects of its substrates (53,61). CYP2D6 PMs consistently exhibit significantly higher concentrations of neuroleptics and tricyclic antidepressants when treated with similar doses of medications. For example, in a study involving the administration of test doses of haloperidol, PMs experienced severe extrapyramidal side effects and had significantly higher serum haloperidol concentrations (61).

The pharmacokinetics and pharmacodynamics of haloperidol have been

demonstrated to differ significantly between Asians and Caucasians. When given comparable doses of medication, Asian schizophrenic patients (62) and normal volunteers (63) exhibited plasma haloperidol concentrations that were approximately 50% greater than their Caucasian counterparts. This probably relates to the very high prevalence rate in Asians of slow metabolizers (SM) who show metabolism between the EM and PM groups. Furthermore, even within a single ethnic group—e.g. Japanese subjects—steady-state levels of haloperidol were correlated with the number of mutant alleles found (64).

Studies of ethnic differences in the pharmacokinetics of the TCAs, in contrast to neuroleptics, have led to inconclusive results (65). Among previous studies comparing Asians with Caucasians, some revealed that Asians metabolize TCAs significantly more slowly than their Caucasian counterparts (66). However, other studies showed differences in the same direction, but these did not reach statistical significance, particularly after controlling for body weight (67). In a recently completed study, Lin and colleagues (unpublished data) compared the pharmacokinetics of imipramine among Asians, African Americans, Hispanics, and Caucasians. With the exception of higher desipramine concentrations in the African-American group, they did not find any significant differences among the four comparison groups. These results are in congruence with an earlier study demonstrating lack of difference in the pharmacokinetics of nortriptyline between Mexican Americans and Caucasians (68). The elevation of secondary amine concentrations also has been previously reported among African-American patients (69).

Our own work has shown that Asians and to a lesser extent Hispanics appear to be more sensitive to the stimulatory effects of TCAs (an unwanted side effect) and to display increased prolactin and cortisol levels as well. Although clinical reports suggest that African Americans are more susceptible to CNS side effects of TCAs (69,70), the mechanisms that might be responsible for such a phenomenon have not been carefully evaluated. Despite the fact the serotonin reuptake inhibitors and other newer classes of antidepressants are recognized as being metabolized through the cytochrome P450 system, there have not been cross-cultural studies with these medications to date.

Confirming earlier clinical and survey reports, controlled studies involving Asians and Caucasians demonstrated significant pharmacokinetic differences with benzodiazepines between the two ethnic groups (71,72). And, in a recent study of the pharmacokinetics and pharmacodynamics of adinazolam, a triazolobenzodiazepine currently being investigated as an anxiolytic and antidepressant, African Americans were found to have both increased clearance of adinazolam, resulting in significantly higher concentrations of N-desmethy-

ladinazolam, a metabolite of adinazolam, and greater drug effects on psychomotor performance (73).

Several cross-national comparison studies have established the use of lower doses of lithium as well as lower therapeutic lithium levels among Asians (44). Thus, it appears that, as compared with their Caucasian counterparts, Asian patients with bipolar disorder may require lower doses of lithium for pharmacodynamic reasons or, more specifically, increased CNS responsivity. The distribution of lithium across cellular membranes is controlled by several membrane transport and countertransport mechanisms; the sodium- lithium countertransport system appears to play a particularly important role. This system is significantly less active among African Americans and African blacks than among Caucasians; this might contribute to a higher red blood cell (RBC)/serum lithium ratio among blacks (74). Since the intracellular concentration of lithium may determine its clinical and side effects, ethnic differences in the RBC/serum lithium ratio may have important clinical significance.

The above discussion is intended to alert clinicians to possible patterns of side effects in patients of minority backgrounds. However, because of the tremendous overlap among subjects in each ethnic group, no rigid guidelines regarding dosing can be provided. Although it is important to consider ethnicity as a factor in drug dosing and side effects, this should not be done in a rigid fashion. One danger in blindly accepting the reports discussed above is that significant cross ethnic/cultural differences in psychotropic drug responses could be interpreted stereotypically, leading to a scenario where all patients from an ethnic group are always treated with, for example, lower doses. This would not take into account the large interindividual variation even within an specific ethnic group. However, if a patient is experiencing untoward side effects at a dose one might think is “too low” to produce those side effects, consider that the person may be a PM and has a higher plasma level than would have been predicted. These patients may cluster within certain ethnic groups, particularly Asians, and, perhaps for benzodiazepines, African Americans.

Another area, although not studied systematically, in which patients from varying ethnic groups may be affected differently is that of drug interactions. Because many different medications (psychotropic and others) are metabolized by the same P450 isozymes, there may be competition for the enzymes' activity. If a patient is a slow metabolizer (SM) or even an EM of one drug (e.g., a TCA) and they are given another drug metabolized through the same system (e.g., an SSRI), the blood levels of the TCA may be markedly

elevated because its metabolism is slowed secondary to the competition with the metabolism of the SSRI. Many drug interactions are now understood to be partially a function of this process. It is important to recognize that nonpsychotropic medications are also metabolized by these same isozymes and care must be taken to find out all medications a patient is taking. As previously discussed, this is particularly important in elderly patients who are not only taking multiple medications but in whom the metabolic processes are slowed down. No controlled studies have looked at elderly minority subjects to see if they have an increased problem with these drug interactions.

VI. CONCLUSIONS

This review given above is not exhaustive regarding all groups of patients who may have unique vulnerabilities to the side effects of psychotropic medications. Rather, it covers a few representative groups who nevertheless make up a significant proportion of patients receiving these medications. As can be seen, the majority of side effects encountered in these patients are not necessarily different from those seen in other patients. Instead, their significance may be more problematic when these side effects occur in a patient who already has other medical problems or has a particular genetic susceptibility. Clinicians should be sensitive to the fact that there is a very wide range of side effects, and patients who develop more severe or perhaps confusing side effects may, indeed, have these on the basis of biological mechanisms (rather than because they are otherwise amplified or psychologically derived).

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11 Management of Side Effects of Other Psychotropic Drugs: Beta Blockers, Sedative-Hypnotic Drugs, and Cognitive Enhancers

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I. INTRODUCTION

A. Preemptive Caveat: Interaction of Biological with Psychological Factors

It is important for the clinician to be aware of all the factors shaping a patients response to treatment. Manuals of psychopharmacological treatment discuss mostly the biochemical and physiological data. However, psychological variables are of great importance, both for desirded effects and undesired side effects. Richard Ader (1) could demonstrate that there is a "placebo" (and ''nocebo") effect even in rats: experimental lupus-nephritis in rodents improved significantly as a response to inert substances (placebo) in the same way as to a response to immunosuppressant agents ("verum"—i.e., the "real" pharmacologically active agent); this worked only, however, if during the first several days the oncological agent was given simultaneously with the

placebo; without creating this initial expectation, (conditioning), the placebo alone did not alter the course of the illness. If an expectation about an effect of a substance can have such powerful effects in rats, how much more powerful must this phenomenon be in humans, with their vastly superior, cortical ways of cognition and imagination. This is true for both beneficial (placebo) and harmful (nocebo) effects (2–4). If patients obtain information about side effects, it is always more than just accumulating intellectual knowledge: it creates certain fears, concerns and expectations, and patients will react to this component of treatment according to the nature of their personality style, defenses, and proneness to somatization.

Therefore, part of the management of side effects is a carefully selected way of informing patients about side effects, how likely they are to occur, how serious or negligible they might be, and what to do about it. This will set the stage for the ensuing treatment response, hopefully maximize benefit, and reduce untoward effects. While this is true for all kinds of treatment, it is so especially for treatment of psychiatric disorders (with the notable exception of obsessive-compulsive patients, who have too many doubts to believe even in benefits or side effects). Management of side effects of psychotropic agents therefore should always inquire about the patient's ideas about the medication, past experience, or rumors (like "Prozac makes people homicidal"), pay attention to the patient's fears and expectations, and use clarification, education, reassurance, and personal guidance by the expert as important factors to minimize unwanted and maximize beneficial effects.

