Michael S. Ritsner *Editor*

Polypharmacy in Psychiatry Practice

Volume I

Multiple Medication Use Strategies

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ISBN 978-94-007-5804-9 ISBN 978-94-007-5805-6 (eBook)
DOI 10.1007/978-94-007-5805-6
Springer Dordrecht Heidelberg New York London

Library of Congress Control Number: 2013932219

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

I dedicate this book to my dear grandchildren Ron, Miriam, Diana and Daniel Ritsner who are funny, smart, obstinate, and sometimes downright willful

About the Editor

Michael S. Ritsner, M.D., Ph.D.

Dr. Ritsner, M.D., Ph.D. is a physician and scientist who spent his career of over 35 years caring for patients and studying the nature and treatment of mental illness. Dr. Ritsner is a Professor of Psychiatry at the Rappaport Faculty of Medicine, Technion – Israel Institute of Technology (Haifa), Israel.

Dr. Ritsner graduated from the Khabarovsk State Medical University, and received his PhD in Psychiatry from the Siberian State Medical University in 1975 (Tomsk, Russia). After gaining clinical practice as a neurologist and clinical psychiatrist he joined the Siberian State Research Center at the Russian Academy of Medical Sciences (Tomsk) as a Head of the Psychiatric Genetics Department in 1981. In 1990 he emigrated to Israel where he chaired a Psychiatry Department and the Research Unit at Talbieh Mental Health Center (Jerusalem). Since 1998

Dr. Ritsner directs the Acute Department of the Sha'ar Menashe Mental Health Center, and Cognitive & Psychobiology Research Laboratory affiliated to the Rappaport Faculty of Medicine, Technion.

Particular areas of interest include schizophrenia spectrum disorders, genetic epidemiology, neuropsychiatric biomarkers, the role of neurosteroids in schizophrenia, novel neuroprotective treatments, and cognitive and quality of life impairments. Dr. Ritsner's research has been supported by grants from the Stanley Foundation. He also currently serves as Principal Investigator of a multi-site research team searching and testing novel agents with neuroprotective properties for treatment of the debilitating effects of schizophrenia and related psychotic disorders.

Dr. Ritsner is the co-author of two books on neuropsychiatry and editor of three books and two handbooks, and has published more than 140 peer-reviewed journal articles, reviews, and more than 20 book chapters. He has given more than 200 presentations including as invited speaker at scientific conferences and medical education events.

This monograph is yet another milestone toward achieving his goals of providing a comprehensive up-to-date state-of-the-art overview of the literature that addresses the challenges facing clinical and biological psychiatry. This series follows 12 volumes:

1. *Quality of Life Impairment in Schizophrenia, Mood and Anxiety Disorders. New Perspectives on Research and Treatment*. Ritsner, Michael S.; Awad, A. George (Eds.), Springer, Dordrecht. The Netherlands, 2007, 388 p.
2. *Neuroactive Steroids in Brain Functions, and Mental Health. Novel Strategies for Research and Treatment*. Ritsner, Michael S.; Weizman A. (Eds.), Springer Science + Business Media, B.V., 2008. 559 p.
3. *The Handbook of Neuropsychiatric Biomarkers, Endophenotypes, and Genes*. Volumes I–IV. Ritsner, Michael S. (Ed.), Springer Science + Business Media, B.V., 2009.

    - Volume I: *Neuropsychological Endophenotypes and Biomarkers*. 231 pp.
    - Volume II: *Neuroanatomical and Neuroimaging Endophenotypes and Biomarkers*. 244 pp.
    - Volume III: *Metabolic and Peripheral Biomarkers*. 231 pp.
    - Volume IV: *Molecular Genetic and Genomic Markers*. 232 pp.

4. *Brain Protection in Schizophrenia, Mood and Cognitive Disorders*. Ritsner, Michael S. (Ed.), Springer Science + Business Media, B.V. 2010. 663 p.
5. *Handbook of Schizophrenia Spectrum Disorders*. Volumes I–III. Ritsner, Michael S. (Ed.), Springer Science + Business Media, B.V. 2011.

    - Volume I: *Conceptual Issues and Neurobiological Advances*. 494 pp.
    - Volume II: *Phenotypic and Endophenotypic Presentations*. 526 pp.
    - Volume III: *Therapeutic Approaches, Comorbidity, and Outcomes*. 461 pp.

6. *Polypharmacy in Psychiatric Practice*. Volumes I–II. Ritsner, Michael S. (Ed.), Springer Science + Business Media, B.V. 2013.

Dr. Ritsner served as Associate Editor, *Quality of Life Research* (an international journal of quality of life aspects of treatment, care and rehabilitation, Amsterdam, The Netherlands); Board Member, *American Journal of Neuroprotection and Neuroregeneration* (USA); *CNS & Neurological Disorders-Drug Targets* (Italy); and member of the Scientific Committee, International Society for the Study of Neuroprotection and Neuroplasticity (Romania). Referee activity: *CNS Drugs*, *Quality of Life Research, Psychiatry Research, Clinical Drug Investigation, Social Psychiatry and Psychiatric Epidemiology, Biological Psychiatry*, etc.

Web: http://md.technion.ac.il/lecturers/lecturer_desc.asp?lecturerID=393

Preface

To the best of my knowledge, this might be the first comprehensive, clinically oriented two-volume collection on the polypharmacy (co-administration of more than one medication) or the use of multiple preparations to treat psychotic, cognitive, mood and anxiety disorders. Despite the large number of psychotropic medications currently available, effective management of mental disorders continues to be a challenging task. Although monotherapy may be desirable, most patients require combinations of two or more psychotropic drugs. Polypharmacy aims to address different aspects of treatment resistance, especially insufficient response of positive and negative symptoms, cognitive disturbances, affective comorbidity, obsessive-compulsive syndromes and side-effects of antipsychotic agents. At the same time, evidence based guidelines in support of polypharmacy and augmentative strategies are scant.

This monograph is divided into four parts. Volume I contains two parts including chapters that serve as an introduction and overview of conceptual issues. Key topics include: a rational polypharmacy, receptor binding targets, drug interactions, preclinical and clinical investigation in this field, dosing regimens, multiple medication use in forensic psychiatry, a naturalistic trial, adjunctive strategies, and multiple medication use for the treatment of somatic symptom disorders.

Volume II contains two parts including chapters that focus on antipsychotic polypharmacy for schizophrenia; clinical practice in USA, Czech Republik, Ukraine, and Italy; polypharmacy and associated phenomena; clozapine combinations; and metabolic syndrome. The authors discuss combination therapy for bipolar disorder, major depressive disorder, obsessive-compulsive syndromes in schizophrenia, and potentially inappropriate medication use among elderly patients with dementia. Finally, each volume includes an Appendix that contains 'Annotated Bibliography on Polypharmacy' and 'List of Psychotropic Medications'.

Since many of the contributors to this collection are internationally known experts, they not only provide up-to-date state-of-the-art overviews, but also clarify some of the ongoing controversies and future challenges and propose new insights for future research. The contents of these volumes have been carefully planned, organized, and edited. Of course, despite the assistance provided by the contributors,

I alone remain responsible for the content of this monograph including any errors or omissions.

Editing this book has been an exciting journey that brought several incredible people into my life. First and foremost, I am grateful and thankful to all contributors for their excellent cooperation. I wish to thank the entire staff, heads of departments, and the medical director of the Shaar-Menashe Mental Health Center, Dr. Alexander Grinshpoon, MD, MHA, PhD, for their commitment, and support. Thanks to Peter Butler and Dr. Martijn Roelandse, publishing editors, who did their utmost to promote this project. And of course, I would like to thank my lovely wife Stella for her tolerance of me having my head stuck in my computer. Without her love, patience and support I would not have completed this project.

I sincerely hope that this book will extend the knowledge in the complex field of treatment of psychiatric disorders and will be of interest to a broad spectrum of readers including psychiatrists, neurologists, neuroscientists, endocrinologists, pharmacologists, general practitioners, geriatricians, graduate students, and health care providers in the field of mental health.

Haifa Michael S. Ritsner
September, 2012

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Part I
Polypharmacy Treatment Strategies

Chapter 1
Multiple Psychiatric Medications Use in Psychiatry: How Rational Can It Be?

Ahsan Y. Khan and Sheldon H. Preskorn

Abstract The focus of this chapter is to discuss how rational it can be to use multiple psychiatric medications in combinations to treat an individual patient and what are the basic principles to follow when doing so. This matter is put in the context of the rest of medicine where multiple medication use (MMU) can be based on a highly sophisticated rationale based on knowledge of the pathoetiology and pathophysiology of the illness being treated (e.g., Human Immuno Deficiency Virus- HIV) to a less sophisticated rationale because of limited understanding of the nature of the illness (e.g., bipolar disorder). In this regard, all diagnoses in medicine including psychiatry can be grouped into four hierarchical levels of understanding ranging from least sophisticated (symptomatic diagnoses) to the most sophisticated where pathoetiology and pathophysiology are known. Parenthetically, the goal of medicine as a field is to achieve the highest level of diagnostic sophistication possible to improve their ability to treat or alter the course of the disease. Unfortunately, most psychiatric diagnoses are still at the syndromic level and hence psychiatric medications are typically aimed at the alleviation of sign and symptoms of these disorders. Moreover, two related phenomena are increasing the frequency and complexity of MMU in psychiatry. The first is the increase in the number and types of psychiatric medications available: Since 1990, the Food and Drug Administration (FDA) approved almost 40 new psychotropic drugs to treat a variety of psychiatric illnesses. Second, the ability to rationally designed psychopharmaceuticals has further increase the potential, perhaps

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M.S. Ritsner (ed.), *Polypharmacy in Psychiatry Practice, Volume I: Multiple Medication Use Strategies*, DOI 10.1007/978-94-007-5805-6_1,

the need and perhaps the rationale behind psychiatric MMU. Nevertheless, until knowledge of the pathoetiology and pathophysiology of psychiatric diagnoses progresses beyond the syndromic level, the rationale underlying psychiatric MMU will remain more limited than is ideal.

Keywords Multiple psychiatric medication use • Rational therapeutics • Diagnostic hierarchy • Pharmacokinetics • Rationale for multiple medication use

Abbreviations

AIDS	Acquired Immuno Deficiency Syndrome
APA	American Psychiatric Association
CO-MED	Combining Medications to Enhance Depression Outcomes
DSM-IV-TR	*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision
EPS	Extra Pyramidal Symptoms
HIV	Human Immuno Deficiency Virus
MMU	Multiple Medication Use
MPMU	Multiple Psychiatric Medications Use
QIDS-SR	Quick Inventory of Depressive Symptomatology-Self Report
SSRI	Selective Serotonin Reuptake Inhibitors
STAR*D	Sequence Treatment Alternatives to Relieve Depression
WHO	World Health Organization

1.1 Introduction

> In diseases of the mind … it is an art of no little importance to administer medicines properly; but, it is an art of much greater importance and more difficult acquisition to know when to suspend or altogether to omit them [1]
>
> —Philippe Pinel

The above quote by Philippe Pinel illustrates the need for knowledge, skills and a philosophy to guide the clinician when prescribing multiple medications.

The World Health Organization (WHO) conference of 1985 in Nairobi, Kenya stated:

> Rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their own requirements, for an adequate period of time, and at the lowest cost to them and their community [2].

In this chapter, the authors first discuss the common reasons for multiple medication use (MMU) & Multiple Psychiatric Medications Use (MPMU). They discuss how new drug development in the last three decades paved the way for MPMU in present day practice of psychiatry. The authors then present the rationale for MMU

Table 1.1 Types of MMU

Type	Definition
1. Total MMU/All MMU	All drugs regardless of therapeutic indication(s) or mechanism of action
2. CNS Active MMU	Only drugs which affect the brain are considered but may not have a FDA approved CNS indication (e.g. beta blockers)
3. CNS Indication MMU	Only drugs which have a FDA approved CNS indication but not necessarily a FDA approved psychiatric indication are considered (e.g. phenytoin)
4. Psychiatric Indication MMU	Only drugs which have a FDA approved psychiatric indication are considered

using dimensional approach which goes from diseases and treatment for which much is known about their pathoetiology and pathophysiology (e.g., Human Immuno Deficiency Virus- HIV) to ones for which much less is known (e.g., most psychiatric illnesses). Finally, authors list principles to guide clinicians about rational MPMU and explain each principle in detail with examples drawn from psychiatric practice.

Traditionally, MMU has been termed "polypharmacy" which has a negative connotation, implying an inappropriate or excessive and perhaps even an irrational use of medications. The authors prefers MMU over polypharmacy because it is less judgmental and because MMU can be highly rational and appropriate depending on how much is known about the nature of the illness and its treatment. MMU is a broad term which includes the use of medications from different therapeutic classes and with different mechanisms of actions. It is beyond the scope of this chapter to cover the topic of MMU completely. MMU can be divided into four different types as outlined in Table 1.1.

1. ***Total/All MMU*** occurs when drugs are used in combination regardless of their therapeutic class, FDA indication or mechanism of action. For example, patients with HIV are not only treated with antiretroviral medications, but are also on medications needed to treat adverse effects from antiretroviral drugs, to treat co-morbid medical conditions with HIV, and to treat co-morbid psychiatric conditions with the disease as well.
2. Second category is Central Nervous System (***CNS) active MMU***: This category includes those medications which can affect brain receptors, chemicals and structures but are not Food and Drug Administration (FDA) approved to treat any specific CNS disorder. For example, pindolol, a beta blocker indicated for heart diseases but can affect brain and can be used as an augmentation option with antidepressants to treat depression. None of the beta blockers have a FDA approved CNS indication.
3. Third type is ***MMU with CNS indications***: This includes those medications which have FDA approved CNS indications but are not FDA approved to treat any psychiatric disorders. However, these medications can affect/treat psychiatric conditions. For example, anticonvulsants like valproate, lamotrigine and extended release formulation of carbamazepine, are FDA approved to treat bipolar disorder

Table 1.2 Questions psychiatrist must be able to answer before MPMU

• Can psychotherapy not address residual or refractory symptoms?
• Why am I using more than one drug to treat a single disorder?
• Is another drug really needed?
• Do the drugs interact?
• If so, what are the data supporting the safety, tolerability, and efficacy of the combination?
• Is this time to revisit the diagnosis?
• Are the co-morbid psychiatric conditions put the patient at special risk for MPMU?
• Can the patient afford to take multiple medications?
• How will MPMU affect overall compliance?
• Does the patient stand to gain more from adding a medication than removing one or lowering the dose?

but other anticonvulsants like topiramate, oxycarbamazepine, and immediate release carbamazepine are in use to treat bipolar disorder but have no FDA labeled indication instead such use may be based on research studies, case reports or series, and/or expert opinion.

4. Last category is ***MMU with psychiatric medications***: This includes MPMU to treat a specific psychiatric condition e.g., combination of FDA approved psychiatric medications to treat bipolar disorder and at time treatment resistant depression. Such combinations may or may not have a FDA labeled indication such as aripiprazole augmentation of a Selective Serotonin Reuptake Inhibitor (SSRI) (labeled) versus mirtazapine to augment venlafaxine (not labeled).

This last category is the main focus of this chapter which will discuss how rational it can be to use multiple psychiatric medications in combinations to treat an individual patient, and what are the basic principles to follow when doing this practice. However, the rational use of multiple medications in general is not an all or none phenomenon, rather it is dimensional. No definition of rational use of multiple medication was found in the literature, but in general, rational use of multiple medications means prescribing drug combinations to maximize the chances of efficacy and at the same time minimize medication induced adverse effects. Based on this dimensional concept, the authors propose the following definition for rational use of multiple medications;

> Rational use of multiple medications is a broad term ranging from completely random use of multiple medications with no logic or rationale to highly rational based on a firm understanding of the pathoetiology and pathophysiology of the illness and how the various drugs interact to affect that pathoetiology or pathophysiology in an effective and safe manner.

Next the authors will discuss what could be the reasons behind MMU and MPMU.

For MMU, the rationale of combining medications may be to produce a pharmacodynamic interaction in which the effect of one drug accentuates or diminishes the effect of another. Alternatively, the rationale could also be to produce a pharmacokinetic interaction in which one drug alters the absorption, distribution, metabolism, or elimination of another drug. For MMU to be rational, the treating psychiatrist must be able to answer several questions as outlined in Table 1.2.

Another reason for MMU is that the treatment over the last several decades has moved from a focus on time-limited therapy (i.e., a few weeks) of an acute illness (e.g., antibiotics for an acute infection) to preventive or maintenance therapy for chronic illnesses as diverse as major depressive disorder (MDD), schizophrenia, Alzheimer's disease, hypertension, HIV, and dyslipidemia. For this reason, patients are much more likely to be on more than one medication at the same time [3–5]. So in reality, MMU is the rule rather than exception in modern medicine.

In general practice of medicine, patients being treated with a psychiatric condition are more likely than patients not on a psychiatric medication to be on MMU and more complex MMU. Silkey et al. reported that psychiatric patients tend to be receiving more medications than age-matched non-psychiatric patients, and have been associated with an increased risk of inappropriate prescribing [6]. Goldman reported that patients with psychiatric disorders have significant co-morbidity with medical conditions. Some of these co-morbid conditions result from or are aggravated by effects of psychiatric medications [7]. For example, new onset diabetes mellitus, hyperlipidemia, obesity and hypertension are all common side effects associated with use of atypical antipsychotics and their development may lead to treatment resulting in MMU. Colley et al. reported that psychotropic medications may also results in worsening or emerging psychiatric symptoms such as anxiety, Extra Pyramidal Symptoms (EPS), insomnia, psychosis and treating those side effects may also result in MMU in those patients [8].