II. SIDE EFFECTS OF BETA BLOCKERS

Beta-adrenergic blockers are used in psychiatry for a variety of indications. None of the conditions is approved by the FDA. Nevertheless, four agents have been reported on for psychiatric use in the United States: propranolol, metoprolol, nadolol, and atenolol (5). Commonly accepted indications include (a) some anxiety disorders (on the somatic end of the spectrum, such as functional cardiovascular symptoms, anxiety in hyperthyroidism; stress-related anxiety such as performance anxiety); (b) lithium-induced tremor; (c) akathisia; and less frequently (d) adjunct treatment of alcohol withdrawal (with benzodiazepines); (e) violence and impulsivity in organic patients; and (f) enhancement of serotonergic antidepressants (pindolol).

Side effects are frequent and often significant. They usually include tiredness, mild hypotension, and bradycardia. Nonselective beta-adrenergic blockers (propranolol, nadolol) may cause bronchospasm (asthma) and periph-

eral ischemia (Raynaud's phenomenon) in predisposed patients. They may mask sweating, tremor, tachycardia and palor in hypoglycemic diabetic patients, thus putting them at increased risk. Although beta1-selective adrenergic blockers (metoprolol, atenolol) are considered safer, they cannot be regarded as “entirely safe,” as even those drugs may trigger asthma attacks or peripheral ischemia. Sensitive individuals may develop gastrointestinal dysfunction (nausea, diarrhea, abdominal pain), impotence, depression, vivid nightmares, insomnia, and fatigue.

A. Cardiovascular Side Effects

1. Description

Due to their blocking of adrenergic receptors, beta-blocking agents may cause hypotension, bradycardia, dizziness, and congestive failure. Mostly for the latter, but even generally, this tends to happen in patients who already are compromised and have conduction blocks, a history of myocardial infarction, myocarditis, or extensive comorbidity and advanced age.

2. Frequency

Beta blockers are among the most widely prescribed and well-tolerated agents in medicine. They have wide cardiovascular applications (treatment of hypertension, arrhythmias, angina pectoris), and are used in ophthalmology (treatment of glaucoma), neurology (treatment of essential tremor, migraine prophylaxis, and treatment of some forms of headache), and endocrinology (cotreatment of hyperthyroidism). While in physically healthy individuals cardiovascular side effects are generally not clinically significant, they may become a serious problem in patients with cardiovascular morbidity. Controlled studies regarding the frequency of cardiovascular side effects of beta blockers in psychiatric patients are lacking. In addition, the simple coexistence of cardiovascular morbidity with a psychiatric disorder does not necessarily mean increased likelyhood of side effects, as beta blockers are successfully used in cardiology to treat hypertension, arrhythmias, angina pectoris, and used prophylactically after myocardial infarction. Therefore, a thorough history and cardiological consult are often required to estimate the probable impact of a treatment with beta blockers in individuals at risk for side effects.

3. Mechanism and Significance for Management

Beta receptors are divided into the beta1 and beta2 subtypes. Beta1 receptors are found in the heart and in the brain. They stimulate the heart and lead to

Table 1 Side Effects of Beta Blockers

Main side effects (SE) are	Cardiovascular SE (bradycardia, atrioventricular block, hypotension)
	Pulmonary SE (bronchonconstriction, asthma attack)
	Gastrointestinal SE (hypoglycemia, nausea, diarrhea)
	Neuropsychiatric SE (fatigue, insomnia, dysphoria)
Differential diagnosis include	Cardiovascular disease, dehydration, low sodium, endocrinological disorders (Addison, hypothyroidism, SIADH), neurological disorders (Parkinsonism, Shy-Drager syndrome, epilepsy, autonomic failure), other drugs, psychogenic causes (anxiety, factitous disorder)
	Asthma, inhalation of irritants, pulmonary edema, embolism, infection or carcinoma; other drugs; psychogenic bronchospasm
	Food allergies, infection, intoxications, tumors, gallstones, colitis, psychogenic causes (“irritable bowel syndrome’’)
	Exhaustion, viral infections, cancer, depression, psychosis, substance abuse, intoxications, multiple sclerosis, factitious
Management includes	Hold or lower the dose; switch to other drug; address specific causes (hydration, pressure stockings, pacemaker), fludrocortisone
	Beta1-selective blocker, adrenergic inhalers, theophylline, cortisone, smoking cessation
	GI work-up, Kaopectate, dimenhydrinate, psychotherapy
	Sleep hygiene, physical activity, trazodone, benzodiazepines, antidepressants as indicated

increased chronotropy and inotropy. Metoprolol, atenolol, and practolol are selective beta1-receptor antagonists. Beta2-receptors are found in the lung, in blood vessels, and in the brain (glial cells). Stimulation of beta2-receptors leads to dilation of blood vessels and brochial airways. Propranolol and nadolol are beta2 antagonists (nonselective, blocking both beta1 and beta2 receptors).

Beta blockers compete with adrenaline and noradrenaline at their betaadrenergic receptor sites. They are competitive antagonists. This explains their peripheral sympatholytic action. Exercise performance can be impaired by propranolol but also by any other beta-blocking agents. Although beta blockers cause only clinically insignificant bradycardia in healthy individuals, they may lead to life-threatening conditions in predisposed subjects. Patients with compensated heart failure, myocardial infarction, or cardiomegaly may therefore suffer heart failure (reduced inotropy and serious bradycardia, especially in patients with partial conduction defects or when combined with other drugs that impair cardiac conduction). Abrupt cessation of beta blockers can cause exacerbation of coronary heart disease and provoke angina pectoris or even myocardial infarction.

Generally, rate and size of any effects are influenced by two other factors: receptor sensitivity, and lipophilicity. Cardiovascular side effects are similar for both selective beta1- and nonselective beta-receptor antagonists (there are no clinical beta2-receptor antagonists). Beta1-receptor antagonists have a lower risk of provoking pulmonary side effects (bronchoconstriction). However, this advantage is only relative, and caution is still recommended when treating patients with asthma. Lipophilicity plays a role in crossing the blood- brain barrier (5). The least lipophilic drugs (nadolol, atenolol) cross the blood- brain barrier much more poorly than highly lipophilic beta blockers (propranolol, metoprolol). Thus, the ratio of central to peripheral effects is low in the former, higher in the latter.

Half-life is another important factor to always consider, especially in the elderly patient. Nadolol (14 to 24 hr) and atenolol (6 to 9 hr) are reported to have rather long half-lives, allowing once-a-day administration, but also showing decreased manageability if quick adjustments are expected to be necessary. Propranolol, on the other hand, has a rather short half-life (3 to 6 hr) and has to be given several times a day unless prescribed in a sustained-release form (5).

Elimination pathways are another issue of potential significance in patients with multiple problems, high comorbidity, polypharmacy, or advanced age. Atenolol and nadolol are excreted via the renal pathway, while propranolol and metoprolol are metabolized in the liver. This explaines why coadministration of certain beta blockers with antidepressants may lead to complica-

tions: fluoxetine has been reported to inhibit the oxidative hepatic metabolism of metoprolol and other lipophilic beta blockers, resulting in higher plasma concentrations of the beta blocker and adverse cardiovascular side effects (6). In reverse, it has also been reported that beta blockers increase the blood level of antidepressants, which, in turn, can give rise to serious cardiovascular toxicity as well (7). Beta blockers are generally metabolized by the mitochondrial enzyme system cytochrome P 450, CYP1A2. The same enzyme system also metabolizes amitriptyline, clomipramine, imipramine, clozapine, caffeine, paracetamol, warfarin, and theophylline (8). Other enzyme systems are involved in the beta blocker metabolism as well. CYP2C19 (important for benzodiazepines and barbiturates), CYP2D6 (the most important subsystem, also metabolizing most tricyclic antidepressants, and some antipsychotic drugs such as haloperidol, thiorodazine, risperidone, and perphenazine). Possible interactions can be easily predicred when considering common metabolic pathways. For details, using Preskorn's pocket manual (8), or Ayd's Lexikon (9) is recommended. Clinically, it is relevant to remember that phenytoin, phenobarbital, and rifampin increase the clearance of propranolol (lowering its blood level), while cimetidine, fluoxetine and some tricyclic drugs inhibit the hepatic mitochondrial enzymes, leading to increased propranolol blood levels. Vice versa, beta blockers reduce the clearance of drugs using the same hepatic pathway, thus leading to increased levels and toxicity of theophylline, tricyclic antidepressants, chlorpromazine and other antipsychotic agents.

There are also other, nonmetabolic effects to be considered. Coadministration of drugs with similar effects can cause serious problems. A combination of calcium channel blockers with beta blockers can cause additive adverse effects on cardiac conduction or blood pressure. Aluminum salts, cholestyramine, and colestipol may reduce intestinal absorption of beta blockers (9).

4. Differential Diagnosis

a. Hypotension. Apart from drugs blocking beta receptors, hypotension can be caused by a multitude of conditions. Most often, dehydration, electrolyte imbalances (especially low sodium), or other drug effects (alpha- adrenergic blockade by low-potency neuroleptic drugs such as chlorpromazine and thioridazine, but also risperidone; antihypertensive medications such as angiotensin-conventing enzyme (ACE) inhibitors, nifedipine, and other calcium antagonists, etc.) are to blame. However, endocrinological disorders [Addison's disease, hypothyroidism, Syndrome of inappropriate antidiuretic hormone secretion (SIADH)], neurological disorders (Parkinsonism, Shy- Drager syndrome, epilepsy, acquired autonomic failure, processes involving

the mediobasal temporal lobe or brain stem, polyneuropathy), idiopathic orthostatic hypotension, and psychogenic causes (psychosomatic syncopes, fainting, anxious or factitious aggravation) have to be considered. Naturally, cardiovascular diseases should always be carefully screened for, including history, physical, and technical exams.

b. Bradycardia. Bradycardia (slowing of the heart rate to less than 60 beats per minute) can be a feature of heart conduction deficits, vagal effects (such as vagovasal syncope, increased intracranial pressure, brainstem processes), intoxication with a variety of agents, especially those with antiarrhythmic qualities, hypothyroidism, a state of physical training (professional sports), a constitutional/idiopathic condition, and even achieved through meditation.

c. Dizziness. This very subjective symptom can be caused by a broad range of factors. From such unspecific somatic causes as lack of proper nurishment, dehydration, lack of sleep to psychological factors such as expectation of dizziness as a reported side effect, anxiety (especially panic attacks, or conditions leading to hyperventilation), stress, psychological conflict, great hights, overwhelming demands, and sudden change of context, everything is of possible influence. Neurological disorders have to be carefully assessed, including peripheral (labyrinthine) and central vestibular disorders, multiple sclerosis, parkinsonism, Meniére's disease, cerebellopontine angle tumors, complex partial seizures, basilar migraine, and multiple sensory deficits in the elderly (11). Intoxications with antibiotics (streptomycin, ampicillin, polymyxin B, sulfonamides), diuretics, salicylates, phenylbutazone, anticonvulsants (phenytoin, valproic acid), and, of course, alcohol, opiates, antihistaminic drugs all can cause dizziness (11).

d. Congestive Heart Failure. This will only happen as a side effect of beta blockers if the patient has had a previous heart attack, myocarditis, or other cardiac disorder. Any severe cardiac illness may cause cardiac failure, as may drugs with negative inotropic effect, critically high blood pressure (systemic or pulmonary hypertension), or electrolyte imbalance. A cardiological consult is strongly recommended in case of serious cardiac symptoms.

5. Clinical Management

Whenever side effects are a source of concern, some general rules apply before specific measures should be considered. Beta blockers should always be begun at low doses, and doses are to be withheld if blood pressure is below 90/60 mm Hg and pulse less than 55 beats per minute. If one has made sure that the dosage of the beta blocker is correct, that there is compliance, that there

is no obvious contraindication, and if the clinical situation is not urgent [obtaining an electrocardiogram (ECG) in all patients over 50 and/or with cardiac history], waiting for remission of the complained symptoms is always an option. Many side effects appear only initially and tend to disappear without any intervention. Depending on the patient's tolerance of symptoms and the risk involved (consider cardiac consult if in doubt), one to several weeks may be an appropriate time for monitoring the situation. The next step would be to lower the dose of the drug inculpated in the side effects. If that does not help, switching to another drug with similar benefits but a different side-effects profile may address the problem. If side effects still persist or if they are too severe to begin with, specific “antidotes” are indicated. Careful monitoring, good documentation, good and responsible information and guidance of the patient, obtaining informed consent, documentation of competence, inclusion of relatives or significant others in the treatment planning if authorized by the patient (and working with the family as a system, instead of isolating a designated patient) are important aspects of treatment and management of side effects with significant bearing on treatment outcome, and legal complications. Side effects are often a reason for a patients' disenchantment with the physician, providing an opportunity to project all other pain and disappointment onto a concrete object that can then be vicariously fought and thus bring some relief from otherwise unbearable pain. Knowing such psychodynamic mechanisms will help the clinician to understand his patient better, avoid confrontation, and avoid malpractice suits.

6. Specific Suggestions

a. Hypotension. After all the above-mentioned general aspects and differential diagnostic issues have been considered, hypotension is clinically often well addressed with simple hydration, monitoring of orthostatis, precautions against falling in the elderly, and pressure stockings to avoid venous pooling in the legs. Specific conditions such as neurological disorders, endocrinological deficiencies or syndromes, cardiac disease, etc., have to be treated accordingly. It is strongly recommended to obtain a consult with specific treatment recommendations, especially in complicated situations (multimorbidity, old age, pregnancy). Often, these measures are not sufficient to alleviate hypotensive symptoms. In this case, the mineralocorticoid fludrocortisone at a dose of 0.1 mg PO qd is often helpful. In elderly patients with idiopathic or drug- induced parkinsonism, a noradrenaline precursor not requiring the deficient dopa-hydroxylase (DOPS) has been tried with success to treat autonomic failure.

b. Bradycardia. When general considerations and measures as of above are not helpful enough and no specific cardiac condition requiring specific intervention is identifiable (conduction block requiring a pacemaker, arrhythmias etc.), anticholinergic drugs such as benztropine mesylate 1 to 2 mg PO (or, in case of urgency, atropine sulfate 0.5 to 1 mg LV) can be administered safely and most often leads to an increase of the pulse rate. Beta blockers with sympathomimetic properties (pindolol) may be another reasonable step— to be coordinated with a cardiologist. Adrenergic drugs should be a domain of the cardiologist but may be indicated for the acute management of severe bradycardia.

B. Respiratory Side Effects

1. Description

Beta blockers may cause bronchoconstriction, bronchospasm, and serious asthma attacks. By blocking the beta2 receptors in the lung, their dilatory action is missing, and any (vagally modulated) bronchoconstrictory tendencies remain unopposed. Wheezing, prolonged expiratory time, effortful breathing, shortness of breath, anxiety, and cyanosis are some of the related signs and symptoms.

2. Frequency

There are no controlled studies regarding the frequency of bronchospastic side effects of beta blockers. While there is practically no risk in physically healthy individuals, these effects may become a serious problem in patients with a history of asthma, chronic obstructive pulmonary disease (COPD), emphysema, or other conditions with a tendency to develop bronchospasms. The risk is somewhat less pronounced with beta1-selective receptor antagonists but still present. The high number of smokers in our patient population requiring treatment for akathisia makes this an important side effect.