On the other hand, MPMU could be the result of the recent approach to modern drug development (i.e., rationally designed psychopharmaceuticals) and may make MPMU even more necessary than it has been in the past. Preskorn et al. reported that one goal of rational drug development is to produce new drugs with limited numbers of mechanisms of action that will have a wider therapeutic index and be better tolerated (i.e., both fewer overall numbers and fewer types of adverse effects) while either maintaining or improving efficacy [9]. However, because of their reduced range of central nervous system effects, such drugs may have more limited clinical applications as single agents. This fact, coupled with the reduced risk of pharmacodynamic interactions when combining drugs with fewer mechanisms of action, sets the stage for more rational drug combination strategies in psychiatry.

Another major reason for MPMU is increase in number of psychiatric medications approved by FDA. Since 1990, the FDA approved almost 40 new psychotropic drugs to treat a variety of psychiatric disorders as shown in Table 1.3 [10].

Another common reason for MPMU is the syndromic nature of the common psychiatric disorders. They usually have multiple signs and symptoms, and therefore treatment aimed at specific symptoms (e.g., insomnia or restlessness) may lead to MPMU. Nichol et al. found that patients diagnosed with mania have been found to be four times more likely to receive multiple psychotropic medications, and those diagnosed with Schizophrenia were three times more likely [11]. Their symptom clusters wax and wane over the course of illness leading to MPMU.

Underutilization of social and behavioral techniques in modern psychiatry practice is a common reason for MPMU. Mintz et al. found decreased utilization of behavioral and social techniques for psychiatric symptoms, even by psychiatrists.

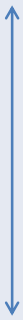
Table 1.3 Psychotropic medications approved since 1991

#s	Approval year	Generic name	Brand name
1	1991	Sertraline	Zoloft
2	1992	Paroxetine	Paxil
3	1992	Zolpidem	Ambien
4	1993	Venlafaxine	Effexor
5	1993	Risperidone	Risperidol
6	1994	Nefazodone	Serzone
7	1996	Mirtazapine	Remeron
8	1996	Olanzapine	Zyprexa
9	1996	Donepezil	Aricept
10	1997	Quetiapine	Seroquel
11	1998	Modafinil	Provigil
12	1998	Citalopram	Celexa
13	1999	Zaleplon	Sonata
14	2000	Rivastigmine	Exelon
15	2001	Ziprasidone	Geodon
16	2002	Aripiprazole	Abilify
17	2002	Escitalopram	Lexapro
18	2002	Atomoxetine	Strattera
19	2003	Memantine	Namenda
20	2003	Lamotrigine	Lamictal
21	2003	Olanzapine and Fluoxetine	Symbyax
22	2004	Duloxetine	Cymbalta
23	2004	Carbamazepine	Equetro
24	2004	Eszopiclone	Lunesta
25	2004	Galantamine	Razadyne (formerly Reminyl)
26	2005	Ramelteon	Rozerem
27	2006	Emsam	Selegiline
28	2006	Paliperidone	Invega
29	2006	Varenicline	Chantix
30	2007	Lisddexamfetamine	Vyvanse
31	2009	Iloperidone	Fanapt
32	2009	Asenapine	Saphris
33	2009	Guanfacine	Intuniv
34	2009	Clonidine XR	Kapvay
35	2010	Lurasidone	Latuda
36	2010	Doxepin	Silenor
37	2010	Trazodone XR	Oleptro
38	2011	Vilazodone	Viibryd

For example, encouragement of proper sleep hygiene in patients complaining of insomnia instead of prescribing sedative/hypnotics and a reluctance to take them off of those medications later can lead to MPMU [12].

A commonly used strategy in psychiatry is to boost or augment the efficacy of the primary treatment by combining it with another drug. For example, combining a

Table 1.4 A dimensional view of rational multiple medication use (MMU)

	Example	Rationale
Highly evolved and substantially evidence based rationale for MMU	HIV combined treatment	Pathoetiology known. Each drug aimed at that Pathoetiology. Substantial evidence of efficacy, safety, & tolerability.
	Cancer	Pathoetiology known in part. Pathophysiology known. Each drug aimed at either Pathoetiology and/or Pathophysiology. Substantial evidence of efficiency outweighing safety & tolerability concerns.
	Parkinson's disease	Pathoetiology unknown. Pathophysiology and biochemistry known. Each drug aimed at pathophysiology. Substantial evidence of efficacy outweighing safety & tolerability concerns.
Not as evolved and/or not as evidence based rationale for MMU	Bipolar disorder or Major depression	Pathoetiology unknown. Pathophysiology understanding limited. Drugs are aimed at signs and symptoms. Evidence of efficacy outweighing safety or tolerability concerns is limited.

SSRI and bupropion to treat a patient with major depressive disorder will necessarily will qualify as MPMU.

Next the authors will discuss the different levels of diagnostic hierarchy and then will present a dimensional view of how to do rational MMU in treating patients with HIV, cancer and Parkinson's disease (Table 1.4).

To explain this aspect of MMU, it is important to understand the hierarchy of diagnostic sophistication and how it is associated with MMU and MPMU. In general, drugs are developed to treat a specific diagnosis. That is the usual requirement for drug approval by regulatory bodies such as the FDA. Response to a specific drug is dependent on having a specific diagnosis that is responsive to drug's mechanism of action. On the other hand, all diagnoses can be grouped into four hierarchical levels of diagnostic sophistication as illustrated in Fig. 1.1 [13]. The least sophisticated level is symptomatic diagnoses (e.g., headache or psychosis). Syndromic diagnoses are at the next level and are based on the observation that a group of patients are presenting with the same cluster of symptoms and signs, suggesting a

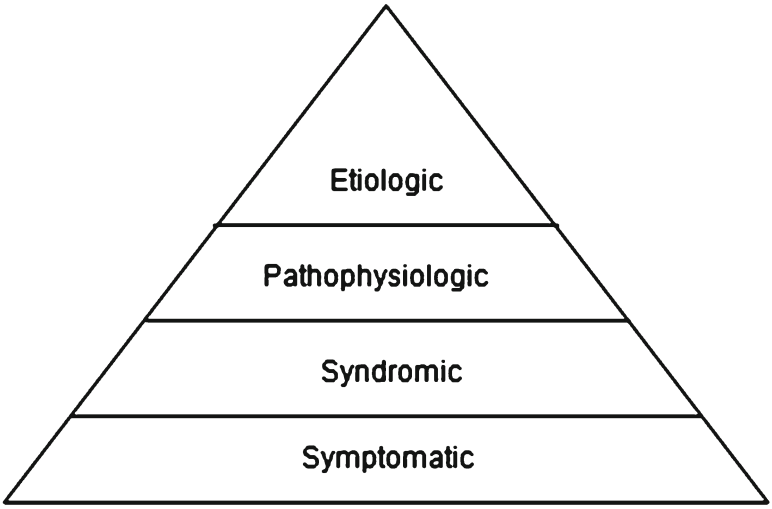


Fig. 1.1 Diagnostic criteria pyramid (Reproduced with permission from S. Preskorn)

common disease process (e.g., rheumatoid arthritis or psychiatric condition). The next level is diagnosis based on pathophysiology which is based on documented biological and physical manifestations which correlate with the stage and/or severity of the illness (e.g., Parkinson's disease). Pathophysiology does not deal directly with the treatment of disease, rather, it explains the processes within the body that result in the signs and symptoms of a disease. Finally, the highest level of diagnostic sophistication is where both pathophysiology and pathoetiology of the disease are known (e.g., infection with HIV). It was first a syndrome without a known pathophysiology or pathoetiology but has now progressed to an etiologic diagnosis (HIV infection) and treatment is aimed at blocking the development of the terminal syndrome (i.e., Acquired Immuno Deficiency Syndrome- AIDS). The goal of the clinician and the researcher is to achieve the highest level of diagnostic sophistication possible i.e., at the pathophysiology and pathoetiologic level to improve their ability to alter the course of the disease process.

Based on this concept of diagnostic sophistication, MMU can be divided into highly evolved and substantially evidence based such as HIV combined treatment, to less evolved and/or less evidence based such as bipolar disorder treatment (Table 1.4).

1.2 Rationale for MMU in HIV

Soon after the identification of AIDS, flood gates opened for research which first led to an improved understanding of the pathophysiology underlying the syndrome—a progressive loss of specific types of lymphocytes and then to an understanding of the

pathoetiology—infection with HIV. Understanding the pathophysiology and pathoetiology are the final two levels of diagnostic sophistication. The identification of HIV as the causative agent in AIDS introduced the development of practices that reduce the risk of acquiring the virus and if already acquired, to the development of drugs that arrest the progression of the disease process thus preventing or delaying the development of AIDS.

Even though there is no cure for HIV/AIDS, multiple medications can be used in combination to control viral replication. Each of the classes of anti-HIV medications blocks the virus in a different way. Gulick et al. reported that there is scientific evidence that suggests combining at least three drugs from two different classes [**non-nucleoside reverse transcriptase inhibitors (NNRTIs), nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), entry or fusion inhibitors (E/FIs), and integrase inhibitors (IIs)**] avoids creating strains of HIV that are immune to a single drug [14]. Each antiretroviral drug aimed at the pathoetiology and pathophysiology of HIV as outlined below.

- NNRTIs disable a protein needed by HIV to make copies of it-self e.g., efavirenz (Sustiva)
- NRTIs are faulty versions of building blocks that HIV needs to make copies of itself e.g., zidovudine (Combvir)
- PIs disable protease, another protein that HIV needs to make copies of itself e.g., ritonavir (Norvir)
- E/FIs blocks HIV entry into CD4 cells e.g., enfuvirtide (Fuzeon)
- IIs works by disabling integrase, a protein that HIV uses to insert its genetic material into CD4 cells e.g., raltegravir (Isentress)

The rationale to use multiple medications in HIV is based on the fact that HIV/AIDS needed a therapy based on simultaneous delivery of a cocktail of drugs, because of the virus' capacity for rapid evolution. Substantial evidence of efficacy, safety and tolerability exist for HIV drug combinations.

1.3 Rationale for MMU in Cancer

Based on our knowledge of pathophysiology and pathoetiology of cancer, it is a disease of cells gone awry, of uncontrolled proliferation, of the loss of normal patterns of cell behavior. Cancer arises from a series of genetic and epigenetic changes (usually DNA-associated proteins that influence gene expression) that endow the cancer cell with its malignant behavior. Researchers study cancer-related mechanisms of DNA damage and repair, and investigate tumor immunology, as well as other responses of the body to cancer, and the biology of malignancies of the immune system.

Researchers have used drugs combinations since the earliest days of cancer therapy. Each drug aims at either pathoetiology and/or pathophysiology of the cancer. As in HIV/AIDS, successful cancer treatments have evolved empirically using a cocktail of low specificity and highly toxic drugs. Modern cancer drugs are

Table 1.5 Parkinson's disease as a model of rational copharmacy

Treatment	Effect
L-Dopa	Increase synthesis of central dopamine (type: pk)
L-Dopa plus carbidopa (Sinemet)	Inhibit peripheral decarboxylase to reduce the dose of L-Dopa needed to increase synthesis of central dopamine (type: pk)
L-Dopa/carbidopa plus dopamine reuptake inhibitor (e.g., bupropion, amantadine)	Potentiate the effect of released central dopamine (type: pk)
L-Dopa/carbidopa plus L-deprenyl	Increase synthesis of central dopamine and block its degradation (type: pk)
L-Dopa/carbidopa plus a bromocriptine	Potentiate central dopamine agonism by addition of direct dopamine agonist (type: pd)

Type refers to type of interaction: *pk* pharmacokinetie; *pd* pharmacodynamic

often developed to hit specific targets within cancer cell. But when using a drug that attacks a single target, the disease often develops resistance to the treatment and comes back in a more aggressive form. Attacking with multiple drugs from the beginning may be able to prevent that process. Substantial evidence of efficacy outweighing safety and tolerability concerns exist.

Next disease in diagnostic hierarchy using dimensional approach for rational MMU is Parkinson's disease.

1.4 Rationale for MMU in Parkinson's Disease

In Parkinson's disease the pathophysiology and biochemistry is known but the pathoetiologic mechanism responsible for initiating nigral cell death remains elusive. Multiple mechanisms have been implicated, including oxidant stress, excitotoxicity, mitochondrial dysfunction, and proteosomal dysfunction. However, most researches would agree that nigral degeneration is most likely due to the cumulative effect of multiple processes such as age—related changes, genetic constitution, and toxin (endogenous or exogenous) exposure predispose individuals to nigral degeneration. Nigral degeneration results in dopamine deficiency, therefore the goal of treatment is to increase central dopamine activity.

It is rare to use a single drug to treat Parkinson's disease (Table 1.5). The cornerstone of treatment is a combination of L-dopa (L-3,4-dihydroxyphenylalanine) and carbidopa (Sinemet) [15]. At least early in the course of the disease, promoting dopamine in the nigrostriatal pathway can be accomplished by supplying the substrate, L-dopa, which is then decarboxylated to dopamine. However, this reaction can occur in the periphery as well as centrally. Dopamine cannot cross the blood-brain barrier. Hence, the conversion in the periphery decreases the effective dose of L-dopa available to reach the target organ (i.e., the brain) [16]. Although increasing the dose of L-dopa can overcome this problem, it may also result in an increased incidence of peripheral adverse effects caused by excessive peripheral dopamine agonism. For this reason,

carbidopa was added to L-dopa to inhibit dopa decarboxylase activity in the periphery and thus increase the bioavailability of the administered L-dopa to the brain. Several other ways to rationally augment the central action of L-dopa are shown in Table 1.5.

It was possible to develop such rational drug combination and even multiple medication model for Parkinson's disease because the pathophysiology of this condition is relatively simple and understood. The dysfunction in Parkinson's disease involves a single neurotransmitter. The neuroanatomy and neurophysiology have been elucidated, can be readily studied, and pharmacologically manipulated [17].

The treatment of Parkinson's disease may also provide a model for understanding a frequently troubling and perplexing phenomenon: many clinicians report that antidepressants, particularly SSRIs, seem to lose their effectiveness over time in a substantial number of patients. Although L-dopa can be a miracle drug early in the treatment of Parkinson's disease, it predictably loses its effectiveness during long-term treatment. The reason is based on the pharmacology of the drug versus the nature of the illness: L-dopa temporarily ameliorates the pathophysiology but does not correct the pathoetiology that results in the loss of central dopamine neurons. As these neurons die, L-dopa can no longer be converted to dopamine and thus it loses its efficacy. At least in some patients, antidepressants may simply correct the pathophysiology of a condition that is pathoetiologically progressive. If so, such drugs will predictably lose their efficacy over time.

Rationale for MPMU in psychiatric disorders is not as evolved and sophisticated as for HIV, some forms of cancer, and Parkinson's disease because knowledge of the pathoetiology and pathophysiology of psychiatric disorders is not as advanced as is the case in the other illnesses. Majority of the psychiatric diagnoses are at the syndromic level and these syndromes are the basis by which patients are grouped into "disease" clusters and are codified in the United States in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) of the American Psychiatric Association [18]. The overlap in symptoms and signs in psychiatric syndromes as currently defined in DSM-IV-TR may have produced some blurring of the diagnostic boundaries, creating high rates of "comorbid" psychiatric diagnosis and thus leading to the apparent increase in the practice of MPMU in psychiatry.

Next, the authors are going to present several principles and the rationale to guide clinicians for MPMU to treat psychiatric conditions. The authors discuss both validated and empirical strategies of MPMU and recommend that validated strategies, when they exist, be tried before other strategies if mono-therapy in adequate doses for an adequate duration has failed.

1.5 The Principles and the Rationale for MPMU

Principles and rationale for MPMU as outlined in Table 1.6.