3. Mechanism

Beta2 receptors are found in the lung, in blood vessels, and brain (glial cells). Stimulation of beta2 receptors leads to dilation of blood vessels and bronchial airways. Blocking beta2 receptors therefore leads to bronchoconstriction. Vagal innervation is bronchoconstrictory, and remains unopposed in that case. Direct stimulation of beta2 receptors with sympathomimetic agents (inhalers) or intravenous noradrenaline are successful countermeasures.

4. Differential Diagnosis

Asthma, inhalation of bronchial irritants, pulmonary edema, and pulmonary embolism are all conditions that have to be considered when the patient has wheezing, increased respiratory effort, and shortness of breath. Less frequent but important to rule out are pulmonary infections and carcinoma. As it is well known that asthma can be triggered by emotional stimuli, a careful psychological assessment of the patient's fears, expectations, feelings, and psychological context is always a high priority.

5. Clinical Management

If a patient has a history or present problems with asthma, COPD, or is a heavy smoker, the prescription of beta blockers should be well weighed against the possible side effects, and if the decision is in favor of beta blocker application, one should prescribe only selective beta1-receptor antagonists such as metoprolol and atenolol.

The general considerations and measures as discussed above do apply: wait for remission of reported side effects if that is clinically and subjectively tolerable; try to alleviate symptoms by shifting the time of medication to the morning by splitting the dose or by dose reduction; or switch to other drugs with similar benefit but different side-effects profile.

Adrenergic inhalers such as albuterol or metaproterenol are of great help in managing acute bronchospastic attacks (usually given as a pm prescription with 2 puffs PO qid). Theophyllin 100 to 300 mg PO tid, cromolyn sodium inhaler and respiratory treatments are other, more chronic treatment interventions able to reduce the risk of asthma attacks. Cortisone (PO or as inhaler) should be given with precaution, as it may increase depression, psychotic symptoms, and has significant systemic side effects if given long term. Again, specific (pulmonological) consults and good monitoring are key factors in managing such conditions. A smoking cessation program with group therapy, nicotine patch, and behavioral interventions is always recommended in smokers.

C. Gastroenterological Side Effects

1. Description

Worsening of hypoglycemia in diabetics on insulin or oral antidiabetic agents and masked adrenergic alarm symptoms (tachycardia, peripheral vasoconstriction, sweating) in hypoglycemic conditions are serious side effects. Nausea, diarrhea, and abdominal pain are unspecific, less serious complaints.

2. Frequency

Gastroenterological symptoms are rather rare and usually not a reason to concern. The are often also reported with placebo and have a tendency to subside spontaneously. However, beta blockers should be avoided in diabetics on insulin or oral antidiabetic medication, as they have a rare but possible serious adverse effect on glucose mobilization (inhibited glycogenolysis) and may increase the risk and in addition mask the symptoms of hypoglycemia (12).

3. Mechanism

By blocking the adrenergic receptors in the gastrointestinal system, parasympathetic influence is increased, resulting in increased intestinal motility, nausea, and pain from intestinal cramps.

4. Differential Diagnosis

Any condition affecting the gut, from food allergies, lactose intolerance (especially in Asian patients), food poisoning, gastrointestinal flu, and other infectious conditions, to intoxications (alcohol) and other drug effects have to be considered. Gastroenterological conditions including tumors, gallstones, colitis, Crohn's disease, and psychosomatic conditions (“irritable bowel syndrome”) are other conditions to be ruled out. If the patient is on an antidepressant, especially an selective serotonin reuptake inhibitor (SSRI), a serotonergic syndrome should be carefully ruled out. Carcinoid syndrome is so dramatic that it will immediately gain clinical attention.

5. Clinical Management

Again, a gastroenterological consult and workup is often indicated if the symptoms do not respond to the general interventions discussed above. As an antidote, Kaopectate (attapulgite 30 mL PO prn after each loose stool) is often very helpful with diarrhea. For nausea, dimenhydrinate 50 mg PO prn q4h is helpful but sedating. Often, a focused psychotherapeutic intervention will uncover fears, expectations of side effects, or conflicts that are expressed in gastrointestinal symptoms. Specific psychotherapeutic and additional psycho- pharmacological measures may be required.

D. Neuropsychiatric Side Effects

1. Description

Lassitude, fatigue, insomnia, and dysphoria are generally reported, while depression, vivid nightmares, and psychosis are rather unusual. Beta blockers

have no apparent effect on memory. They may even improve performance on tasks that require perceptual-motor, learning, and memory skills (5).

2. Frequency

Reduced energy, lassitude, a feeling of tiredness, and "chronic fatigue" are not infrequent (exact numbers regarding the incidence and prevalence of these side effects are lacking). However, the usefulness of beta blockers in performance anxiety, where it actually improves performance without any sedative action, speaks against sedation as a significant side effect. Depression is a rare side effect: After 1967, reports in the medical literature associated the use of beta blockers with clinical depression, although a later study found no evidence for a causal connection between beta blockers and depression (9,13). Psychotic symptoms are also very rare as a consequence of beta-blocker action. Vivid nightmares have been reported only occasionally.

3. Mechanism

As beta-adrenergic blockers are effective in the treatment of (mostly essential) tremor, anxiety, and violence, some central nervous system (CNS) action can be assumed. It is through this central antagonism of adrenergic transmission that tiredness and dysphoria/depression can be explained.

4. Differential Diagnosis

Tiredness, fatigue, and lassitude have a broad spectrum of possible factors causing such conditions. This ranges from exhaustion, viral (HIV) and other systemic infections, to cancer, chronic fatigue, major depression, bipolar illness, psychotic illness with predominant negative symptoms, substance abuse and dependence, intoxications, and neurological disorders such as multiple sclerosis, tumors, migraine, and any other medical condition. Psychologically, passivity and withdrawal are among the most frequent "protective" reflexes to reduce stress, gain rest, and recover some energy. Possible conflicts with significant others, with life tasks (see Erikson's life stages), and with the therapist should be considered. Primary insomnia, pain, Posttraumatic Stress Disorder (PTSD), caffeine abuse, psychological conflicts (marital discord), sleepapnea syndrome, and alcohol abuse are only some of the many possible factors interfering with sleep and leading to insomnia and parasomnic symptoms (nightmares).

5. Clinical Management

Tiredness, fatigue, and insomnia may respond well to sleep hygiene. This includes reduction of caffeine and nicotine (avoidance in the afternoon), pleasant sleep environment, physical activity and workouts, regular bedtimes, relaxation techniques, light food in the evening, and a glass of milk (high on tryptophan) at bedtime. Additional measures include trazodone 50 to 100 mg PO hs, benzodiazepines, or diphenhydramine 50mg PO hs. Depression may respond well to discontinuation as the first management approach. If that fails, it should be treated appropriately with antidepressants, preferably sedating (tricyclic) drugs if insomnia is a problem. If insomnia or dysphoria symptoms persist to a significant extent and general measures such as shifting dosage schedules and lowering the dose are not satisfactory, beta blockers should be discontinued. Psychotic symptoms, if in fact induced by beta blockers, should be another reason to discontinue beta blockers. However, most often beta blockers are not only well tolerated in otherwise psychotic patients but psychotic patients become less stressed, less prone to suicidal actions, and more amenable to other treatment modalities if their akathisia is successfully addressed by beta blockers. A careful risk/benefit analysis is recommended to avoid withholding a potentially beneficial and necessary treatment from psychotic patients.

III. SIDE EFFECTS OF BENZODIAZEPINES AND OTHER SEDATIVE HYPNOTIC DRUGS

There are now 39 different benzodiazepines, which are the main drugs used today for sedative-hypnotic purposes. Older drugs such as ethanol, paraldehyde, bromides, chloral hydrate, and meprobamate are rarely used these days, with the possible exception of barbiturates. Zolpidem is a new-generation non-benzodiazepine hypnotic with a short half-life (2.4 hr) and action on the benzodiazepine type-1 receptor (9, p. 681). Zopiclone is another new nonbenzodiazepine hypnotic with a short half-life (4 to 6 hr) and high affinity for benzodiazepine receptors. It is said to be safe; the antidote is flumazenil, but it may induce a metallic taste (9, p. 682–683). Given the advantages of benzodiazepines, the use of most of the older compounds for anxiolysis or sedation is now seen as ‘‘irrational’’ and not recommended (5, p. 145).

Benzodiazepines are central nervous system depressants, with anxiolytic properties at low doses and sedative-hypnotic effects at higher doses. Com-

pared to older anxiolytic and sedative-hypnotic drugs, they are much safer, less addictive, and have a lower abuse potential.

Barbiturates, meprobamate, and other older-generation drugs are quite dangerous in overdose (leading to coma, respiratory arrest, and death), with a low ratio of median effective dose to median lethal dose (LD50/ED50), while benzodiazepines have a considerably higher LD50/ED50 ratio. Since Adolph von Bayer first synthesized barbituric acid in 1862, more than 2500 derivatives have been developed, and more than 50 have found their way into clinical application. Their high rate of dependence and lethality in overdosage led to their almost complete replacement by benzodiazepines in the 1970s. Also, withdrawal can be life-threatening, with seizures, agitation, and delirium occurring if the tapering process is done too fast. Pentobarbital, secobarbital, and phenobarbital should therefore not be used anymore for treating insomnia or anxiety for reason of their potential to cause tolerance, dependence, and dangerous overdose: e.g., 1000 mg of amobarbital in a single dose may be lethal (5; 9, p 64; 32, p. 203). An indication is still seen in some forms of epilepsy and for detoxification of patients with abuse of barbiturates. Amobarbital (amytal) was sometimes used to calm psychotic agitation and catatonic states and to induce a trance-like state to allow catharsis of traumatic memories in PTSD and hysterical states of amnesia and conversion/paralysis. Its use is controversial, however. Lorazepam is a much safer alternative (e.g., to dissolve a catatonic mutism).

Of the barbiturate-like drugs, chloral hydrate appears to be least problematic (5, p. 168), with relatively low abuse potential. Meprobamate holds an intermediate position between the barbiturates and benzodiazepines. It has muscle relaxant and sedative properties, and good antianxiety effect. However, despite a relative safety compared to barbiturates, it induces tolerance and dependence, and may lead to malcoordination, sedation, withdrawal seizures, and delirium (32, pp. 208–209).

Sedative antihistamines (diphenhydramine, hydroxyzine HCl, hydroxyzine pamoate) are less effective than benzodiazepines and lead to more daytime sedation, in addition to their often marked anticholinergic effects (dry mouth, constipation, cave delirium in the elderly and polypharmacy patient). They should not be prescribed in combination with other anticholinergic drugs.

All benzodiazepines have sedative, anxiolytic, anticonvulsant, and muscle relaxant properties. Although benzodiazepines are advertised for different indications (flurazepam, temazepam, quazepam, estazolam and triazolam for insomnia; diazepam for anxiety, muscle relaxation, and preoperative sedation), it is generally assumed that all benzodiazepines share most of their therapeutic properties. The main side effects of benzodiazepines include sedation and ef-

fects on memory, dependence and overdose, disinhibition, and depression (see also Chapter 7).

A. Sedation and Cognitive (Memory) Side Effects

1. Description

Sedative-hypnotic drugs show many similar side effects. Sedation is a main effect of benzodiazepines, barbiturates, zolpidem, zopiclone, and antihistaminic drugs; it is often seen as a desired feature, used in treating insomnia. However, based on dosage and half-life of the individual drug, sedation during daytime activities can become a serious problem. This can take on the form of a "hangover" or be more subtle, such as slow reaction times, lassitude, and a tendency of dozing off. Patients report feeling sedated or drowsy and may show ataxia or slurred speech (5,9,14,15). Under experimental conditions, signs of slowed performance were evident (14). Especially in the elderly, benzodiazepine-induced muscle relaxation (in particular with diazepam, midazolam, but generally with any benzodiazepine) and impaired motor coordination can lead to falls and (hip) fractures (18). Amnesia (anterograde, i.e., beginning with drug intake) is partly a wanted effect, as in anaesthesia induction (16), but is sometimes an unwanted serious adverse effect, especially with short- acting, high-potency agents such as triazolam (17). Given its potency and half- life, zolpidem may cause amnesia as well, although there are no sufficient data to decide that at this point (5).

2. Frequency

Sedative symptoms such as drowsiness, fatigue or tiredness are the most common side effects of benzodiazepines. Acute dosages of all benzodiazepines may produce short, transient periods of anterograde amnesia, independent of the degree of sedation. In this stage, acquisition of new information (learning) is impaired. The risk of sedation and amnesia is greatly enhanced by combining barbiturates, benzodiazepines, zolpidem, or antihistaminic drugs with alcohol. Other factors influencing the manifestation of sedative and cognitive side effects include combination with other CNS depressants, and interference with other drugs using the same metabolic pathway (CYP3A3/4) (see 8, p. 159), such as analgesics (acetaminophen, codeine, dextrometorphan), antiarrhythmics (amiodarone, disopyramide, lidocaine, propafenone, quinidine), anticonvulsants (carbamazepine, ethosuximide), antidepressants (amitriptyline, clomipramine, imipramine, sertraline, nefazodone, O-desmethylvenlafaxine), most calcium channel blockers, antihistamines (astemizole, terfenadine, loratadine),

Table 2 Side Effects of Sedative-Hypnotic Drugs

Main side effects (SE) are	a) Sedation (hangover, slowness, drowsiness, ataxia)
	b) Disinhibition
	c) Dependence
	d) Depression
	e) (Suicidal) overdose
Differential diagnosis includes	a) Substance abuse, other drugs, neurologic disease, infections (HIV!), metastatic cancer, endocrinological disorders, mental illness
	b) Mostly in preexisting brain damage, elderly patients
	c) Strong for barbiturates,; low-dose for benzodiazepines; screen for comorbid substance abuse or dependence
	d) Dysphoria by antihypertensive drugs, other drugs, major depression and other mental illness, endocrinological disorders (hypothyroidism, Addison's disease)
	e) Suicide attempt, confusion, drug-drug interaction (especially with cimetideine, fluoxetine), accumulation in the elderly with prolonged half-life (reduced metabolism)
Management includes	a) Hold or lower dose, discontinue, switch to drug with shorter half-life, flumazenil (benzodiazepine antagonist), special measures addressing specific causes as indicated
	b) Dose reduction or discontinuation; try anticonvulsive drug
	c) Always specify duration of prescription and reassess need; screen for substance abuse; monitor for abuse
	d) Hold or discontinue; antidepressant or other specific measures where indicated
	e) Barbiturate overdose requires intensive medica workup and monitoring (respiratory arrest!); gastric lavage, supportive measures, induced emesis

steroids, macrolide antibiotics (erythromycin, clarithromycin, triacetylolean- domycin), clozapine, and immunosuppressants (8).

3. Mechanism

Gamma-aminobutyric acid (GABA) is the most important inhibitory transmitter in the brain, and all benzodiazepines bind to the GABA receptor. By binding to the GABA-A receptor, benzodiazepines change the configuration of this receptor, allowing chloride ions to enter through an effector ion channel into the neuron, thereby hyperpolarizing the cell, thus the net inhibitory effect of GABA. Benzodiazepines but also barbiturates and ethanol bind to different sites of the GABA receptor, potentiating the inhibitory effect of GABA. This happens by allosteric regulation of the receptor (configurational changes) with a resulting increase of affinity for GABA. All of the drugs also enhance affinity for each other. At higher doses, ethanol and barbiturates, but not benzodiazepines, can open the chloride ion channel independent of GABA within the receptor. Only GABA receptors with gamma subunits interact with benzodiazepines.