1. ***Scientific evidence that the combination is more effective than mono-drug therapy.*** The basis for using a drug combination is based on reliable data from formal studies comparing the efficacy and safety of different combinations in

Table 1.6 Principles and rationale for MPMU in psychiatry

1. Scientific evidence that the combination is more effective than mono-drug therapy.
2. Neurobiological rationale for MPMU.
3. Drug combinations should not pose greater safety or tolerability risks than mono-therapy unless offset substantially by sufficiently better efficacy.
4. Use only those drug combinations that do not interact both pharmacokinetically and pharmacodynamically.
5. When drug combinations are used as part of augmentation strategy.
6. Each drug in combination should have only one target.
7. Combination drugs should not have a broad-acting mechanism of action.
8. Combination drugs should not have the same mechanism of action.
9. Combination drugs should not be working against each other.
10. Parent drug and its metabolite/s should not have different or opposing mechanisms to each other.
11. Each drug in combination should have an intermediate half-life.
12. Each drug in combination should have linear pharmacokinetics.
13. Each drug in combination should not have high protein binding.
14. Treating patients suffering from complex psychiatric conditions.
15. Following APA practice guidelines in treating psychiatric disorders.

adequately powered and properly controlled studies. In Psychiatry, relatively few large and rigorous studies have analyzed combining medications. Rush et al. reported design and results of a National Institute of Mental Health (NIMH) funded study titled Combining Medications to Enhance Depression Outcomes (CO-MED). Two antidepressant medication combinations were compared with a selective serotonin reuptake inhibitor (SSRI) monotherapy to determine whether either combination produced a higher remission rate in an acute (12 weeks) as well as long-term (7 months) treatment phases [19]. This single-blind, prospective, randomized trial enrolled a total of 665 outpatients with moderately severe non-psychotic chronic or recurrent major depressive disorder [19]. Three arms of the study were escitalopram (up to 20 mg/day) plus placebo, sustained-release bupropion (up to 400 mg/day) plus escitalopram (up to 20 mg/day), and extended-release venlafaxine (up to 300 mg/day) plus mirtazapine (up to 45 mg/day). The primary outcome was remission, based on the last two consecutive measurements of the 16-item Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) during the 12 weeks acute phase of the study with at least one of those measurements had to be <6, while the other had to be <8. The reason to have two consecutive measurements of QIDS-SR is to ensure that a single "good week" did not lead to a false impression of a sustained and meaningful remission. Unfortunately, remission rates were not different among treatment groups at 12 weeks. The remission rates were 38.8% for escitalopram plus placebo, 38.9% for bupropion plus escitalopram, and 37.7% for venlafaxine plus mirtazapine [19]. At 7 months, remission rates were not significantly different either. The study has certain limitations, one of which is the doses used during the study. In the acute phase, a dose of escitalopram,

20 mg/day, was used in escitalopram plus placebo arm; but it was an average of 12.5 mg/day of escitalopram in escitalopram plus bupropion arm; and finally, it was an average of 200 mg/day of venlafaxine and an average of 20 mg/day of mirtazapine in venlafaxine plus mirtazapine arm of the study. This study concluded that neither medication combination outperformed monotherapy [19]. However, other antidepressant combination studies done by Carpenter, Stewart and Blier reported higher remission rates for depression [20–22]. In all of those studies, higher doses of antidepressants were used compare to COMED study. Until more convincing data is available, clinicians trying to evaluate a particular form of drug combination will frequently have to rely on existing evidence or on the opinions of "experts."

2. ***Neurobiological rationale for MPMU:*** Single psychiatric disorder may involve multiple brain regions or circuits each producing its own sign(s) and/or symptom(s) which combined yield a syndrome. Nevertheless, that same combined pathophysiology sets the stage for MMU. For example, in panic disorder, the locus coeruleus (norepinephrine system), raphe nucleus (serotonin system), amygdala and frontal cortex (Glutamate and GABA system as well as others) are all involve in sign and symptom cluster and are targets for medications. As a result, clinicians may end up with MPMU to treat this disorder. Same is true for post traumatic stress disorder (PTSD) where the hippocampus and frontal cortex are the main neuroanatomical targets involving serotonin, GABA and norepinephrine systems. Medications working on those systems and structures belongs to different classes and that is how treating psychiatrist ended up with MPMU.
3. ***Drug combinations should not pose greater safety or tolerability risks than mono-therapy unless offset substantially by sufficiently better efficacy.*** A clinician would obviously have to have a compelling reason to use two or more drugs in combination when each drug has significant safety and/or tolerability problems. This guidance would be particularly true when each of the drugs is associated with the same type of problem and the problem is serious (e.g., risk of agranulocytosis, seizures). For example, the agranulocytosis risk associated with clozapine and carbamazapine individually may well have additive and possibly even potentiated when they are used together [23]. Similarly, adding benztropine to an antipsychotic is not always necessary and beneficial, especially if the antipsychotic has inherent anticholinergic activity. Tune reported that clinicians at times failed to consider the cumulative anticholinergic effects when using multiple medications especially in elderly [24].
4. ***Use only those drug combinations that do not interact both pharmacokinetically and pharmacodynamically.*** A drug-drug interaction (DDI) is a measurable change in magnitude, nature, or duration of the action of one drug as a result of concomitant administration of another drug. DDIs can be complex, can cross therapeutic classes, can occur across prescribers, and can present in "masked" ways. In fact "masked" DDIs can ironically lead to more MMU and MPMU to treat the apparent worsening of the primary condition or to treat the apparent emergence of a new condition.

Drugs are approved and generally considered from the perspective of their therapeutic use; however, they interact on the basis of their pharmacodynamics and pharmacokinetics. They also are frequently used for reasons other than their initial labeled indication. The logic behind MMU and MPMU is to achieve a greater overall response by increasing efficacy and/or safety and tolerability through either a pharmacodynamic or a pharmacokinetic interaction. The treatment of Parkinson's disease provides examples of both kinds of drug interactions used intentionally and rationally. One of the four strategies listed in Table 1.5 is based on a planned pharmacodynamic interaction (i.e., L-dopa/carbidopa plus a D2 agonist), and three are based on a pharmacokinetic interaction (i.e., the L-dopa and carbidopa combination itself, L-dopa/carbidopa plus dopamine reuptake inhibitor, and L-dopa/carbidopa plus L-deprenyl). However, a combination that involves both a pharmacodynamic and a pharmacokinetic interaction will be inherently more variable across patients and therefore less predictable and should be avoided when possible. In this section, we first discuss the mechanisms involved in pharmacokinetic interactions, then those involved in pharmacodynamic interactions, and then consider some of the problems involved in using strategies that involve both types of mechanisms.

1.5.1 Pharmacokinetic Drug Interactions

Knowledge about pharmacokinetic drug interactions is critical for the safe and effective use of multiple medications. Pharmacokinetic drug interactions are those in which one drug potentiates or diminishes the action of the other drug by affecting its absorption from the site of administration, its disposition within the body, or its metabolism or excretion. Absorption of orally administered medications may be changed by other drugs that alter gastrointestinal motility, e.g., medications with anticholinergic effects can decrease the gut motility and interact with the absorption of other drugs. Other examples of such interactions include those that occur between some SSRIs (e.g., fluoxetine, paroxetine) and Tricyclic Antidepressants (TCAs), or between thiazide diuretics and lithium, and drugs or dietary factors that inhibit or induce drug transporters such as P-Glycoproteins (pgp).

Preskorn and Callahan reported that pharmacokinetic interactions are based on the fact that one of the drugs has a pharmacodynamic effect on the pharmacokinetics of the other (i.e., the target) drug [9, 25]. The effect of this strategy is most often to alter the functional activity (either induction or inhibition) of the enzyme that mediates the biotransformation of the target drug as a necessary step in its elimination. Such was the case in the two strategies for MMU in Parkinson's disease mentioned above (i.e., the L-dopa and carbidopa combination itself and L-dopa/carbidopa plus L-deprenyl). The goal may be either to block the formation of a metabolite, as happens when carbidopa is added to L-dopa, or to block the degradation of the desired substance to prolong its biological activity, as happens when L-deprenyl is added to L-dopa/carbidopa. Although pharmacokinetic

strategies are rarely used in psychiatry, an example would be using fluvoxamine to inhibit the enzyme P450 1A2, which mediates the conversion of clomipramine to desmethylclomipramine, with the rationale being that the demethylated metabolite is a much more potent inhibitor of the norepinephrine uptake pump than the serotonin uptake pump, whereas the converse is true for the parent drug. If the beneficial effects of clomipramine in obsessive-compulsive disorder are due to its ability to inhibit the serotonin uptake pump, then treatment with that drug might fail in a patient who extensively and rapidly converts it to the demethylated metabolite. We cite this interaction merely by way of example and not as a recommendation, since the same pharmacological goal should be achieved by simply using an SSRI that does not lose its selectivity by biotransformation to such a metabolite.

The problem with pharmacokinetic interactions is that the outcome is dependent on both the concentration of the inhibitor and the activity of that enzyme in the specific patient. There can be substantial variation between patients in such activity because of genetic or environmental influences such as exposure to inducers of the enzyme (e.g., smoking and P450 1A2). For example, Preskorn reported that the effect of the CYP1A2 inhibitor, fluvoxamine at the same dose, on plasma concentrations of olanzapine is greater in smokers than in non-smokers [26].

1.5.2 Pharmacodynamic Drug Interactions

In pharmacodynamic drug interactions, the effect of one drug potentiates or diminishes the effect of another drug without affecting its metabolism or disposition (i.e., pharmacokinetics). For example, a sympathomimetic drug and an anticholinergic drug may additively cause dry mouth, or two sedating drugs (a benzodiazepine and trazodone) can produce additive sedation without affecting each other's pharmacokinetics. An antagonistic pharmacodynamic interaction might be seen with drugs that produce sedation and stimulation, as would occur when a sedating antidepressant is co-administered with a psychostimulant.

Pharmacodynamic interactions are based on the fact that one of the drugs alters the effect of another by affecting the same or a different mechanism of action. The combined use of an SSRI and pindolol to increase antidepressant efficacy is based on a planned pharmacodynamic interaction. The SSRI increases serotonin (5-HT) availability at various serotonin receptors including the presynaptic 5-HT1A receptor sites. However, increasing serotonin at the 5HT-1A receptor will slow the firing rate of these neurons, initially decreasing the effectiveness of the SSRI. Artigas et al. reported that pindolol, although primarily an adrenergic blocker, can also block the 5-HT1A receptor. This action should augment the effects of the SSRI by initially blocking the feedback effect on the 5HT-1A autoreceptor [27]. Kalia et al. reported that this theory lead to the development of vilazodone which combines serotonin uptake inhibition and 5HT1A partial agonism in the same molecule [28].

1.5.3 Interactions Involving both Pharmacokinetic and Pharmacodynamic Mechanisms

Examples of drugs that can produce both pharmacokinetic and pharmacodynamic interactions include some SSRIs (e.g., fluoxetine), which inhibit one or more P450 enzymes in addition to their intended effect on the serotonin uptake pump, and several anticonvulsants (e.g., carbamazepine) which induce one or more P450 enzymes in addition to their desired anticonvulsant action [29]. In general, the use of such drugs as part of a drug combination strategy should be avoided, because the outcome could be due to either a pharmacodynamic or pharmacokinetic interaction. In fact, those two interactions may have opposing effects on the benefit/risk ratio. For this reason, valproate would generally be preferred to carbamazepine as the first choice for a combination strategy for bipolar disorder unless there are compelling data to support the superiority of the alternative. The rationale is that valproate could add mood stabilization properties while being less likely to alter the pharmacokinetics of most but not all other drugs. In a similar way, Hyttel reported that sertraline would be preferred to fluoxetine in combination therapy, because at it's usually effective therapeutic dose sertraline provides the serotonin uptake pump inhibition without causing a clinically significant effect on P450 enzymes such as 2D6 [30].

Preskorn reported that fluoxetine is the most problematic of all the SSRIs to use with multiple medications for two reasons. First, it inhibits more than one P450 enzyme in addition to its desired effect of inhibition of the serotonin uptake pump [9]. Second, Hyttel reported that the potential adverse consequences of its actions are further aggravated by the extended half-lives of both fluoxetine and norfluoxetine [30]. Both of these molecules are active with regard to both the inhibition of the serotonin uptake pump and more than one P450 enzyme. The magnitude and the duration of their effects on these various mechanisms of action are dependent on the concentration and half-life, respectively, achieved on the dose being taken. Thus, the magnitude of these effects can increase for many weeks after the drug has been started or the dose increased and can similarly persist for many weeks after it has been discontinued or the dose reduced [30]. Because fluoxetine follows nonlinear pharmacokinetics, the magnitude and the duration of these effects are increased in a nonlinear fashion with dose increases. Taken together, these factors make MMU and MPMU with this drug particularly complicated.

5. ***When drug combinations are used as part of augmentation strategy.*** This consideration is relevant for pharmacodynamically based comedication strategies. Although having such information about the mechanisms of action of the drugs involved alone is not as ideal as knowing the impact of the combination on the pathophysiology of the illness, it is nonetheless substantially more rational than simply using trial and error in combination strategies.

Trivedi et al. reported that a recent NIMH funded study titled Sequence Treatment Alternatives to Relief Depression (SATR*D), during the second phase, randomly assigned 279 adult outpatients with non-psychotic major depressive disorder who did

not achieve remission despite taking up to 60 mg of citalopram (an average dose of 55 mg) for a mean of 11.9 weeks during the initial phase of the study to sustained-release bupropion (at a dose of up to 400 mg/day), and another 286 participants were assigned to receive buspirone (at a dose of up to 60 mg/day) as an augmentation arm of the study. Both groups reported similar rates of remission, 29.7 and 30.1 respectively [31]. Augmentation of citalopram with either sustained-release bupropion or buspirone appears to be useful in actual clinical settings. During the same phase, beside augmentation/combination strategy, three switching options were used as well. Patients were switched from citalopram to sertraline, bupropion or venlafaxine [31].

Nierenberg et al. reported that during the third phase of the same study, two other drug combinations were tried to achieve remission. A total of 69 adult outpatients with non-psychotic major depressive disorder were assigned to combine their antidepressant with lithium (up to 900 mg/day) and 73 were assigned to take T3 (up to 50 μg/day) for up to 14 weeks [32]. After a mean of 9.6 weeks, results showed a remission rate of 15.9% with lithium combination and 24.7% with T3 combination. During the same phase, patients were randomly assigned to two switching options, i.e., nortriptyline or mirtazapine [32]. However, one can not directly compare the switch options to the augmentation options in STAR*D because patients who were doing better tended to want augmentation whereas those who were doing poorly wanted to switch so it was biased in favor of augmentation.

The next four criteria in Table 1.6 (numbers 6–9) are based on pharmacodynamic principles.

6. ***Each drug in combination should have only one target.*** The more mechanisms of action that each drug in the combination has, the more likely that there will be an increase in either safety or tolerability problems, and more ways the drugs can interact pharmacodynamically, e.g., amitriptyline in combination with a sedative hypnotic, clozapine or an antiarrythmic medication.
7. ***Combination Drugs should not have a broad-acting mechanism of action.*** A drug may have only one mechanism of action, but that action may have wide ranging effects on brain function due to its fundamental nature. An example would be monoamine oxidase inhibitors, which profoundly affect four different central neurotransmitters systems (i.e., dopamine, epinephrine, norepinephrine, and serotonin), and SSRIs, which affect all presynaptic serotonin terminals via their effect on the serotonin transporter (i.e., "uptake pump").
8. ***Combination drugs should not have the same mechanisms of action.*** It would generally be more reasonable to simply increase the dose of one drug rather than to use two drugs with the same single mechanism of action. The main exception to this principle is when the goal is to take advantage of a difference in the pharmacokinetics of the two drugs to achieve a difference in the magnitude of the effect over a dosing interval. For example, in alcohol detoxification a patient could initially be treated with lorazepam, which has rapid absorption and is not dependent on hepatic bio-transformation for its elimination and rapid absorption, and could then be switched to clonazepam because of its long half-life, which can facilitate gradual subsequent discontinuation to avoid rebound symptoms [33].

9. ***Combination drugs should not be working against each other.*** The rationale for avoiding drugs with fully opposing mechanisms should be obvious. There might be specific circumstances in which combinations involving partial or limited opposing mechanisms can be beneficial; however, the data supporting the efficacy of such combinations would have to be substantial to offset this general principle. For example the first drug may have a broad effect on a neurotransmitter system (e.g., SSRIs), and the goal of adding the second drug with specific antagonistic properties may be to intentionally make the combined effects more limited. Hendrickes et al. reported that although SSRIs are generally thought of as being selective, their basic mechanism of action is blockade of the serotonin transporter at all serotonin terminals. As a result, they promote serotonin actions at a wide number of postsynaptic receptors. Some of these actions produce desired effects, whereas others have undesired effects. For example, stimulation of 5-HT2A receptors may interfere with sleep architecture [34] a problem that can be addressed by adding trazodone (which has 5-HT2A blocking action) to a SSRI. Stimulation of the 5-HT3 receptor in the brain and/or the gastrointestinal tract is responsible for the nausea that can be produced by SSRIs. This can be addressed by adding ondansetron or similar 5-HT3 antagonist early in treatment and then gradually discontinuing it to allow for this receptor to down regulate. In fact, an investigational antidepressant, LuAA21004, is in development by Lundbeck and Takeda Pharmaceuticals and was developed intentionally to combined serotonin inhibition and 5HT3 receptor blockade to reduce the incidence of nausea and has other specific serotonin antagonist effects to either theoretically boost efficacy or reduce adverse effects [35].

Criteria 10 through 13 are based on pharmacokinetic principles. Each principle is based on making the outcome more predictable within a patient and across patients.

10. ***Parent drug and its metabolite/s should not have different or opposing mechanisms to each other.*** The rationale behind criterion ten is that many drugs are transformed into metabolites that are biologically active, with activity that can vary substantially from the parent drug. Desmethylclomipramine is one example we have already discussed. Another is methylchlorpiperazine, a metabolite of trazodone that is a 5- HT2C agonist and has anxiogenic properties. The presence of these metabolites makes the outcome more variable because the effect of the drug is a function of the relative concentration of the metabolite to the parent drug. This ratio *is* dependent on the rate of biotransformation, which can vary substantially across individuals.
11. ***Each drug in combination should have an intermediate half-life.*** The length of drug's half life determines the time needed to reach steady state, and that can be important in determining the magnitude and nature of the response to the drug (i.e., efficacy versus safety). The rationale for generally preferring drugs with an intermediate half-life when using drug combinations is that the concentration of each drug will be reasonably stable over a dosing interval, but at the same time the relative concentration of each drug can still be adjusted within a reasonable time frame to achieve the desired magnitude of the combined effect.