Barbiturates have been used widely in the past, with longer-acting barbiturates such as phenobarbital or barbital aimed for daytime sedation and shorter-acting derivatives such as secobarbital, amobarbital, and pentobarbital used for sleep induction and maintenance. Phenobarbital is the only one used medically nowadays, either in the treatment of certain forms of epilepsy or for detoxification from barbiturate abuse. It is the "methadone" of barbiturates—i.e., a long-acting sedative, useful in withdrawing patients from sedative drugs including alcohol (32, p. 201). Barbiturates are known to lead to enzyme induction, with subsequent lowering of blood levels via increased clearance. This will affect all drugs metabolized by the same, now increased enzyme system (tricyclic antidepressants [TCAs], clozapine, beta blockers, and warfarin for CYP 3A3/4 in phenobarbital, and analgesics, antiarrhythmics, anticonvulsants, macrolide antibiotics, TCAs, SSRIs, clozapine, benzodiazepines, calcium-channel blockers, steroids and immunosuppressants for CYP1A2 in secobarbital, according to Ref. 8).

Zolpidem interacts with a smaller subset of GABA receptors than the benzodiazepines (5). It lacks any muscle-relaxant, anxiolytic, or anticonvulsant effects, binding selectively to the benzodiazepine 1-receptor subtype. Although it is believed to not alter sleep architecture in therapeutic doses between 10 and 20 mg, it has been reported to cause coma mimicking narcotic overdose, amnestic psychotic reactions, or visual illusions such as palinopsia and macropsia (9, p. 682). Zopiclone competes directly with benzodiazepines at receptor sites, although it is a nonbenzodiazepione hypnotic (cyclopyrrolone

derivative). The benzodiazepines oxazepam, lorazepam, and temazepam are metabolized only through glucuronization and have no active metabolites. Glucuronidation is less affected by age and liver disease. Thus, these three benzodiazepines are preferred in the treatment of the elderly and those patients with impaired liver function. The other benzodiazepines are metabolized through oxidation and demethylation pathways, which may be slowed down as much as fivefold (5, p. 157) in liver cirrhosis, with a possibility of routine doses becoming toxic.

The benzodiazepines also differ in alpha- and beta-phase half-lives. Diazepam has a distribution (alpha phase) half-life of 2.5 hr but an elimination (beta-phase) half life of 30 hr. Desmethyl-diazepam, its major (active) metabolite, extends the half-life to another 60 to 100 hr (5; p. 155), up to 200 hr in the elderly. This means that if given as an acute first dose, diazepam will act quickly and for a relatively short time, disappearing in the tissue pool. However, with chronic administration, diazepam will have filled up the tissue storage and its half-life will solely be determined by its elimination, giving it a tenfold longer duration. On the other hand, lorazepam may hang around longer than diazepam, despite its relatively short elimination half-life of 10 hr as its distribution volume is smaller than that of diazepam.

4. Differential Diagnosis

Sedation and cognitive impairment can be caused by a multitude of factors. One has always to screen for benzodiazepine abuse, comorbid substance abuse and dependence (especially alcohol), or other medication (especially antidepressants, antipsychotic medication, and any drugs metabolized via the same CYP3A3/4 pathway, as outlined above). Alternatively, any process involving the CNS can cause sedation and cognitive impairment. The spectrum extends from head injury, cerebrovascular disease, brain tumors, epilepsy, multiple sclerosis, HIV infection, other systemic viral diseases, metastatic cancer, severe hypertension, endocrinological disorders such as Cushing's disease, Addison's disease, hypothyroidism, to major psychiatric disorders such as major depression, bipolar disorder, schizophrenia (especially prodromal or residual states), or prominent negative symptoms. Neurodevelopmental disorders, abnormal shyness, generalized anxiety disorder, dissociative states, and FTSD are other (rare) conditions to be considered.

5. Clinical Management

If general measures such as waiting for remission of the sedative and cognitive side effects (especially for the transient amnestic symptoms), shifting the dose

to bedtime (or back to the late afternoon if hangover is the problem), or dose adjustment have failed to bring about the expected improvement and no other condition as discussed above interferes, switching to another drug may be the best option. The choice of which benzodiazepine to prescribe should be carefully made, given the individual patients history and life circumstances. For instance, diazepam is not a good choice in the elderly or in alcoholic patients with compromised liver function because of its tendency to accumulate, especially its first active metabolite desmethyldiazepam. The long half-lives of diazepam and chlordiazepoxide (30 to 100 hr), clonazepam (15 to 50 hr), flurazepam and quazepam (50 to 160 hr) make them prime candidates for causing daytime sedation. In such a case, switching to intermediate-half-life agents such as oxazepam (8 to 12 hr) or temazepam (8 to 20 hr) is indicated and may eliminate the sedation while preserving the benefits of improved sleep and reduced anxiety.

Short-acting compounds such as alprazolam, triazolam, or zolpidem may cause rebound insomnia, or breakthrough anxiety attacks; they also have a higher potential to be addictive. In case of doubt whether the observed sedation is indeed attributable to benzodiazepine action or other causes, a test with flumazenil 0.2 mg IV over 15 sec, 0.2 mg per minute up to a total of 1 mg, can be revealing. In case of benzodiazepine overdose, up to 3 mg can be given safely.

Of the many possible drugs interacting with benzodiazepines, cimetidine and disulfiram are worth remembering, as they are often coadministered in patients with comorbid conditions such as (alcoholic) gastritis and alcohol abuse; they tend to rise the benzodiazepine level (8,19), especially the long- acting substances chlordiazepoxide and diazepam (14). Reduction of the benzodiazepine dose or discontinuation of the drug competing with the metabolizing enzyme system may help address the problem.

Barbiturates should not be prescribed nowadays as sedative-hypnotics. If a patient needs to be tapered and switched to a benzodiazepine, a slow and controlled tapering process (in unreliable or at-risk patients on an inpatient ward) will help avoid seizures, agitation, and delirium. Meprobamate, although used as indicated in rare patients with otherwise unresponsive anxiety disorder, should also be consigned to history (32, p. 210).

B. Disinhibition, Dependence, Depression, and Overdose

1. Description

Disinhibition is a paradoxical effect of benzodiazepines, more often seen in the elderly or brain-damaged individuals (9; p. 68). Agitation, belligerence,

and assaultiveness may be provoked by any substance of this class. Increased hostility and aggressiveness range from subjective symptoms (feelings) to rage reactions, irritability, and suicide attempts. Alprazolam has been reported as a more likely candidate, but alcohol, benzodiazepines, and other sedative-hypnotic substances may all provoke this rather primitive syndrome, which is understood as a weakening of inhibitory (frontal-lobe) control over limbic behavioral programs (20). This may be observed as well with barbiturates, alcohol, or other sedative-hypnotics. Even zolpidem has been reported to lead to psychotic agitated states in rare cases (9, p. 682).

Dependence on barbiturates is well known, with increasing tolerance for anxiolytic and sedative-hypnotic effects but no change for motor side effects (ataxia, malcoordination, dysarthria) and the threshold for lethal effects. Benzodiazepine dependence, however, is a controversial issue. Studies have found in general no evidence for patients escalating their dosage (14), but benzodiazepines may induce a "low-dose-dependence," with discontinuation leading to three groups of significant clinical symptoms (5): recurrence of the primary disorder (original symptoms), rebound (temporarily intensified original symptoms), and withdrawal (original symptoms plus tachycardia and hypertension).