An intermediate half-life also means that washout can be accomplished within a reasonable time after drug discontinuation if safety or tolerability problems develop in a specific patient.

12. ***Each drug in combination should have linear pharmacokinetics.*** If the drug has linear pharmacokinetics, then the magnitude of the effect produced by dose adjustment will also be more predictable. An exception to this guideline is when compliance is an issue. For example, in treating a patient with schizoaffective disorder with both an antipsychotic and an antidepressant, it would be ideal to first be able to test the efficacy, safety, and tolerability of the combination therapy with intermediate-lived formulations of the drugs and then switch to depot formulations. Unfortunately, both types of formulation are available for only a few drugs. If the patient had first been treated with oral haloperidol and sertraline, one possibility would be to switch to depot haloperidol and fluoxetine, since fluoxetine is essentially a depot drug. This approach should be taken fully realizing that fluoxetine will also produce inhibition of more than one P450 enzyme, which may have consequences such as elevating the plasma levels of haloperidol. As mentioned previously, one or more of these combinations might conceivably be found in empirical studies to have benefits that outweigh the concerns encompassed by these principles.
13. ***Each drug in combination should not have high protein binding.*** Routledge reported that most psychotropic drugs are highly protein bound [36]. Such bound fraction often accounts for >90% of the total plasma concentration. Although free fraction is small, that fraction determines the concentration of the drug at the site of action and hence is important. Thurmann and Hompesch reported that when use combination of highly protein bound drugs, a small change in the bound fraction, e.g., from 95% to 90%, doubles the concentration at the site of action from 5% to 10% may result in loss of efficacy or worsening of the side effects [37]. Therefore using combinations of highly protein bound drugs have the potential for a displacement drug-drug interaction (DDDI). There are also populations at increased risk for DDDI. For example, protein binding is lower in women than men [38]. Also exogenous hormones and pregnancy can alter protein binding and re reduced in elderly and in patients with chronic hepatic and renal diseases [36].
14. ***Treating patients suffering from complex psychiatric conditions.*** Psychiatric disorders such as bipolar and schizoaffective disorders are complex symptom clusters that wax and wane over the course of illness. Patients with these illnesses may need multiple medications (e.g., it is not unusual for a schizoaffective disorder patient to be on an antipsychotic, mood stabilizer or antidepressant, anxiolytic, benztropine and a sleep aid).
15. ***Following American Psychiatric Association (APA) Practice Guidelines in treating psychiatric disorders.*** APA has published practice guidelines for treating various psychiatric conditions. Muller-Oerlinghausen B reported that for treatment of acute phase of manic or mixed episodes, APA practice guidelines recommend using a combination of lithium and an atypical antipsychotic, or valproate plus an atypical antipsychotic [38]. These recommendations are

based on randomized, placebo-controlled research trials. Yatham LN reported that the studies compared combination therapies e.g., an antipsychotic combined with either valproate or placebo, lithium or valproate combined with either olanzapine or placebo, lithium or valproate combined with either risperidone or placebo [39].

The same is true for panic disorder. APA practice guidelines recommend with substantial clinical confidence using a combination of a benzodiazepine and an antidepressant in the treatment of the acute phase of panic disorder. Studies by Pollack MH et al. and Goddard AW et al. suggested that this combination produces quicker stabilization of panic disorder symptoms. This faster onset has been demonstrated in clinical trials of clonazepam plus sertraline and a clonazepam plus paroxetine [40, 41]. The rationale for using this combination is that benzodiazepines facilitate early improvement of panic symptoms while the brain is adjusting to SSRI.

1.6 Conclusions and Future Directions

Until knowledge of the pathoetiology and pathophysiology of psychiatric diagnoses progresses beyond the syndromic level, the explosion in the number of psychiatric syndromes will continue to blur diagnostic boundaries and that in turn will contribute to the rise in use of drug combinations. Psychopharmacologic treatment of psychiatric disorders can be successfully and safely accomplished with multiple medications when the treating psychiatrist is cognizant about the potential difficulties stemming from MPMU and by following the principles outlined in this chapter. There is widespread awareness of the MMU and MPMU, and "thoughtful" MPMU is evidence-based. It's based on knowledge of the individual drugs, their mechanism of action, metabolism and their known interactions. As the MMU and drug expenditure rise, tradeoffs between the cost and benefits of medications are becoming major clinical and policy issues. As a result of all of these variables, there is a growing and urgent need for further research to

- Evaluate the potential benefit and risk associated with MPMU, such as developing drug classification or grouping based on pharmacodynamics and pharmacokinetics characteristics,
- Identify the most prevalent drug combinations and evaluate their potential to interact for good and/or ill
- Implement online drug screening or computerized drug alert systems, and
- Develop expert consensus guidelines regarding specific drug combinations.

This need will become even more pressing with the increase in rational drug development in psychiatry. The drugs that are being produced lend themselves to more effective, safe, and better-tolerated forms of drug combination for which the clinician will increasingly be able to tailor the treatment to fit the needs of a given patient.

Acknowledgments To my wife Naila, and my sons Maaz and Faraz For your love and support
In memory of my parents, Mohammed and Raisa

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Chapter 2
Receptor Binding Targets for Antipsychotic Efficacy

Maureen M. Grainger, Rebecca Ahlbrand, Paul S. Horn, and Neil M. Richtand

Abstract In order to identify the contribution of individual serotonin and dopamine receptor subtype binding targets to antipsychotic medication efficacy, we analyzed correlations between binding affinity to cloned dopamine and serotonin receptor subtypes and clinically effective drug dose for atypical antipsychotic medications. The strongest correlation was observed between binding affinity to the D_3 subtype dopamine receptor and clinically effective atypical antipsychotic medication drug dose ($r=0.77$, $p=0.005$). In contrast, binding affinity to the D_2 ($r=0.59$, $p=0.056$) and D_4 subtype dopamine receptors ($r=0.23$, $p=0.23$) exhibited lower correlations with atypical antipsychotic medication dosages. No direct correlations were identified between atypical antipsychotic medication dose and binding affinities to serotonin 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, or 5-HT_7 receptor subtypes. Highly significant correlations were also observed between atypical antipsychotic medication dose and the ratios of D_2/5-HT_{1A} ($r=0.69$, $p=0.019$); D_3/5-HT_{1A} ($r=0.69$, $p=0.02$); $D_3 \times$ 5-HT_{2A} ($r=0.71$, $p=0.014$); ($D_2 \times D_3$)/5-HT_{1A} ($r=0.81$, $p=0.002$); ($D_2 \times D_3 \times$ 5-HT_7)/5-HT_{1A} ($r=0.74$, $p=0.010$); ($D_2 \times D_3 \times$ 5-HT_{2A})/5-HT_{1A} ($r=0.76$, $p=0.007$); ($D_2 \times D_3 \times$ 5-HT_{2C})/5-HT_{1A} ($r=0.76$, $p=0.007$); and ($D_2 \times D_3 \times$ 5-$HT_{2A} \times$

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M.S. Ritsner (ed.), *Polypharmacy in Psychiatry Practice, Volume I: Multiple Medication Use Strategies*, DOI 10.1007/978-94-007-5805-6_2,

5-HT_{2C})/5-HT_{1A} ($r = 0.72$, $p = 0.013$) receptor binding affinities. These observations suggest opposing interactions among three distinct domains of receptor binding targets contribute to the antipsychotic effects of atypical antipsychotic medications: (1) D_3 and D_2 dopamine receptor binding affinity enhance atypical antipsychotic medication potency. (2) Binding affinity to serotonin 5-HT_{2A}, 5-HT_{2C}, and 5-HT_7 receptors also facilitates antipsychotic efficacy. (3) In contrast, enhanced binding affinity to serotonin 5-HT_{1A} receptor reduces antipsychotic medication potency.

Keywords Dopamine • Serotonin • Schizophrenia • Psychosis • Neuroleptic • Antipsychotic

Abbreviations

5-HT	Serotonin
FDA	Food and Drug Administration
NIMH	National Institute of Mental Health
PDSP	Psychoactive Drug Screening Program

2.1 Introduction

Thirty-five years after Seeman and Creese published their seminal observations on the relationship between D_2 dopamine receptor binding affinity and antipsychotic medication potency [1, 2], mechanism(s) of action underlying the efficacy of antipsychotic medications continues to be a topic of interest and controversy [3–5]. Since the original observations of Seeman and Creese, each of the receptor targets for antipsychotic medications have been cloned, and binding data for each antipsychotic medication to the cloned human receptor is available. Additionally, recommended therapeutic dosages of antipsychotic medications have decreased substantially since those initial observations. Based on those developments, we analyzed the relationship between antipsychotic drug dose and binding affinity to cloned human dopamine and serotonin receptors [6]. That analysis suggested therapeutic efficacy for typical antipsychotic medications derived largely from D_2 dopamine receptor binding, while D_3 dopamine receptor binding affinity was not directly correlated to clinically effective dose for typical antipsychotic medications. Additionally, serotonin 5-HT_{1A} receptor binding inhibited potency for typical antipsychotic medications. In contrast, therapeutic efficacy for atypical antipsychotic medications was most highly correlated with combined effects of binding at D2, 5-HT_{2A}, and 5-HT_{2C} receptors, while serotonin 5-HT_{1A} receptor binding also inhibited potency for atypical antipsychotic medications. At the time of that earlier evaluation, full data was available for only seven atypical antipsychotic medications.

Since that initial analysis, four additional atypical antipsychotic medications have received FDA approval for therapeutic efficacy targeting psychotic symptoms in schizophrenia. The increase in sample size achieved by the addition of data for these newer medications increases the statistical power to identify relationships between receptor binding affinity and clinical potency for atypical antipsychotic medications. Additionally, there has been recent interest in potential therapeutic effects of serotonin 5-HT_7 antagonists in schizophrenia [7] as a result of data from preclinical studies examining effects of selective serotonin 5-HT_7 antagonists in animal models of relevance to psychotic and cognitive symptoms of schizophrenia [8–11]. Based upon those developments, we analyzed correlations between dopamine and serotonin receptor binding affinities, and clinically effective drug dose for 11 atypical antipsychotic medications with approved indications for the treatment of psychotic symptoms of schizophrenia.

2.2 Methods

Drug affinity K_i values determined by the NIMH Psychoactive Drug Screening Program (PDSP) [12] were used for data analysis, in order to minimize the influence of assay condition variability on receptor K_i values [13]. K_i values chosen for analysis were those listed as NIMH Psychoactive Drug Screening Program assay certified data, determined from assays using the cloned human receptors with drug of interest as test ligand. For K_i values for which PDSP certified assay data were not listed, the average K_i value from assay data compiled on the PDSP web site [12] using the cloned human receptor with drug of interest as the test ligand was utilized. K_i values from cloned human receptor for drug/receptor combinations not listed in the PDSP database were identified from published literature [14–16]. Tables 2.1 and 2.2 list K_i values used in our analysis along with data source. All binding data analyzed in our study has been previously reported, as described in Tables 2.1 and 2.2.

Average daily antipsychotic drug dose was determined from data in randomized, controlled clinical trials where possible [17], supplemented by the recommended dosage ranges from the ePocrates Rx drug reference guide (ePocrates, San Carlos, California). The midpoint of the dose range was utilized in subsequent calculations. Values for antipsychotic drug dose used in our analyses are included in Tables 2.1 and 2.2.

2.2.1 Data Analysis

Antipsychotic medication doses and binding affinities were log-transformed prior to analysis. Data were analyzed by Pearson correlation using GraphPad Prism software (GraphPad Software, Inc., La Jolla, CA) to test for correlations between antipsychotic doses and binding affinities for individual receptor subtypes and interactions between receptor subtypes. The linear correlation coefficient (r) is reported as a standardized measure of strength of association for each regression.

Table 2.1 Antipsychotic medication dopamine receptor K_i values

Drug	Clinically effective dose (mg)	K_i Values (nM)								
		D_1	D_2	D_2 short	D_2 long	D_3	D_4	$D_{4.2}$	$D_{4.4}$	D_5
Aripiprazole	10–15	387	0.95		*0.74*	4.5	*>1,000*			1,676
Asenapine	10–20	*8.85*	*8.9*	*8.84*	*8.9*	*9.38*	*8.95*			
Clozapine	300–600	189	431	*143.3*	*196*	646	*22.5*	*45.2*	*30*	235
Iloperidone	12–24	*216*	*3.5*	*13.3*	*6.3*	*10.55*	*13.75*		*21.37*	*319*
Lurasidone	40–80	***262***	***1.68***		***0.329;0.994***	***15.7***	***29.7***		***29.7***	
Olanzapine	10–15	58	72	*34.6*	*33.2*	63	*17.1*	*44.2*	*40.5*	90
Paliperidone	6	41.0	9.4			*2.6*	54.3			29
Quetiapine	150–750	712	567	*555*	*702*	483	*2,276*	*1,233*		1,738
Risperidone	1–4 mg	60.6	4.9	*4.73*	*6.0*	12.2	*7.12*	*16.7*	*26.3*	16
Sertindole	12–24		*4.14*	*5.8*	*4.87*	*5.76*	*9.29*	*17.67*		
Ziprasidone	140–160	30	4.0	*4.2*	*4.6*	17	*500.8*	*35.3*		152

Normal font PDSP certified data, *italic font* PDSP Ki database mean, *italic underlined* [16], *italic bold* [15], *italic bold underlined* [14]

Table 2.2 Antipsychotic medication serotonin receptor K_i values

Drug	Clinically effective dose (mg)	K_i Values (nM)											
		5-HT_{1A}	5-HT_{1B}	5-HT_{1D}	5-HT_{1E}	5-HT_{1F}	5-HT_{2A}	5-HT_{2B}	5-HT_{2C}	5-HT_{3}	5-$HT5_{A}$	5-HT_{6}	5-HT_{7}
Aripiprazole	10–15	5.6	833	63	8,000		*17.5*	*0.36*	*22.4*	628	1,241	574	10
Asenapine	10–20	*8.6*	*8.4*				*10.15*	*9.75*	*10.46*		*8.84*	*9.6*	*9.94*
Clozapine	300–600	105	398	2,132	966	*130*	*9.15*	*7.38*	*14.9*	241	3,857	17	18
Iloperidone	12–24	*93.21*	*89.12*	*15*			*1.94*		*146.99*	*10,000*		*63.09*	*112*
Lurasidone	40–80	***6.75***					***2.03***		***415***				***0.495***
Olanzapine	10–15	2,063	509	1,582	2,408	*310*	*4.90*	*11.8*	*14.2*	202	1,212	6.0	105
Paliperidone	6 mg	637.8	108.7	15.01	>10,000		1.9	61.86	*48*	>10,000	277.9	2,414	2.7
Quetiapine	150–750 mg	431	1,109	>10,000	2,402	*2,240*	*526*		*1,843*	>10,000	3,120	1,864	308
Risperidone	1–4 mg	427	53.6	29.2	>10,000	*1,240*	*0.481*	41.6	*33.4*	>10,000	205.8	2,241	6.6
Sertindole	12–24 mg	*280*	*60*	*96*	*430*	*360*	*0.387*		*0.9*			*5.4*	*28.*
Ziprasidone	140–160 mg	76	4	9	1,279		*0.73*		*13*	>10,000	291	61	6

Normal font PDSP certified data, *italic font* PDSP Ki database mean, *italic underlined* [16], *italic bold* [15]

2.3 Results

The correlation between average clinically effective antipsychotic dose and binding affinity to the cloned human D_2 receptor is illustrated in Table 2.3 and Fig. 2.1. Clinically effective dose and binding affinity to D_2 dopamine receptor were modestly correlated for second-generation antipsychotic medications ($r=0.59$, $p=0.056$). In contrast, average clinically effective atypical antipsychotic medication dose and binding affinity to the cloned human D_3 receptor are highly correlated [($r=0.77$, $p=0.005$), Table 2.3 and Fig. 2.1]. Average clinically effective atypical antipsychotic medication dose and binding affinity to the cloned human D_4 receptor are not correlated [($r=0.23$, $p=0.23$), Table 2.3 and Fig. 2.2].

The relationship between average clinically effective antipsychotic dose and binding affinity to the cloned human 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, and 5-HT_7 receptors is shown in Table 2.3. No direct correlations were identified between atypical antipsychotic medication dose and binding affinities to these serotonin receptor subtypes.

In order to evaluate possible interactions between receptor subtypes playing a role in mechanism of antipsychotic efficacy, we analyzed correlations between log (average dose) and log (ratio of binding affinities) for combinations of individual receptor subtypes, as summarized in Tables 2.3, 2.4, 2.5 and 2.6. Significant correlations were identified between dose and D_2/5-HT_{1A} ($r=0.69$, $p=0.019$) and D_3/5-HT_{1A} binding affinity ratios ($r=0.69$, $p=0.020$) (Fig. 2.3). In contrast, there was not a significant correlation between clinically effective antipsychotic dose and D_4/5-HT_{1A} binding affinity ratio ($r=0.41$, $p=0.21$) (Table 2.3).