Depression has been associated with all ''downers'' in the psychophar- macological arsenal of treatment tools, including barbiturates, antihistamines (although their anticholinergic potential is somewhat antidepressant), and most of the older compounds such as paraldehyde, chloral hydrate, meprobamate, and alcohol. Also, all compounds of the class of benzodiazepines have been associated in one way or other with causing depression. Whether they were truly causative or only failed to prevent an otherwise caused depression is not known (5). Dysphoria, slow mentation, low energy, and reduced interest are the main features of this syndrome.

Overdose of barbiturates is still a common cause of death and needs to be treated under optimal conditions with the possibility of monitoring and assisting breathing and cardiovascular function and preventing aspiration. Although less dangerous, meprobamate overdose should be treated with similar caution. Overdose of benzodiazepines is rarely seen without combination with other substances, mainly alcohol, or antidepressant medication, which have a much higher toxicity than the relatively safe benzodiazepines (5,9). Taken alone, they produce only mild to moderate signs of toxicity in most cases, such as somnolence, diplopia, dysarthria, ataxia, and cognitive impairment. Coma is rare (9, p. 73; 23).

2. Frequency

Disinhibition is also called "behavioral dyscontrol syndrome" or "paradoxical reaction" and is not a direct, more intense expression of the drugs usual pharmacological action. It is reported to occur in approximately 10% of patients treated with sedatives (9, p. 72). A history of impulsivity, brain damage, advanced age, neurological disorder, or borderline personality disorder is a predisposing factor. In younger, healthy individuals, it is rarely observed, but many clinicians feel that the highest frequency of such paradoxical reactions is seen in patients with personality disorders and a history of dyscontrol. Alprazolam is reported as a more likely candidate to provoke disinhibition, while the lower-potency, slowly absorbed oxazepam is reported to be less likely to trigger this effect (5; p. 177). Dependence has a high incidence in barbiturates and meprobamate and even in benzodiazepines, especially "low-dose-dependence" (21). Except for a history of prior substance abuse and dependence on other drugs, it is impossible to predict who is going to become dependent (9; p. 69). Potential abuse or addiction in the routine patient is generally not supported by the available scientific evidence: long-term follow-up studies found no evidence for a general tendency to increase the benzodiazepine dosage or abuse the substances (14,22). Depression may occur with any CNS depressant agent and has also been described as a consequence of benzodiazepine administration (5; p. 177). There are no data from controlled studies addressing the exact incidence. In otherwise healthy individuals, depression induced by benzodiazepines does not seem to be a source of major concern. If used as a treatment for insomnia in major depression, benzodiazepines are more beneficial than harmful, although in themselves they do not represent an appropriate treatment for depression (5). Data on incidence of overdose with benzodiazepines (rarely taken in isolation), although frequently part of suicide attempts in combination with other substances, are not documented in controlled studies. Overdose with barbiturates is not always suicidal but possible even accidental if the patient increases the dose because of loss of benefit, being unaware of the unaltered lethality threshold.

3. Mechanism

Disinhibition is seen as a weakening of (frontal lobe) cortical inhibitory control over subcortical (limbic) behavioral programs. Dependence is seen as a consequence of low-dose tolerance, which is shared by all substances interacting with the GABA receptor. Depression may either be a direct drug effect, as postulated in ethanol-induced depression (partially by leading to an asymmet-

rical impairment of euphoric left hemisphere processes, disinhibiting right hemisphere processes with predominantly negative emotions), or seen as an independent feature which was not prevented by benzodiazepine treatment. Overdose is usually a voluntary act but may well be caused by organic disinhibition with increased impulsivity and suicidal tendencies or accidentally (see above).

4. Differential Diagnosis

Disinhibition, seen as a paradoxical rage reaction mediated through the limbic system, must be differentiated from an underlying limbic ictal disorder (in the spectrum of temporal lobe epilepsy). Preexisting brain damage has to be screened for. Mania (especially ‘‘delirious mania’’ or “Bell's mania”) may lead to similar behavioral dyscontrol, but usually responds well to benzodiazepines. Impulse dyscontrol disorders, mental retardation, neurological disorders (especially postictal states, frontal lobe processes) have to be considered. Psychological factors are often overlooked in a hospital context: a conflict between patient and staff may be seen by staff as “behavioral dyscontrol” (and representing a countertransference manifestation) but may well be a justified disagreement from the patient's side and should not routinely be “treated” and medicalized unless careful assessment supports this. Dependence has to be seen in context, and coexisting abuse or dependence on other medication-legal or illegal drugs—has to be carefully screened for. In mental hospitals, some benzodiazepines (lorazepam, diazepam) are part of a “black market” where substance-abusing patients obtain those drugs under false premises and sell them to their fellow patients. Depression has to be differentiated between causation by sedative-hypnotic drugs and primary major depression, or dysthymia, induced by other drugs (especially antihypertensive medication), hypothyroidism, or any other condition from the long list of differential diagnoses of depression. Overdose has to be treated as a psychiatric emergency, and a drug screen, suicide precautions, and appropriate detoxification measures are indicated.

5. Clinical Management

The best clinical management of barbiturates is not to prescribe them. Much better alternatives are now available. Careful selection of the right indication for benzodiazepines will help to avoid giving these compounds to individuals likely to react with behavioral dyscontrol (disinhibition). If encountered, severely symptomatic dyscontrol can be successfully managed by haloperidol 5 mg IM (5; p. 177). Discontinuation of the sedative-hypnotic medication is

the primary choice and sufficient to address the problem in less pronounced cases. In mild cases of behavioral dyscontrol, waiting for spontaneous alleviation of symptoms is often helpful, combined with behavioral psychotherapeutic interventions. Dosage reduction, especially in cases without any of the mentioned predisposing factors, often addresses the problem successfully (24). However, if there is preexisting brain damage, such conservative measures, including dose reduction, often fail, and the patient has to be taken off the sedative-hypnotic drug.

Dependence has to be addressed from the very beginning of prescribing benzodiazepines or other sedative-hypnotic drugs (like zolpidem or zopiclone). A benzodiazepine-responsive syndrome should be present, the approximate duration of treatment should be determined, and regular reassessments should monitor the course. A careful assessment of risks and benefits should include the caveat to not prescribe benzodiazepines to individuals who are substance abusers or in any way addicted to drugs. Monitoring for abuse and slow tapering of the compounds used after an appropriate trial, including reconsideration of diagnosis are other measures helpful to avoid the development of dependency (5, p. 148). However, it is important to differentiate between dependence and addiction. Addiction is understood as a "cluster of cognitive, affective, behavioral and physiologic signs that indicate compulsive use of a substance and inability to control intake despite negative consequences such as medical illness, failure in life roles, and marked interpersonal difficulties" (5, pp. 148–149). In contrast, a patient with panic disorder may become dependent on a prescribed but beneficial benzodiazepine (i.e., the patient will have discontinuation symptoms such as rebound anxiety, and withdrawal symptoms such as tachycardia if the medication is abruptly stopped). But this patient is in no way an addict and will usually not show any tendency to increase the dose or to divert the drug to other individuals. The fear of benzodiazepine dependence should therefore not lead to undertreatment where the drug is clearly indicated.

Depression will often respond to waiting out the spontaneous course of initial side effects, which tend to subside over weeks. However, if marked, depression should be treated by antidepressants. In case of panic disorder treated with benzodiazepines, a switch to an antidepressant and tapering off the benzodiazepine is the most appropriate step in case of a serious depressive comorbidity, whether drug-induced or not. Often, lowering the dosage will address the problem sufficiently. Regular reevaluation of benefits, side effects, and the lowest possible beneficial dose is part of the routine management of treatment with benzodiazepines.