The relationship between receptor subtype binding and clinical efficacy was further evaluated for atypical antipsychotic medications using a more comprehensive set of binding affinity ratios. While there is not a universal consensus on this issue, it has previously been suggested that the antipsychotic effect of atypical antipsychotic medications results from a balance of inhibition at serotonin 5-HT_{2A}, 5-HT_{2C}, and dopamine D_2 receptors [18–21], coupled with simultaneous agonist effects at serotonin 5-HT_{1A} receptors [22–24]. In order to identify therapeutic benefits resulting from the interaction between simultaneous effects at these receptor subtypes, we

Table 2.3 Correlation between clinically effective antipsychotic dose and receptor binding affinity

D_2			D_3			D_4			5-HT_{1A}			5-HT_{2A}		
n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value
11	.59	.056	**11**	**.77**	**.005**	11	.23	.23	11	.11	.76	11	.52	.10
5-HT_{2C}			5-HT_7			D_2/5-HT_{1A}			D_3/5-HT_{1A}			D_4/5-HT_{1A}		
n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value
11	.33	.32	11	.23	.49	**11**	**.69**	**.019**	**11**	**.69**	**.020**	11	.41	.21

Bold font indicates p-value < 0.05

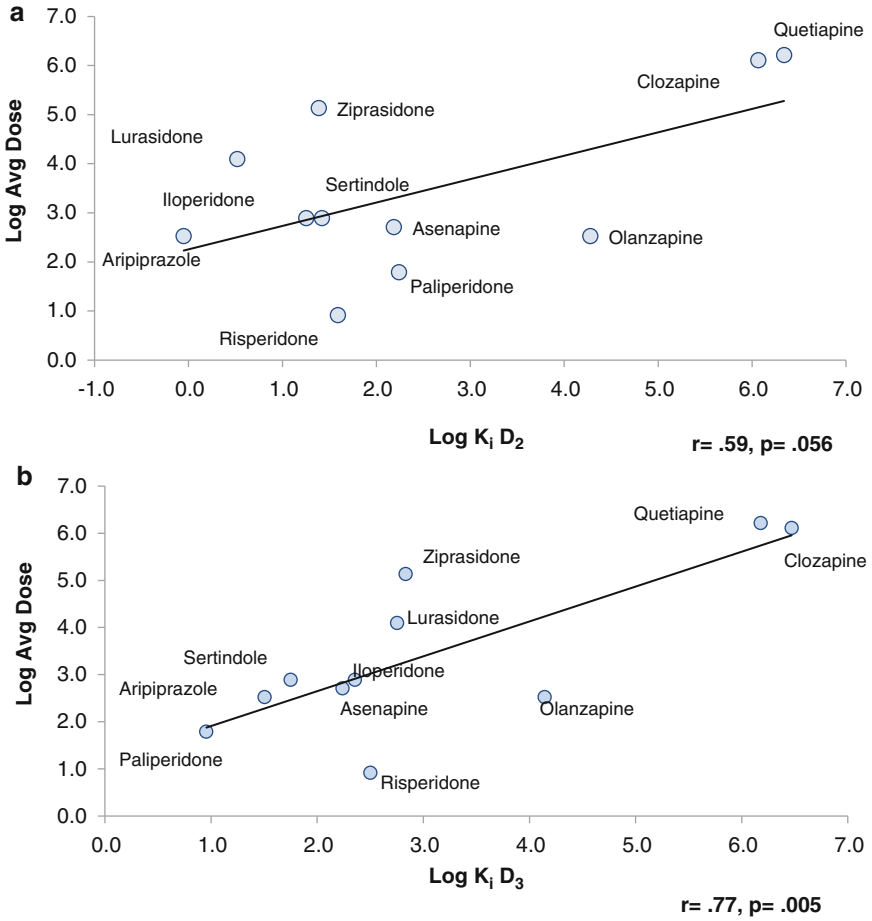

Fig. 2.1 Clinically effective atypical antipsychotic medication dose vs. binding affinity to cloned human dopamine D_2 (*upper panel*) and D_3 receptor (*lower panel*)

analyzed the relationship between clinically effective antipsychotic medication dose and ratios incorporating the binding affinities for each of these receptor systems. We also included serotonin 5-HT_7 receptor binding affinity in the data analysis. As shown in Table 2.4, atypical antipsychotic medication dose and binding affinity ratios to D_2 (5-HT_{2A}/5-HT_{1A}) ($r=0.66$, $p=0.027$) and D_3 (5-HT_{2A}/5-HT_{1A}) ($r=0.70$, $p=0.017$) are highly correlated. Similar correlations were observed between atypical antipsychotic medication dose and D_2 (5-HT_{2C}/5-HT_{1A}) ($r=0.65$, $p=0.030$) and D_3 (5-HT_{2C}/5-HT_{1A}) ($r=0.64$, $p=0.033$) binding affinity ratios (Fig. 2.4).

Combining binding affinity at D_2, D_3, and 5-HT_{2A} receptors identifies a significant correlation between these variables and clinically effective antipsychotic medication dose ($D_2 \times D_3 \times$ 5-HT_{2A}, $r=0.70$, $p=0.018$, Table 2.4). Modifying the relationship

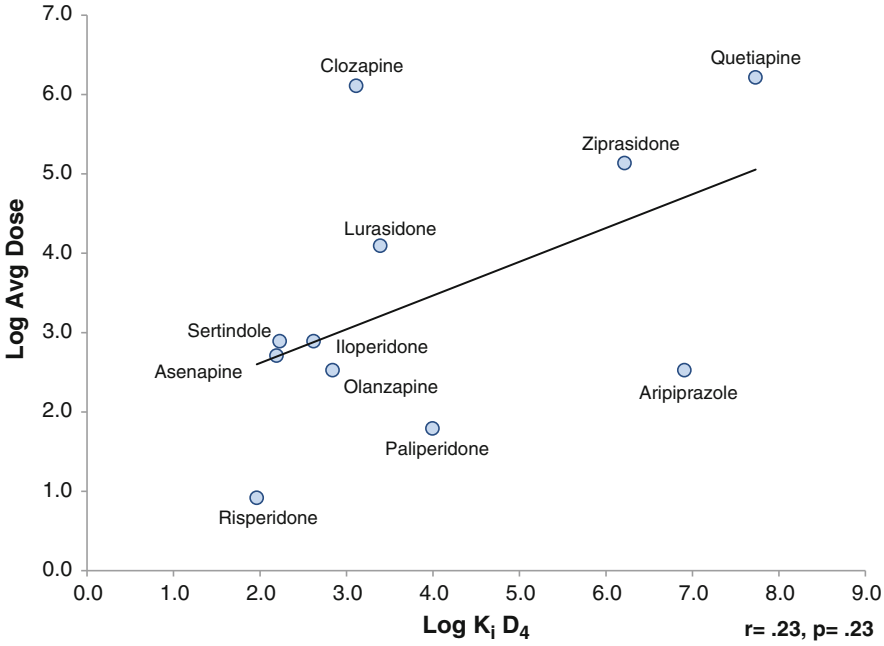

Fig. 2.2 Clinically effective atypical antipsychotic medication dose vs. binding affinity to cloned human dopamine D_4 receptor

via the inclusion of a functionally opposing role for serotonin 5-HT_{1A} receptor (i.e. $D_2 \times D_3 \times$ 5-HT_{2A}/5-HT_{1A}) strengthens the resulting degree of correlation (Table 2.5). Similar results were observed by including or omitting terms for serotonin 5-HT_{1A} receptor effects on the combined binding affinity at D_2, D_3, and 5-HT_{2C} receptors ($D_2 \times D_3 \times$ 5-HT_{2C}, r = 0.69, p = 0.020; $D_2 \times D_3 \times$ 5-HT_{2C}/5-HT_{1A}, r = 0.76, p = 0.007, Fig. 2.5).

The receptor binding relationships can also be modified so that dopamine D_2 or D_3 and serotonin 5-HT_{1A} receptor binding no longer have functionally opposite roles, and D_2 or D_3 binding no longer has a functionally similar action as 5-HT_{2A} and 5-HT_{2C} binding, by inverting the serotonin receptor affinity terms [i.e., D_2 (5-HT_{1A}/5-HT_{2A}); D_2 (5-HT_{1A}/5-HT_{2C}); D_3 (5-HT_{1A}/5-HT_{2A}); and D_3 (5-HT_{1A}/5-HT_{2C}), Table 2.6, right two columns]. This modification completely eliminates the correlation between binding affinity ratio and drug dosage for atypical antipsychotic medications.

2.4 Discussion

The data presented above extend our prior analysis of the relationships between receptor binding affinity to dopamine and serotonin receptor subtypes, and clinically effective antipsychotic medication drug dosage [6]. These examinations

Table 2.4 Correlation between clinically effective antipsychotic dose and receptor binding affinity ratios

D_2 (5-HT_{2A}/5-HT_{1A})			D_2 (5-HT_{2C}/5-HT_{1A})			D_3(5-HT_{2A}/5-HT_{1A})			D_3(5-HT_{2C}/5-HT_{1A})			$D_2 \times D_3$			$D_2 \times D_3 \times$ 5-HT_{2C}		
n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value
11	**.66**	**.027**	**11**	**.65**	**.030**	11	.70	.017	**11**	**.64**	**.033**	**11**	**.69**	**.018**	**11**	**.69**	**.020**
D_2(5-HT_{2A}/5-HT_7)			D_3(5-HT_{2A}/5-HT_7)			D_2(5-HT_7/5-HT_{1A})			D_3(5-HT_7/5-HT_{1A})			$D_2 \times D_3 \times$ 5-HT_7			$D_2 \times D_3 \times$ 5-HT_{2A}		
n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value
11	**.62**	**.042**	**11**	**.70**	**.016**	11	.66	.029	**11**	**.70**	**.016**	**11**	**.61**	**.048**	**11**	**.70**	**.018**

Bold font indicates p-value < 0.05

Table 2.5 Correlation between clinically effective antipsychotic dose and receptor binding affinity ratios

$(D_2 \times D_3)/5\text{-}HT_{1A}$			$(D_2 \times D_3)/5\text{-}HT_7$			$(D_2 \times D_3 \times 5\text{-}HT_{2A})/5\text{-}HT_{1A}$			$(D_2 \times D_3 \times 5\text{-}HT_{2C})/5\text{-}HT_{1A}$		
n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value
11	**.81**	**.002**	**11**	**.69**	**.018**	**11**	**.76**	**.007**	**11**	**.76**	**.007**
$(D_2 \times D_3 \times 5\text{-}HT_7)/5\text{-}HT_{1A}$			$D_2(5\text{-}HT_{2A} \times 5\text{-}HT_{2C} \times 5\text{-}HT_7)/5\text{-}HT_{1A}$			$D_3(5\text{-}HT_{2A} \times 5\text{-}HT_{2C} \times 5\text{-}HT_7)/5\text{-}HT_{1A}$			$(D_2 \times D_3 \times 5\text{-}HT_{2A} \times 5\text{-}HT_{2C})/5\text{-}HT_{1A}$		
n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value
11	**.74**	**.010**	**11**	**.62**	**.042**	**11**	**.65**	**.031**	**11**	**.72**	**.013**

Bold font indicates p-value < 0.05

follow the approach of the original analyses by Seeman and Creese demonstrating a linear correlation between a drug's binding affinity to D_2-family dopamine receptors and clinically effective antipsychotic drug dose [1, 2]. The assessment of binding data from cloned human dopamine and serotonin receptor subtypes provides an opportunity to test correlations between clinically effective drug dosages and affinity to catecholamine receptor subtypes which were not available for binding analyses at the time of these original studies in the 1970s. Here we include data from four additional atypical antipsychotic medications more recently approved by the United States Food and Drug Administration for efficacy targeting psychotic symptoms in schizophrenia. The increased sample size adds statistical power to identify significant relationships between antipsychotic effects of atypical antipsychotic medications and receptor binding targets. The major findings identified by these analyses are discussed below.

2.4.1 D3 Dopamine Receptor Provides a Molecular Binding Target for Antipsychotic Efficacy

Compared to earlier analyses, the addition of four new atypical antipsychotic medications to the data set increased the strength of correlation between D_3 dopamine receptor binding affinity and antipsychotic drug dose ($r = 0.77$, $p = 0.005$). The modest correlation between D_2 dopamine receptor binding affinity and atypical antipsychotic medication dose ($r = 0.59$, $p = 0.059$) is also strengthened in the current analysis, and is comparable in magnitude to the correlation between these measures for typical antipsychotic medications identified in our earlier study [($r = 0.54$, $p = 0.046$) [6]]. The earliest reports describing D_3 dopamine receptor expression suggested a role for this receptor as a molecular target for antipsychotic medications based upon the highly restricted pattern of D_3 receptor expression within limbic brain regions believed to play an important role in psychotic symptoms [25, 26]. D_3 dopamine receptor is believed to have primarily extrasynaptic localization, based

Table 2.6 Correlation between clinically effective antipsychotic dose and receptor binding affinity ratios

$5\text{-HT}_{2A} \times D_2$			$5\text{-HT}_{2C} \times D_2$			$5\text{-HT}_{2A} \times D_3$			$5\text{-HT}_{2C} \times D_3$			$D_2(5\text{-HT}_{1A}/5\text{-HT}_{2A})$			$D_2(5\text{-HT}_{1A}/5\text{-HT}_{2C})$		
n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value
11	**.62**	**.042**	11	.59	.057	**11**	**.71**	**.014**	**11**	**.65**	**.029**	11	.0024	.99	11	.098	.77
$5\text{-HT}_7 \times D_2$			$5\text{-HT}_7 \times D_3$			$D_2/5\text{-HT}_7$			$D_3/5\text{-HT}_7$			$D_3(5\text{-HT}_{1A}/5\text{-HT}_{2A})$			$D_3(5\text{-HT}_{1A}/5\text{-HT}_{2C})$		
n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value	n	*r*	p value
11	.48	.16	11	.58	.06	11	.45	.16	11	.52	.10	11	.039	.91	11	.15	.65

Bold font indicates p-value < 0.05

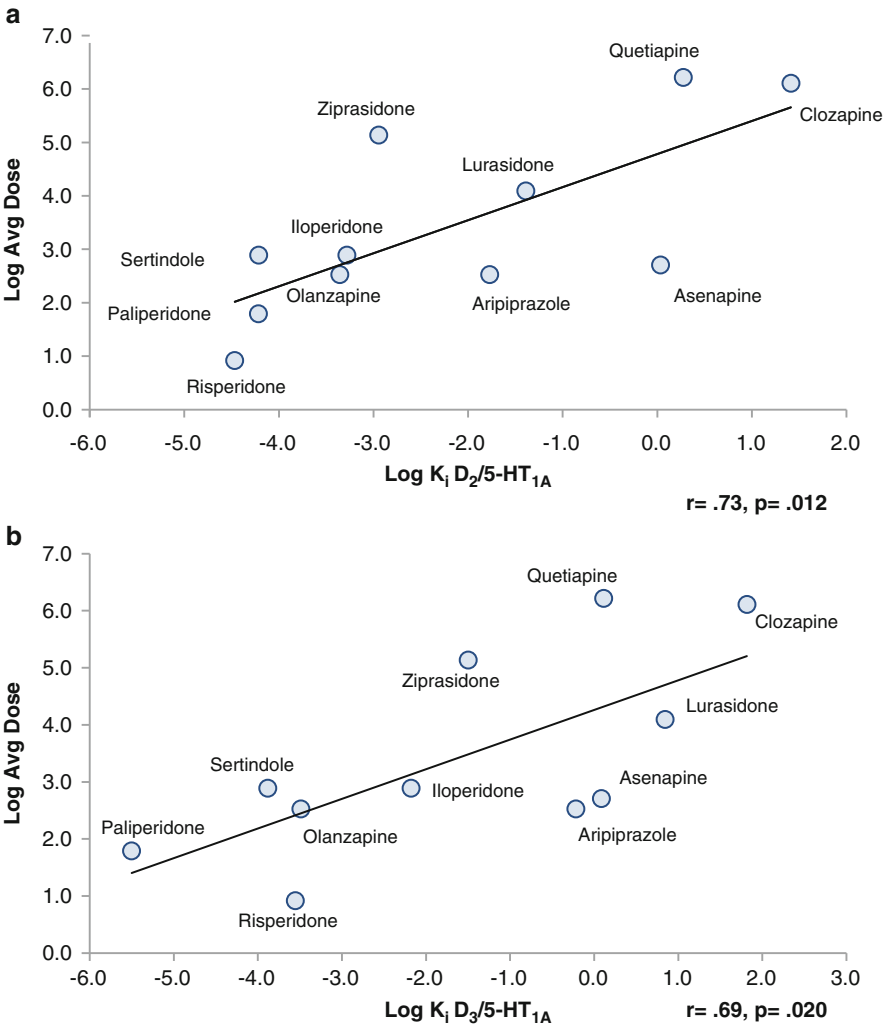

Fig. 2.3 Clinically effective antipsychotic medication dose vs. ratio of binding affinities to cloned human dopamine D_2/serotonin 5-HT_{1A} receptor (*upper panel*) and dopamine D_3/serotonin 5-HT_{1A} receptor (*lower panel*)

upon the lack of overlap between D_3 receptor protein expression and synaptic proteins such as synaptophysin [27]. Further evidence for a functional role sampling extra-synaptic dopamine concentrations comes from the high affinity of the D_3 receptor for dopamine. The low affinity state D_3 receptor Ki = 30 nM [26], close to basal extracellular dopamine concentrations (3–5 nM [28, 29]). In contrast, D_1 and D_2 receptor affinity for dopamine are far lower: D_2 K_i [(nM)] = 2,000, and D_1 K_i [(nM)] = 2,300 [26]. These differences in dopamine binding affinity are consistent

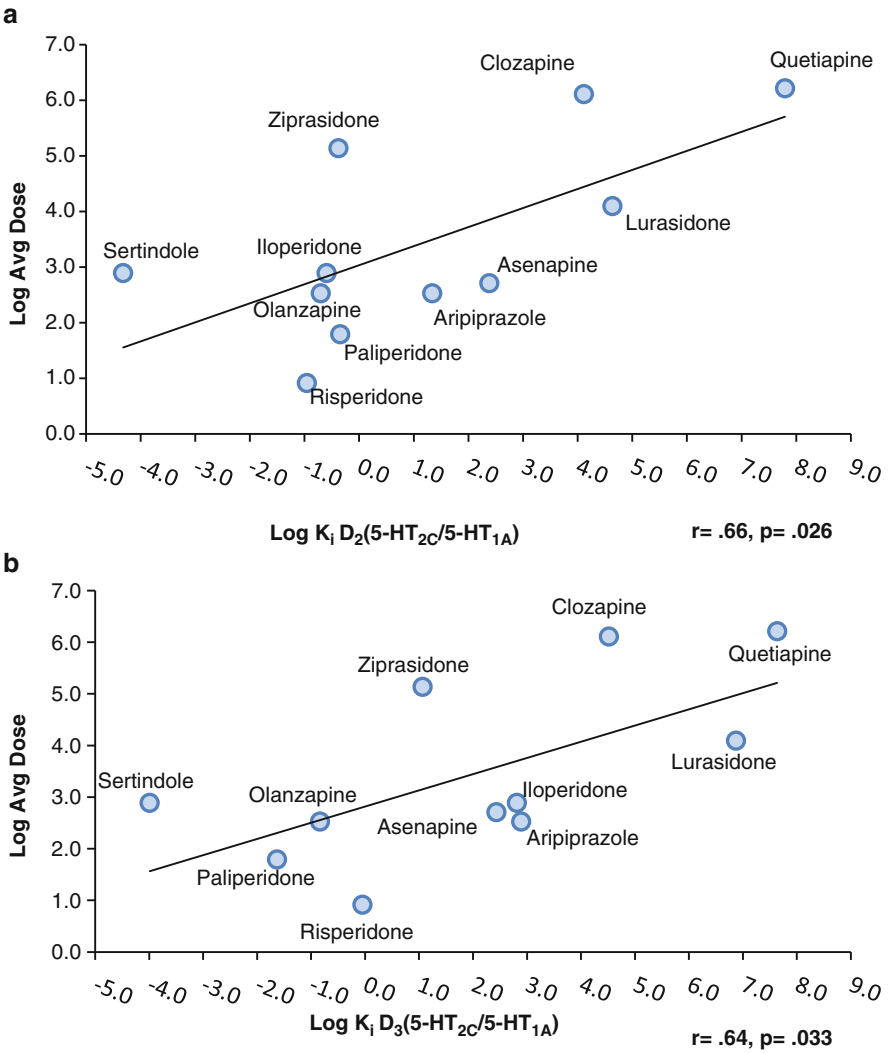

Fig. 2.4 Clinically effective antipsychotic medication dose vs. ratio of binding affinities to cloned human dopamine D_2 × (serotonin 5 -HT_{2C}/serotonin 5-HT_{1A}) receptor (*upper panel*) and dopamine D_3 × (serotonin 5 -HT_{2C}/serotonin 5-HT_{1A}) receptor (*lower panel*)

with the cellular localization of the D_3 receptor, suggesting D_3 receptor stimulation signals tonic dopamine concentrations, while post-synaptic D_1/D_2 receptor stimulation signals phasic dopamine concentrations.

Direct clinical evidence for D_3 receptor as a molecular target for effective treatment of psychotic symptoms of schizophrenia is more limited and variable. The D_3 receptor antagonist (+)-UH232 further worsened positive psychotic symptoms in schizophrenia patients following a single treatment dose. Patients receiving (+)-UH232

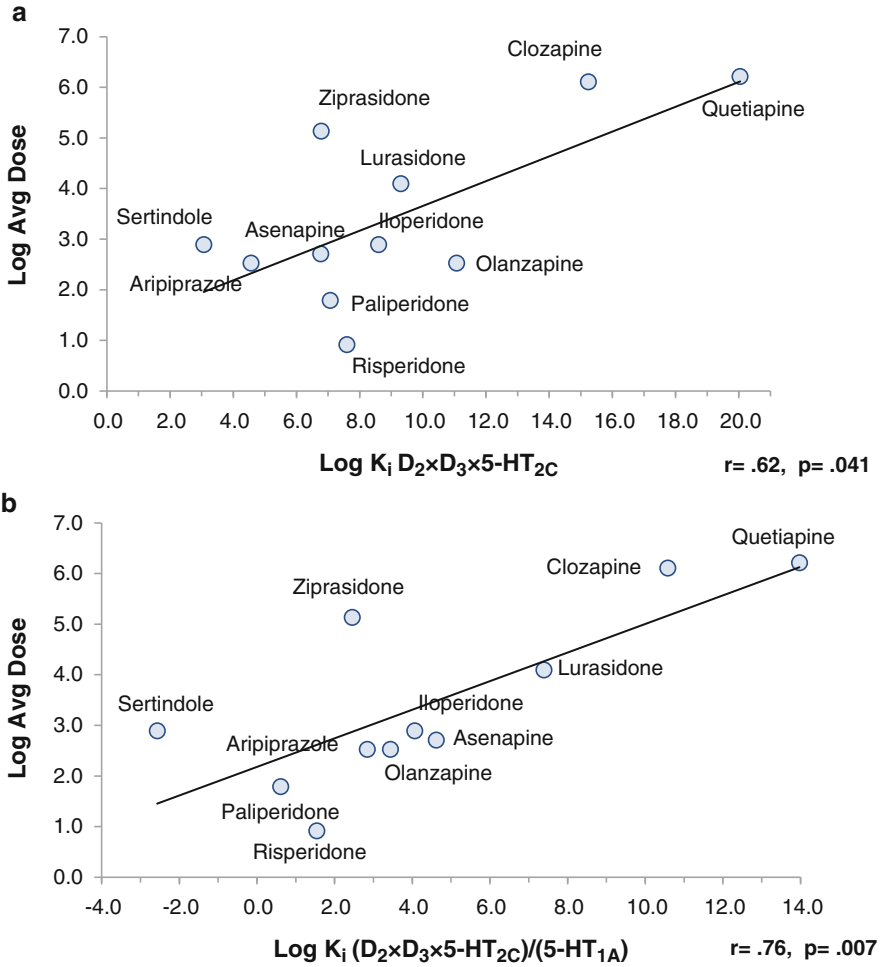

Fig. 2.5 Clinically effective antipsychotic medication dose vs. ratio of binding affinities to cloned human dopamine $D_2 \times D_3 \times$ serotonin 5 -HT_{2C} receptor (*upper panel*) and dopamine $D_2 \times D_3 \times$ serotonin 5 -HT_{2C}/serotonin 5-HT_{1A} receptor (*lower panel*)

in a placebo-controlled study experienced worsening of symptoms including unusual thought content, anxiety, activation, and hostility during the 8 h following single dose treatment [30]. In contrast, the partial D_3 dopamine receptor agonist (-)-3-(3-hydroxyphenyl)-N-n-propylpiperidine [(-)-3PPP] improved psychotic symptoms in schizophrenia patients for up to 1 week. The therapeutic benefit did not persist with repeated treatment in this study [31]. Because [(-)-3PPP] is a non-selective partial agonist with intrinsic activity at D_4 (83 %) and D_2 (35 %) as well as at D_3 (44 %) dopamine receptors [31], a specific role targeting D_3 dopamine receptor cannot be clearly determined from these observations. In a similar fashion, the

D_3 preferring agonist pramipexole exhibits approximately seven-fold greater potency at human D_3 relative to human D_2 receptor [32]. The addition of pramipexole to treatment with haloperidol improved symptoms in 60 % of schizophrenia patients [33]. Studies utilizing medications with higher D_3 receptor selectivity [34] would be needed to determine if psychotic symptoms in schizophrenia are effectively treated by monotherapy targeting the D_3 dopamine receptor in isolation, or if effective intervention requires coordinated effects simultaneously targeting multiple receptors in concert.

2.4.2 Serotonin Receptor Contributions to Antipsychotic Efficacy

Based upon preclinical studies examining effects of selective serotonin 5-HT_7 antagonists in animal models of relevance to psychotic and cognitive symptoms of schizophrenia [8–11], there has been considerable recent interest in potential therapeutic effects of serotonin 5-HT_7 antagonists in schizophrenia [7]. Our data analyses do not identify direct correlations between atypical antipsychotic medication dose and binding affinity to 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, or 5-HT_7 subtype serotonin receptors (Table 2.3). Therapeutic efficacy for atypical antipsychotic medications has been suggested to result from a balance of inhibition at dopamine D_2, serotonin 5-HT_{2A}, and 5-HT_{2C} receptors [18–21], while serotonin 5-HT_{1A} receptor stimulation appears to contribute to antipsychotic efficacy in rat models [23, 24, 35]. Consistent with these concepts and similar to our earlier analyses [6], the addition of four new atypical antipsychotic medications to the data set suggest therapeutic actions of atypical antipsychotic medications are impacted by combined binding effects at different receptor subtypes. Clinically effective dosages of atypical antipsychotic medication are highly correlated with the ratios of D_2/5-HT_{1A}, D_3/5-HT_{1A}, $D_3 \times$ 5-HT_{2A}, $D_2 \times$ 5-HT_{2A}, ($D_2 \times D_3 \times$ 5-HT_7)/5-HT_{1A}, ($D_2 \times D_3 \times$ 5-HT_{2A})/5-HT_{1A}, and ($D_2 \times D_3 \times$ 5-HT_{2C})/5-HT_{1A} receptor binding affinities. Thus, therapeutic potency of atypical antipsychotic medications is influenced by interactions among the following different domains: (1) Increasing D_3 and D_2 dopamine receptor binding affinity enhances antipsychotic potency. (2) Increasing serotonin 5-HT_{2A}, 5-HT_{2C}, and 5-HT_7 receptor binding affinities also facilitate antipsychotic efficacy. (3) Increasing 5-HT_{1A} receptor binding affinity, in contrast, reduces antipsychotic efficacy.

2.5 Limitations

Our analyses are limited to antipsychotic medication effects on positive psychotic symptoms, and do not address efficacy for negative symptoms or cognition which may be more important in terms of long-term functional outcome. Importantly, the strength of correlations between receptor binding and antipsychotic efficacy

identified in our analyses are restricted by a wide range of limiting factors. Medication differences in absorption; metabolism; protein binding; and the presence of pharmacologically active metabolites all serve to weaken the observed correlations. Additionally, the antipsychotic medication dose prescribed to patients may be determined in part by side effects, and might therefore not accurately reflect the "ideal" efficacy dose. The limited number of adequately powered clinical trials to determine optimal dose for antipsychotic medications further limits the accuracy of medication dosages employed in our analyses. Also, the binding data used in our analyses, measuring ligand binding to cloned human receptors expressed in cell culture systems, may be distinct from binding to limbic neurotransmitter receptor populations *in vivo*. Differences in receptor phosphorylation, glycosylation, and/or dimerization to hetero-oligomers [36–39] between in vivo and cell culture systems lacking post-translational machinery could potentially alter receptor binding affinity. And finally, this correlational approach is inherently limited by the complexities of brain circuitry in which dopamine and serotonin receptors may function as a "brake" in one brain region, and simultaneously as an "accelerator" in a different brain region. For example, blockade of D_2 dopamine autoreceptors in cell body regions of the ventral tegmentum increases both synthesis and release of dopamine, which could worsen psychotic symptoms, while blockade of postsynaptic D_2 receptors in limbic terminal regions would likely have an opposite behavioral effect. Thus, the dysfunction of schizophrenia, resulting from a complex interaction of multiple receptor and neurotransmitter systems [40], does not lend itself ideally to an analysis of isolated receptor systems.

2.6 Conclusions and Future Directions

In summary, the data presented above demonstrate correlations between clinically effective atypical antipsychotic medication dose and binding affinities to D_2, D_3, D_4, 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C} and 5-HT_7 receptor subtypes. Given the numerous limitations inherent in this approach (listed above), the strength of correlations described in these analyses suggest the dopamine and serotonin receptor subtypes analyzed provide the preponderance of antipsychotic effect of these medications. The specific mechanism(s) underlying this clinical effect, however, remains obscure. The "disconnect" between the pharmacokinetics of receptor blockade and the extended time lag until clinical benefit suggest antipsychotic efficacy, while initiated through binding to neurotransmitter receptor target(s), is likely the consequence of a downstream cascade of alterations in gene transcription and translation. Studies identifying the specific targets of altered gene transcription resulting from these drug-neurotransmitter receptor interactions would therefore have high likelihood of improving specificity and efficacy of antipsychotic medications.

Acknowledgements Supported by the Department of Veterans Affairs Medical Research Service, and National Institute of Mental Health (R21MH083192-01).

Conflict of Interest The authors disclose the following relationships which might potentially bias this work:

Neil M. Richtand: Consultant: Bristol-Meyers Squibb, Gerson Lehrman Group, Sunovion Pharmaceuticals Inc./Sepracor. Speaker's Bureau: Bristol-Meyers Squibb, Otsuka America Pharmaceutical, Schering - Plough Corporation/Merck, Novartis Pharmaceuticals, Sunovion Pharmaceuticals Inc./Sepracor. Grant/Research Support: Ortho-McNeil Janssen Scientific Affairs, LLC; AstraZeneca Pharmaceuticals

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Chapter 3
Drug Interactions and Polypharmacy

Jessica L. Gören and Ashley Tewksbury

Abstract Over the past 20 years the number of psychotropic medications has increased dramatically. As a result, the use of psychotropic polypharmacy has rapidly expanded. One outcome of psychotropic polypharmacy has been an increase in the number of drug interactions that occur in routine clinical practice. Although drug interactions resulting in death are rare, the effects of drug interactions are often misinterpreted as drug inefficacy or toxicity. Therefore an understanding of pharmacodynamic and pharmacokinetic drug interactions is essential when using polypharmacy. This chapter reviews the mechanisms of drug interactions, describes the most commonly seen drug interactions and offers suggestions for addressing drug interactions in clinical practice. Given polypharmacy is common in psychiatry; clinicians must routinely assess which medication combinations are safe to prescribe, require dose adjustments and are best avoided. Future research should focus on the role of genetics and interventions to decrease adverse drug reactions related to drug interactions.

Keywords Drug-drug interactions • Adverse drug reactions • Psychotropics • Polypharmacy

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M.S. Ritsner (ed.), *Polypharmacy in Psychiatry Practice, Volume I: Multiple Medication Use Strategies*, DOI 10.1007/978-94-007-5805-6_3,

Abbreviations

CNS	Central nervous system
CYP450	Cytochrome P450
EPS	Extrapyramidal side effects
GABA	Gamma-amino butyric acid
INR	International normalized ratio
MAOI	Monoamine oxidase inhibitor
NSAID	Non-steroidal anti-inflammatory drug
PD	Pharmacodynamic
P-gp	P-glycoprotein
PI	Prescribing information
PK	Pharmacokinetic
PPI	Proton pump inhibitor
QTc	Corrected QT interval
SNRI	Serotonin, norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant

3.1 Introduction

Drug interactions are defined as events in which the effects of a drug are altered by a second agent [1–3]. Often times, the second agent is a prescription medication. However, complementary and herbal supplements, over-the-counter medications, illicit drugs, alcohol, cigarette smoking and food can all impact the disposition of drugs. Given the number of patients exposed to multiple medications, the potential number of individuals affected by drug interactions is high [2].

There are two types of drug interactions, pharmacodynamic and pharmacokinetic. Both can be unilateral (drug A affects drug B) or bidirectional (drug A affects drug B and drug B affects drug A) [3]. Pharmacodynamic interactions occur when the effects of one drug are changed by another. Pharmacokinetic interactions result from alteration of a drug's pharmacokinetic properties leading to increased or decreased drug concentrations. Mixed types, both pharmacodynamic and pharmacokinetic, occur and may result in a net effect that can be difficult to predict.

Certain genetic polymorphisms, older age and polypharmacy all increase the risk of drug interactions. Drugs that undergo significant hepatic metabolism, alter hepatic metabolism and are prescribed for long periods of time are often involved in drug interactions. As such, patients receiving psychotropic polypharmacy are at an increased risk for drug interactions.

In clinical practice drug interactions can be advantageous or detrimental. For example, anticholinergic medications are often used to counteract the adverse effects of high potency first generation antipsychotics while combinations of highly anticholinergic drugs can lead to delirium. It is the later scenario, adverse drug events induced by drug interactions, that is a primary safety concern.

Approximately 5% of adverse drug events in the hospital are due to drug interactions though few result in significant morbidity or death [4]. More commonly drug interactions lead to adverse drug events or are misinterpreted as drug inefficacy [1, 2]. Therefore, assessment of potential drug interactions is relevant in daily clinical practice. This chapter focuses specifically on drug-drug interactions but the principles apply to drug interactions with other substances such as food or dietary supplements. While this chapter is not meant to provide an exhaustive list of psychotropic drug interactions, commonly encountered drug interactions are presented in the Appendix.