Overdose with benzodiazepines is fortunately much less dangerous than

overdose with barbiturates or older sedative-hypnotics; this is part of the reason why those older drugs are now obsolete for indications such as anxiety disorders and insomnia (5). Benzodiazepines themselves except for triazolam (25) have only rarely been implicated in fatal overdoses owing to their excellent safety margin (23). When taken with other drugs (alcohol, barbiturates, narcotics), they may contribute to the lethality of the drug cocktail. Treatment includes gastric lavage, supportive measures (respirator, monitoring, warmingup, Intravenous nutrition, etc.), and in lesser cases induction of emesis. The benzodiazepine antagonist flumazenil can be administered in doses of 0.2 mg IV over 30 sec, then 0.3 to 0.5 mg every 30 sec pm up to a total dose of 3 mg.

IV. COGNITIVE ENHANCERS

A. Description

Cognitive enhancers are substances developed to treat dementia or more general states of cognitive impairment. They are called “nootropica” in Europe. In the United States, only two anticholinesterases are approved: 1,2,3,4-tetrahydroacridine (THA, tacrine) and donepezil (A-ricept). Physostigmine, an older cholinesterase inhibitor, has not shown convincing benefits. Its limited efficacy and significant interindividual variability with an inverted U-shaped dose-response curve make it a rather unpredictable agent (27. p. 392). Alone or in combination with lecithin, THA has been shown to lead to modest improvement of performance on psychometric tests and global assessment scales (26). Other treatment principles for dementia (cholinergic agonists, oxotremorine, nicotine, glutamatergic agents) are still in clinical trials. Bethanechol, a cholinergic agonist, is a synthetic beta-methyl analog of acetylcholine. It does not cross the blood-brain barrier, so it has to be administered by intracerebroventricular catheter, which bears substantial risks (inflammation, seizures, chronic subdural hematoma). Studies in AD patients have reported modest improvements but variable dose responses (27, p. 395). Arecoline, oxotremorine, and nicotine are similarly controversial and not introduced into the clinical arsenal of therapeutics.

Interestingly, there is some use for (over-the-counter) anti-inflammatory agents supposed to stop acute phase inflammatory protein and glial cell action (27, p. 399). Chronic exposure to anti-inflammatory agents (given for other reasons such as prophylaxis of cardiovascular disease) is protective against the development of Alzheimer's disease (AD) (27,29). L-Deprenyl, a MAO- B inhibitor, has been shown to improve performance on attention, memory,

and learning tasks (30). Not yet available in the United States but well introduced and documented in Europe are compounds such as meclofenoxat, pyritinol, pentoxifyllin, gingkolid B, co-dergocrin, nicergolin, and piracetam. Their usefulness for the treatment and prophylaxis of dementia is controversial (28).

Side effects of THA include gastrointestinal cholinergic symptoms such as emesis, nausea, dyspepsia, diarrhea, bradycardia, hypersalivation, and sweating as well as hepatotoxicity with increased transaminases and bilirubin (reversible). Coexisting parkinsonian symptoms are worsened, as to be expected. Donepezil seems to have several advantages over THA: it is better tolerated, has no reported, liver toxicity and is effective at the starting dose of 5 mg/day given once a day. At 10 mg/day, it may lead to diarrhea, nausea, and vomiting.

L-Deprenyl may lead to intolerance of tyramine similar to other MAO inhibitors, but only in high doses (not at the recommended therapeutic dose of 10 mg PO qd). It may also lead to nausea, dizziness, abdominal dyscomfort, and dry mouth (27).

B. Frequency

THA is not well tolerated. At a dose of 160 mg PO qd, only 28% of patients finished the treatment course as planned; 72% dropped out because of side effects (27; 28, p. 383; 31). Women are at an especially high risk for side effects. At least one-third of all patients show gastrointestinal side effects at higher doses, causing about 20% of the dropouts. In 30% of patients, transaminases rise threefold, in 5% even tenfold (28, pg. 383). This is not seen in donepezil, which seems to be well tolerated at 5 mg a day (33). Gastrointestinal side effects in L-deprenyl at the recommended dose are very rare.

C. Mechanism

THA (Tacrine) and donepezil (Aricept) are reversible synthetic acetylcholinesterase inhibitors. Blocking of acetylcholinesterase leads to an increase of acetylcholine, with ensuing cholinergic symptoms. THA is metabolized by the hepatic cytochrome P450 system. Hepatic toxicity is dose dependent and reversible. Coadministration of THA and theophylline has been shown to double theophylline's half-life and plasma concentration (27, p. 393).

L-Deprenyl is a reversible MAO-B inhibitor without the intolerance of tyramine (cheese, red wine, etc.) known in other MAO-inhibitors at the recommended therapeutic dose of 10 mg a day. However, accidental overdose and individual sensitivity may represent risk factors. Coadministration of levodopa

Table 3 Side Effects of Cognitive Enhancers

Main side effects (SE) are	Gastrointestinal (nausea, diarrhea, vomiting, hepatotoxicity)
	Glandular (hypersalivation, sweating)
	Cardiovascular (bradycardia)
	Neurological (worsening of parkinsonian symptoms)
Differential diagnosis includes	Food intolerance, GI infection, biliary disease, pancreatitis or pancreatic insufficiency, intoxication with ethanol or other drugs, multisystem failure
	Infections, hypercholinergic crisis
	Intracranial pressure, conduction block
	Parkinson crisis, dopamin blockade, emotional crisis
Management includes	Monitoring of liver function tests, administration with meals, lowering dose or discontinuation; milk of magnesia, sucralfate, attapulgite as indicated
	Amitryptiline or clonidine in low doses
	ECG, cardiac consult, discontinue drug or pacemaker as indicated Lower dose or discontinue; adjust antiparkinsonian medication

may lead to an exacerbation of levodopa-related side effects (hyperkinesis, hallucinations).

D. Differential Diagnosis

Gastrointestinal symptoms may be caused by a great variety of factors, including food intolerance, GI infection, biliary disease, pancreatic insufficiency and pancreatitis, other drugs and substances such as ethanol, as well as increased intracranial pressure and any process leading to an increased activity of the (cholinergic) parasympathetic nervous system. Increased hepatic enzymes are found in hepatitis, biliary disease, intoxication with other medication or drugs such as ethanol, or in polysytemic disorders and multisystem failure. A gastro-

enterological consult is recommended. Interaction with other drugs metabolized though the cytochrome P450 system should always be considered.

E. Clinical Management

If treatment with THA is started, low doses should be preferred, and titration upward should also be slow. Weekly controls of liver function tests over 30 weeks or at least 6 weeks after increase of doseage, then once every 3 months are recommended. If abnormal liver function tests force a discontinuation of THA, enzyme levels usually return back to baseline within 4 to 6 weeks. If bilirubin was at or higher than 3 mg/dL, no reexposure is recommended. Otherwise, a reexposure can be tried but may lead to repeat increase of liver function tests, often with shorter latency than before. Interactions are reported with fluvoxamine, theophylline, and cimetidine (level increase), while nicotine (in smokers) may lead to lower plasma levels (28, p. 384). Administration of THA with meals may lower levels by 30%, and reduce side effects (especially nausea, diarrhea, and dyspepsia). Any comedication with potentially hepatotoxic drugs (acetaminophen) has to be avoided. Asthma, sick-sinus syndrome, and peptic ulcer disease can be worsened by THA application. Precautions are recommended. In women where the activity of P450 enzymes is supposedly lower, THA toxicity is higher and reported THA levels up to 50% higher (28, p. 384).

In case of nausea, dyspepsia, and emesis, the administration of milk of magnesia, sucralfate, or specific antacid drugs (omeprazole 20 mg PO qd) or antiemetic drugs (metoclopramide 10 to 30 mg PO qid) are helpful. Diarrhea is addressed with unspecific (tea, biscuits) and specific measures (attapulgite 30 mL, after each loose stool pm). Hypersalivation may respond well to amitryptiline (75 to 100 mg PO qd) or clonidine, most often applied as a patch (9). Tyramine-related symptoms in L-deprenyl treatment require an MAO diet.

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Index

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