3.2 Pharmacodynamic Interactions

Pharmacodynamics (PD) refers to the biochemical and physiological effects of exogenous/pharmacological substances on the body. Put more simply, PDs refer to what a drug does to the body. Therefore, PD interactions can be predicted based on drugs' mechanisms of action. Clinically PD interactions magnify, diminish or antagonize the effects of drugs.

Drugs' primary mechanism of action can be associated with interactions. However, drugs have secondary effects that are often implicated in PD interactions. For instance, tricyclic antidepressants (TCAs) antagonize muscarinic and histaminic receptors, in addition to the therapeutic monoaminergic effects. Thus a wide array of side effects, often unrelated to the desired clinical effect, occur with TCAs. This lack of PD specificity also means TCAs are more likely to interact with multiple drugs.

The receptor binding profile of drugs differs across dose. Initially a drug will bind to its primary, highest affinity target but once saturated the drug will begin binding to lower affinity, secondary targets. This concept is helpful in contemplating the likelihood or extent of a drug interaction. For example, there is a theoretical drug interaction between multifunctional trazodone and other serotonergic agents. Trazodone has high binding affinity for serotonin-$_{2A}$, alpha-$_{1}$, and histamine-$_{1}$ receptors below 125 mg. Thus at lower doses trazodone acts primarily as a hypnotic. However, once this dose threshold is exceeded, trazodone acts on serotonin transporter proteins, inhibiting the reuptake of serotonin into the presynaptic membrane. Thus, a drug interaction resulting in serotonin toxicity is unlikely when a serotonergic agent is co-administered with low dose trazodone [5].

Another key concept in drug interactions is binding affinity of two drugs competing for binding sites at the same receptor. Consider a patient who is receiving a dopamine antagonist with a moderate binding affinity for dopamine-$_{2}$ receptors. Partial dopamine-$_{2}$ agonist aripiprazole is then added for dual antipsychotic therapy. Because aripiprazole has a stronger binding affinity for dopamine-$_{2}$ receptors, it will displace the original antipsychotic from its binding sites. In the patient's present neurological landscape of low dopamine (due to original dopamine-$_{2}$ antagonist), aripiprazole will exert agonist properties. Binding affinity and relative binding affinity (binding affinity of a drug in relation to its highest affinity site), are important

factors in PD interactions. Unfortunately, unequivocal translation of binding affinity (often in vitro) data into clinical practice is not currently feasible, and only rough estimations can be made. A direct comparison between drugs is an imperfect approach, as the binding affinities are derived from trials of disparate methodology and assessment techniques [6–9].

3.2.1 Pharmacodynamic Drug Interaction Classification

Additive PD interactions occur when two or more drugs with similar properties are combined. Interactions involving single or multiple PD effects can lead to additive effects. For example, patients may experience increased somnolence when hydroxyzine is combined with chlorpromazine due to both drugs' antihistaminic properties or zolpidem due to combined gamma-aminobutyric acid (GABA) and antihistaminic effects. Synergistic interactions are additive interactions where a drug combination leads to extreme or exaggerated effects. This is exemplified by the increased rate of severe central nervous system (CNS) depression when benzodiazepines are co-ingested with alcohol compared with benzodiazepine use alone. Antagonism occurs when one drug prevents or decreases the effect of a second drug. These effects can occur due to direct effects at the receptor site or indirect effects. Direct effects occur when two drugs with opposing mechanisms compete for the same receptor site as seen when the dopamine antagonist haloperidol is given with levodopa. Indirect interactions involve more complex mechanisms. For example, mirtazapine increases norepinephrine within the synapse via pre-synaptic alpha-$_2$ blockade. Thus mirtazapine's antidepressant effect may be antagonized by the post synaptic alpha blocker, prazosin [9].

The magnitude of a PD interaction is based, in part by the tightness with which a drug binds to a receptor, relative concentrations of the drugs at the site of action and availability of target neurotransmitters within the synapse. Since these factors are unknown for any individual patient, prediction of the magnitude of a pharmacodynamic interaction is often based on patients' previous drug reactions. While significant morbidity or mortality resulting from pharmacodynamic interactions is uncommon, increased side effects or diminished treatment efficacy can be problematic. As shown in Table 3.1, notable exceptions include monoamine oxidase inhibitor (MAOI) interactions (serotonin syndrome, hypertensive crisis), antipsychotics (QTc prolongation) and CNS depressants [8–10].

3.2.2 Time Course of Pharmacodynamic Interactions

The time course for PD interactions can vary but typically effects are seen shortly after (1) starting a drug combination, (2) increasing or decreasing the dose of a drug, (3) discontinuation of a drug or (4) reaching steady state [3, 7]. While starting and increasing medications are obvious triggers for assessment of drug interactions,

Table 3.1 Potentially serious pharmacodynamic interactions [8–10, 16–23]

	SS	HTN	QTc	CNS
Antidepressants				
Selective serotonin reuptake inhibitors	X		X	
Tricyclic Antidepressants	X	X	X	
Serotonin, norepinephrine reuptake inhibitors	X	X		
Monoamine oxidase inhibitors	X	X		
Antipsychotics				
Second generation (except aripiprazole)			X	
Olanzapine IM (short and long acting)				X
Thioridazine			X	
Haloperidol (highest risk with IV)			X	
Anxiolytics				
Benzodiazepine				X
Analgesics				
Tramadol (unlikely)	X			X
Opioids	X			X
Methadone			X	
Herbal				
St. John's wort	X			
Illicit				
LSD	X			
Cocaine		X	X	
Anti-infectives				
linezolid	X	X		

SS serotonin syndrome; *HTN* hypertensive crisis; *QTc* prolongation; *CNS* central nervous system depression

achieving steady state, dose reduction and medication discontinuation may be overlooked. For example, methadone has a half-life of 60 h with repeat administration [11]. Due to this long half-life the full range of side effects may not be seen for weeks after initiating the medication. In other cases, medication discontinuation may result in changes such as intolerable insomnia with bupropion after a sedating antipsychotic is discontinued.

3.2.3 Serious Pharmacodynamic Interactions

3.2.3.1 Hypertension and Hypertensive Crisis

Norepinephrine plays a role in numerous physiologic processes through interactions with alpha and beta receptors [9, 12, 13]. Given the widespread distribution of alpha and beta receptors, drugs that affect the noradrenergic system lead to the diverse physiologic outcomes detailed in Fig. 3.1.

Clinical manifestations of excessive noradrenergic activity include tachycardia, vasoconstriction, diaphoresis, mydriasis, urinary retention, constipation, blurred

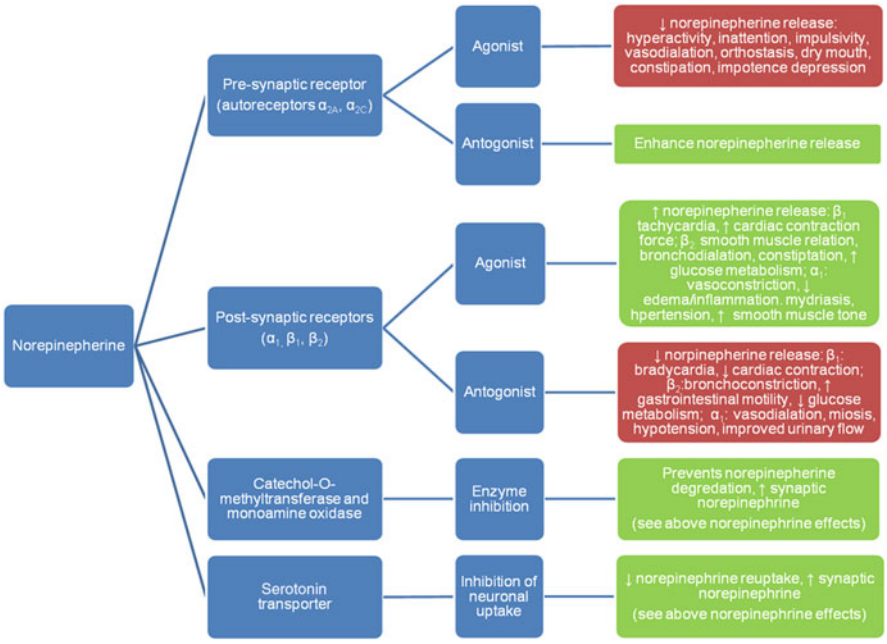

Fig. 3.1 Physiologic effects of norepinephrine

vision, dry mouth, anxiety, headache, and shortness of breath [9, 13]. While changes in blood pressure are typically limited, hypertensive crisis resulting in organ damage or stroke is possible with noradrenergic over stimulation. Few psychotropics are associated with hypertensive crisis but it is most likely to occur when MAOIs are co-prescribed with drugs that increase noradrenergic function [9]. High dietary tyramine intake can also cause hypertensive crisis in patients on MAOIs [9]. When hypertensive crisis does occur the offending drugs should be discontinued and supportive care should be initiated [9, 14].

More commonly seen in clinical practice are interactions involving antagonism of noradrenergic effects. For example, when mirtazapine, a presynaptic α-2 blocker, is added to clonidine, an alpha-2 agonist, patients may experience reemergence of hypertension despite continued use of clonidine [9].

3.2.3.2 Serotonin Syndrome

While low levels of serotonin may be implicated in some psychiatric disorders, the primary drug interaction of concern is serotonin syndrome from overstimulation of the serotonergic system (Fig. 3.2) [9, 13]. The clinical findings associated with serotonin syndrome are primarily neuromuscular in nature and include hyperreflexia, inducible clonus, spontaneous clonus, ocular clonus, myoclonus, peripheral hypertonicity, and

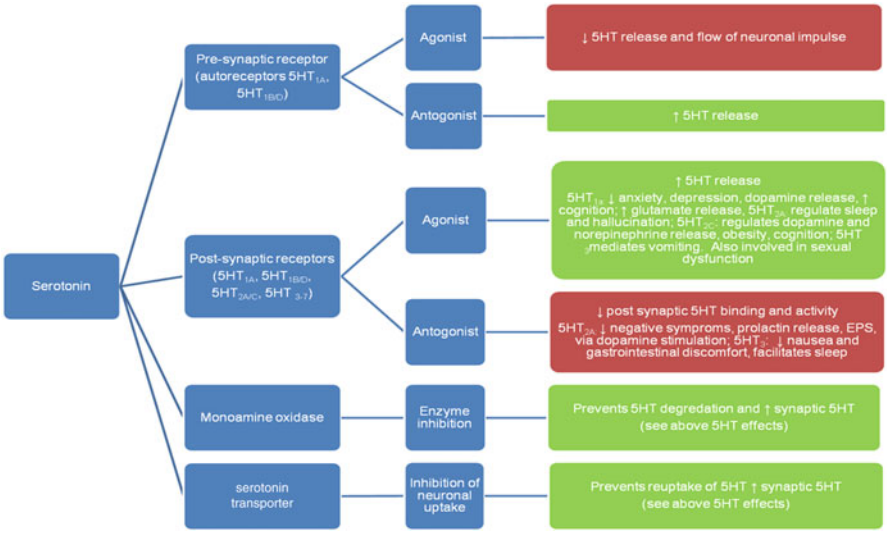

Fig. 3.2 Physiologic effects of serotonin. *5HT* serotonin; *EPS* extrapyramidal side effects

shivering (Table 3.2) [9, 13, 15–23]. Regardless of pharmacology, any combination of drugs, over-the-counter medications or herbal supplements that enhance serotonergic effects will trigger a serotonin syndrome alert on most drug interaction software programs. However, animal models suggest that serotonin syndrome is mediated through stimulation of serotonin-$_{1A}$ and serotonin-$_{2}$ receptors, particularly the latter [24]. Thus drugs that affect serotonin-$_{1A}$ and serotonin-$_{2}$ receptors are much more likely to result in serotonin syndrome compared with other mechanisms of increasing central serotonin activity [8, 14, 23, 24]. The primary exception to this would be utilization of drugs that increase total serotonin levels in the brain as serotonin itself acts on all serotonin receptors. This knowledge is important for assessing the clinical relevance of serotonin syndrome warnings since regulatory agencies have issued alerts for drug combinations unlikely to cause serotonin syndrome. For instance, a 2006 FDA alert based on 29 case reports cautioned health care providers about concomitant prescription of serotonin reuptake inhibitors (SSRIs) and the triptan class of anti-migraine medications. However, the validity of these cases has been called into question as only seven of the 29 case reports meet the Sternbach criteria for serotonin syndrome, while none fit the more rigorous Hunter criteria [19, 25]. Pharmacodynamically the interaction is implausible since triptans are agonists at serotonin-$_{1B}$, serotonin$_{-1D}$, and serotonin$_{-1F}$ receptors, which are distinct from the serotonin receptor subtypes implicated in the development of serotonin syndrome [19, 24]. Thus careful assessment of the mechanism of action at specific serotonergic receptors is necessary to discern which serotonin syndrome warnings are relevant in clinical practice. It is interesting also to note, data from the Hunter Area Toxicology Service indicate serotonin syndrome resulting in death is likely only when MAOIs are combined with drugs that decrease serotonin reuptake such as SSRIs, serotonin norephinephrine reuptake inhibitors (SNRIs) and TCAs [8, 16].

Table 3.2 Serotonin syndrome [9, 13, 16–23]

Onset	• Typically rapid • 60% of cases present within 6 h after initial use or dosage adjustment of medication and 75% within 24 h
Signs and symptoms	• Mild: tachycardia, shivering, diaphoresis, mydriasis, intermittent tremor, myoclonus or hyperreflexia • Moderate: mild symptoms plus hypertension, hyperthermia, hyperactive bowel sounds, diarrhea, hyperreflexia and clonus greater in lower extremities, mild agitation or hypervigilance, pressured speech • Severe: previous symptoms plus severe hypertension and tachycardia, agitated delirium, muscular rigidity, hypertonicity, rhabdomyolysis
Monitoring parameters	• Heart rate • Temperature (severe cases >40°C) • Blood pressure • Neurologic examination • Basic metabolic panel (increased serum creatinine and metabolic acidosis in severe cases)
Associated drugs	High risk: • Antibiotics: linezolid (*nonselectively inhibits MAO*) • Dietary supplements: Hypericum perforatum (St. John's Wort), tryptophan, S-adenosyl-methionine (SAMe) • Illicit Substances: methylenedioxymethamphetamine (MDMA), lysergic acid diethylamide (LSD), cocaine • MAOIs: tranylcypromine, phenelzine, moclobemide • SNRIs: venlafaxine • SSRIs: citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline • Serotonin releaser stimulants: amphetamine • TCAs: clomipramine, imipramine Low risk: • Anticonvulsants: carbamazepine, valproate • Antiemetics: ondansetron, metoclopramide • Antimigraine drugs: sumatriptan, dihydroergotamine • Cyclobenzaprine (*controversial*, *mimics TCA chemical structure*) • Lithium • Methylene blue (*inhibits MAO-A*) • Misc. Antidepressants: buspirone, trazodone • Opioid analgesics: fentanyl, meperidine, pentazocine, tramadol, dextromethorphan

If serotonin syndrome is suspected, all serotonergic medications should be promptly discontinued. When supportive therapy is necessary treatment may include stabilization of autonomic dysregulation and control of hyperthermia and agitation. In some cases benzodiazepine treatment may be necessary to treat agitation. In severe cases, limited data suggest administration of 12 mg of the $5HT_{2A}$ antagonist cyproheptadine followed by 4–8 mg every 6 h may be beneficial for some patients [8, 23, 26]. Most cases of serotonin syndrome subside within 24 h of discontinuing the offending agent [9].

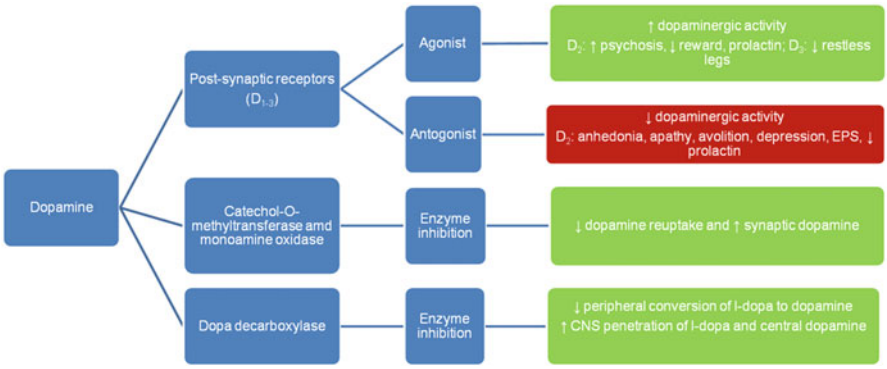

Fig. 3.3 Physiologic effects of dopamine. *EPS* extrapyramidal side effects; *CNS* central nervous system

3.2.3.3 Bleeding

Increased risk of bleeding is another potential adverse effect of drug interactions involving SSRIs and SNRIs. Reduced serotonin uptake into platelets with SSRIs and SNRIs decreases platelet aggregation which can lead to increased risk of bleeding when combined with anticoagulants. The risk is highest with fluoxetine, paroxetine, and sertraline, as they inhibit serotonin reuptake to the greatest degree [14].

Although the absolute risk of bleeding with SSRI monotherapy is low, observational studies indicate concomitant use with nonsteroidal anti-inflammatory drugs (NSAIDs) increases the absolute risk of bleeding three to 15-fold while co-administration of SSRIs and warfarin increases the risk of hospitalization due to non-gastrointestinal bleeding [27–29]. Risk reduction strategies include using (1) acetaminophen, (2) NSAIDs with less gastrointestinal effects, such as ibuprofen and cyclo-oxygenase 2 inhibitors, (3) the lowest effective dosage, and (4) a proton pump inhibitor (PPI) to protect against gastrointestinal bleeding [27, 28]. Caution should be taken when using PPIs with citalopram, as PPIs inhibit citalopram metabolism and could result in prolonged corrected QT interval (QTc) [30].

Due to the mechanism by which SSRIs and SNRIs affect platelets, the international normalized ratio (INR) would not reflect the increased bleeding risk. However, INR monitoring should be considered when starting an SSRI/SNRI in a patient on warfarin to ensure they are not at an elevated risk of bleeding due to a supratherapeutic INR [9, 27, 28].

3.2.3.4 Psychosis and Extrapyramidal Side Effects

In rare cases, elevated dopamine levels may lead to life threatening changes in cardiovascular function (Fig. 3.3) [9, 13]. More commonly, excessive dopaminergic activity causes symptoms of impulsiveness and psychosis, including cognitive impairment,

agitation, hallucinations, paranoia, and delusions [31]. Dopamine antagonists, such as antipsychotics, may inhibit the effects of drugs increasing dopamine levels, including MAOIs, dopamine agonists (ex. ropinirole, pramipexole), bupropion, and illicit substances such as cocaine. This effect is bidirectional, with dopaminergic medications markedly exacerbating psychotic symptoms in schizophrenia, and potentially aggravating dyskinesias in Huntington's disease [31]. Drugs effecting some serotonin receptors influence dopamine release and should be incorporated into assessments of net dopamine function. For example, serotonin-$_{2A}$ receptors serve as a break on dopamine function, whereas serotonin-$_{1A}$ receptors stimulate dopamine release [6, 9, 14].

3.2.3.5 CNS Depression

Substances that enhance the inhibitory neurotransmitter GABA, including benzodiazepines, barbiturates, anticonvulsants, alcohol, and non-benzodiazepine hypnotics (e.g. zaleplon, zolpidem, eszoplicone), can have additive or synergistic effects on sedation and motor impairment when used in combination [9]. Other sedating medications that work through alternate mechanisms may also enhance sedation and motor impairment. These include opioids, antihistamines, trazodone, mirtazapine and antipsychotics, particularly quetiapine and chlorpromazine [9, 13]. This adverse effect is of particular concern in elderly patients, as increased drowsiness and motor impairment elevate the risk for debilitating falls [6, 14]. Combinations of intramuscular olanzapine and benzodiazepines are particularly concerning for all patients as the peak olanzapine blood concentration is five times higher than with the oral formulation and deaths from cardiorespiratory depression have been reported with the combination [32].

When there is clinical concern of excessive CNS depression, signs and symptoms of sedation, lethargy, gait/motor impairment, slurred speech, cognitive dulling, and respiratory depression should be monitored while anxiety, panic attacks, dysphoria, and seizures may occur with rapid reversal of benzodiazepine induced CNS depression seen with administration of flumazenil [6, 9, 33].

3.2.3.6 Anticholinergic Effects

Numerous psychiatric medications antagonize acetylcholine at muscarinic and nicotinic receptors, often to a much lesser extent than their primary mechanism of action. Combinations of anticholinergic agents, including those used to treat urinary incontinence (e.g. oxybutynin, tolterodine, darifenacin), can lead to PD drug interactions. Additive anticholinergic activity manifests as confusion, orthostatic hypotension, dizziness, blurred vision, constipation, dry mouth, and urinary retention [9, 13]. Excessive or synergistic anticholinergic activity can lead to tachycardia, tachypnea, fecal impaction, anuria, increased body temperature, diplopia, mydriasis resulting in photophobia, cognitive impairment/delirium, xerostomia, and impaired coordination [6, 9, 13].

Anticholinergics exacerbate many symptoms that may already be present in the elderly population, including urinary retention and constipation. Additive

Table 3.3 Medications that may induce anticholinergic delirium [9, 36–38]

- Antiparkinsonian agents (e.g. trihexyphenidyl, benztropine)
- Antipsychotics
  Lower potency first generation (e.g. thioridazone, chlorpromazine)
  second generation/atypical (ex. clozapine, olanzapine)
- Antispasmodics for urinary incontinence (e.g. oxybutynin)
- Histamine (H_1) antagonists (particularly first generation, such as diphenhydramine)
- Histamine (H_2) antagonists (GI agents, such as cimetidine, ranitidine)
- Muscle Relaxants: cyclobenzaprine pancuronium
- Tricyclic Antidepressants (particularly tertiary)
- Tropane Alkaloids: scopolamine, hyoscyamine, atropine

anticholinergic effects such as orthostatic hypotension can lead to falls and therefore are important in elderly patients [34]. This is partially due to receptor changes that occur with aging, which heightens the brain's sensitivity to anticholinergic effects [35].

Due to decreased cholinergic reserve patients with Alzheimer's disease are particularly sensitive to polypharmacy induced anticholinergic delirium [9]. However, even in elderly patients without Alzheimer's disease, high anticholinergic load from polypharmacy has been associated with cognitive decline and delirium [36, 37]. Deficits noted include decreased processing speed, attention/concentration, psychomotor performance and disorganized thinking with wavering alertness [29].

Polypharmacy is an important cause of cognitive impairment as cognitive impairments are believed to be due to anticholinergic polypharmacy rather than a single medication with strong anticholinergic effects [36, 37]. Tools such as the anticholinergic drug scale and drug burden index, which incorporates anticholinergic and sedative drug load, have been utilized in clinical trials and may be applied to individual patients [38]. Common medications associated with anticholinergic delirium are listed in Table 3.3 [9, 36–38].

3.2.3.7 Arrhythmias/QTc Prolongation

Various psychotropic medications have potential cardio-toxic effects. Prolonged QTc is typically associated with drugs that block the sodium and potassium channels [10]. The risk is greatest with medications that block potassium channels but in vulnerable patients sodium channel blockade can also be associated with QTc prolongation [39]. The risk of QTc prolongation increases with the number of QTc prolonging drugs prescribed (Table 3.4) [40]. Selective serotonin reuptake inhibitors, SNRIs, TCAs and antipsychotics have all been reported to prolong the QTc. Citalopram, ziprasidone, thioridazine, mesoridazine, pimozide and haloperidol (particularly when used in high doses intravenously) are all labeled in the USA with boxed warnings for QTc prolongation [10, 25, 40–42].

Table 3.4 Drug which may prolong QTc [40]

Moderate or high risk of torsades	Torsades under some conditions[a]	QTc prolongation but rare torsades
Antipsychotics		
Chlorpromazine		
Haloperidol[b]		Asenapine
Pimozide		Clozapine
Thioridazine		Iloperidone
Ziprasidone		Paliperidone
		Quetiapine
		Risperidone
Antidepressants		
	Amitriptyline	Desvenlafaxine
	Citalopram	Mirtazapine
	Clomipramine	Venlafaxine
	Desipramine	
	Escitalopram	
	Fluoxetine	
	Imipramine	
	Nortriptyline	
	Paroxetine	
	Protriptyline	
	Sertraline	
	Trazodone	
	Trimipramine	
Miscellaneous		
Methadone		Amantadine
		Amphetamine
		Atomoxetine
		Chloral Hydrate
		Lithium

Excerpted with permission from PL Detail-Document, Drug-induced Long QT Interval. Pharmacist's Letter/Prescriber's Letter. January 2012. www.pharmacistsletter.com

[a]The drug may cause torsades under certain conditions (e.g. high dose, overdose, drug interactions, patients with long QT syndrome or other risk factors) but otherwise unlikely to cause torsades

[b]Highest with IV administration

QTc prolongation can be dose related as seen with thioridazine, ziprasidone and citalopram [9, 43, 44]. Therefore, PK interactions which increase the concentration of these drugs are particularly concerning and will be discussed later in the chapter.

In relation to psychotropic polypharmacy, two small studies reported no statistically significant differences in QTc prolongation in patients on antipsychotic/antidepressant polypharmacy versus monotherapy with either class alone [43]. However, combinations of QTc prolonging medications should be used with

caution, as other studies have found an increased risk of death when QTc prolonging drugs were used in combination [45].

Prior to initiating combinations of QTc-prolonging psychotropics any electrolyte abnormalities should be corrected. Potential causes of electrolyte abnormalities should be followed during polypharmacy with QTc prolonging drugs (e.g. vomiting, diarrhea, malnourishment, alcohol abuse, and diuretic therapy). For patients with multiple risk factors, consider obtaining an ECG recording prior to drug initiation and after steady state has been achieved. Monitoring parameters include ECG, serum potassium, and signs/symptoms of dizziness, palpitations, convulsions, or syncope [9].

Combinations of QTc prolonging medications should be used with caution in women, patients over the age of 60, those with a history of myocardial infarction or ischemic heart disease, persistent or recurrent bradycardia, previous episode of drug-induced QTc prolongation or electrolyte abnormalities (or a predisposition to abnormalities resulting from eating disorders or diuretic use) [9, 46].

Typically QTc prolongation occurs early in treatment (90 days) and in patients with other risk factors [10, 45]. Patients who have been maintained on a combination of QTc prolonging medications for extended periods of time are at a lower risk of adverse cardiovascular outcomes than patients initiating or increasing QTc prolonging drugs [10, 45].

3.3 Pharmacokinetic Drug Interactions

The effects of pharmacokinetic (PK) drug interactions are directly attributable to changes in drug concentrations [3]. Therefore PK interactions produce a quantitative rather a qualitative change in the response. Pharmacokinetic interactions can result in drug concentrations that are either sub-therapeutic or toxic. Often, they present as a "sensitivity" or "resistance/lose of efficacy" problem that may be incorrectly attributed to administration of a drug rather than a drug interaction [1, 14]. Pharmacokinetic interactions can occur as a result of changes in the absorption, distribution, metabolism or excretion of a drug.

Absorption. Absorption is the movement of a drug from its site of administration into the body. Absorption of a drug from the gastrointestinal tract is governed by multiple factors such as surface area for absorption, blood flow to the site of absorption, dosage form (e.g. solution, suspension or tablet/capsule), water solubility and drug concentration at the site of absorption [3]. Drug interactions involving absorption occur through both direct and indirect effects affects on the gastrointestinal tract. The absorption of drugs can be altered through changes in gastric acidity, chelation or altered gastrointestinal motility rate. Typically absorption interactions result in decreased or delayed drug absorption, although there are psychotropic medications that require ingestion with food to maximize absorption (e.g. ziprasidone) [9].

Alterations in pH. Many drugs are weak acids or bases whose absorption is influenced by the pH of the gastrointestinal contents. Since the non-ionized form of a drug is

more lipid soluble, acidic drugs are more readily absorbed from the upper GI tract, where they are primarily in a non-ionized form [3]. Thus changes in the pH of the gastric contents will influence drug absorption. While separating administration of the medications by several hours may improve absorption in some cases, drugs that consistently alter the stomach acidity (e.g. proton pump inhibitors) will cause interactions that cannot be avoided with separation of medication administration. However, these types of interactions are not common with psychotropic medications [47].

Complexation/Adsorption. Drugs can combine with other substances such as calcium, magnesium, aluminum, and iron in the GI tract to form insoluble complexes. Certain foods, vitamins and drugs can significantly decrease the absorption of drugs via this mechanism. Typically complexation interactions can be avoided by altering the timing of medication administration. Clinically significant interactions are possible but uncommon with psychotropic medications [47].

Alterations in Motility. The majority of drugs are absorbed in the intestine rather than the stomach. Any acceleration in gastric emptying will likely increase the rate of absorption, while the converse is true for drugs that decrease gastric emptying. In addition, medications that decrease gastrointestinal motility may alter drug absorption via changes in dissolution secondary to slowed gastric emptying or increases in a drugs' presence at the site of absorption. It is important to remember gastrointestinal motility effects may vary between with specific dosage forms. For example, enteric coating or sustained release dosage forms may be more susceptible to motility interactions [3, 47]. However, alterations in gastrointestinal motility are not a common source of psychotropic drug interactions.

Distribution. Within the blood drugs can bind to multiple plasma proteins. Albumin is the primary protein carrier for drugs although nonspecific binding to other plasma proteins can occur [3]. As there are limited binding sites available, drugs compete for protein binding sites [3, 48]. Since only unbound drug is active, displacing a drug from its protein binding site may alter the level of active drug without altering the total blood concentration. In low extraction drugs (i.e. minimal first pass metabolism) displacement usually leads to transient increases in free drug concentration that is offset by compensatory increases in drug clearance [3, 48]. Thus while there is a potential for increased adverse reactions with protein displacement, the risk is usually transient as the amount of drug available to be metabolized will increase correspondingly. Displacement interactions warrant less concern for high extraction drugs (e.g. antidepressants and antipsychotics) because they are highly cleared by the liver [47, 48]. In any case, displacement interactions are primarily a concern only for drugs with a narrow therapeutic window that are >90% protein bound [3, 9].

The most common protein binding interactions in psychiatry involve valproate, which can be displaced by medications such as aspirin or can saturate its own protein binding sites at higher concentrations. As plasma valproate concentrations increase more valproate is free or active. Thus the total valproate concentration will not change but the amount of unbound or active drug is increased. So at higher blood concentrations, small increases in plasma concentrations may lead to significant changes in clinical effects.

Metabolism. For an orally administered drug to enter into systemic circulation, it must first be absorbed through the gut wall and transported to the liver via the hepatic portal system [3, 9]. During this process a drug can be metabolized by enzymes in the gut and/or the liver before entering systemic circulation. The degree to which a drug is metabolized prior to entry into systemic circulation directly affects the plasma concentration of the drug [3, 9]. Drugs that reach systemic circulation with little to no metabolism are considered highly bioavailable. Conversely, drugs that are metabolized significantly in the gut or liver prior to entering systemic circulation are considered to have poor bioavailability [3]. The primary drivers of psychotropic drug bioavailability are the cytochrome P450 (CYP450) enzymes, a large super-family of proteins involved in the metabolism of a wide variety of both exogenous and endogenous compounds [9, 47, 49].

The CYP450 enzymes are located on the smooth endoplasmic reticulum of cells predominately in the liver and, to a lesser extent, the small intestine. These enzymes are responsible for the metabolism of many psychotropic medications to both active and inactive metabolites [47]. While metabolites can be less active than the parent compound, many psychotropics form metabolites with significant activity that differs from the parent compound. For example, the carbamazepine 10-, 11-epoxide metabolite is associated with seizure efficacy but can also lead to neurotoxicity and exacerbate seizures [50, 51]. Thus care should be taken to assess CYP450 effects not only on drug clearance but also generation of specific metabolites.

The CYP450 enzymes are divided into families based on amino acid sequence similarities and are designated by an Arabic number (e.g. CYP1). In humans more than 18 families of CYP450 enzymes have been identified [49]. Each family is further divided into subfamilies, which are designated by capital letters following the family designation (e.g. CYP1A). Individual enzymes are designated by the Arabic numeral following the subfamily designation (e.g. CYP1A2). The CYP450 enzymes most commonly involved in psychotropic metabolism are CYP450 1A2, 2C9, 2C19, 2D6, and 3A4 (Table 3.5) [9, 49, 52]. CYP450 3A4 is the predominant CYP450 enzyme in the human liver and intestine, thus accounting for a large number of drug interactions [9, 49, 52].

An individual enzyme of CYP450 is capable of metabolizing many different drugs while a large, intermediary, or small percentage of a single drug can be metabolized by a specific enzyme or multiple enzymes. Clinically significant interactions are more likely to occur when one enzyme is a major or moderate contributor to a drug's metabolism, while drugs with only minor metabolism via this pathway are less likely to result in clinically significant interactions [53].

Metabolism via CYP450 enzymes is partially dependent on genetics with clinically significant genetic polymorphisms (i.e. genotype) noted in CYP450 1A2, 2C9, 2C19 and 2D6 enzymes [47, 54]. The amount of drug exposure resulting from CYP450 genotype (i.e. phenotype) has direct implications for drug dosing (Fig. 3.4) [54]. For example, people unable to manufacture fully functional enzymes due to genetic polymorphisms do not efficiently metabolize specific drugs, have greatly increased levels of drug exposure and require lower doses than extensive metabolizers. Poor 2D6 metabolizers may also experience extreme increases in plasma drug

Table 3.5 Human CYP enzymes involved in drug metabolism [9, 49, 52]

1A1	2A6	3A3/4[a]	4A11	7A1	11A1	17A1	19A1	21A2	27A1	39A1	46A1	51A1
1A2[a]	2A7	3A5	4A22	7B1	11B1				27B1			
1B1	2A13	3A7	4B1		11B2				27C1			
	2B6	3A43	4F2									
	2C8		4F3									
	2C9[a]		4F8									
	2C18		4F11									
	2C19[a]		4F12									
	2D6[a]		4F22									
	2E1		4V2									
	2F1		4X1									
	2J2		4Z1									
	2R1											
	2S1											
	2U1											
	2W1											

[a]Denotes CYP450 enzymes most commonly involved in psychotropic drug

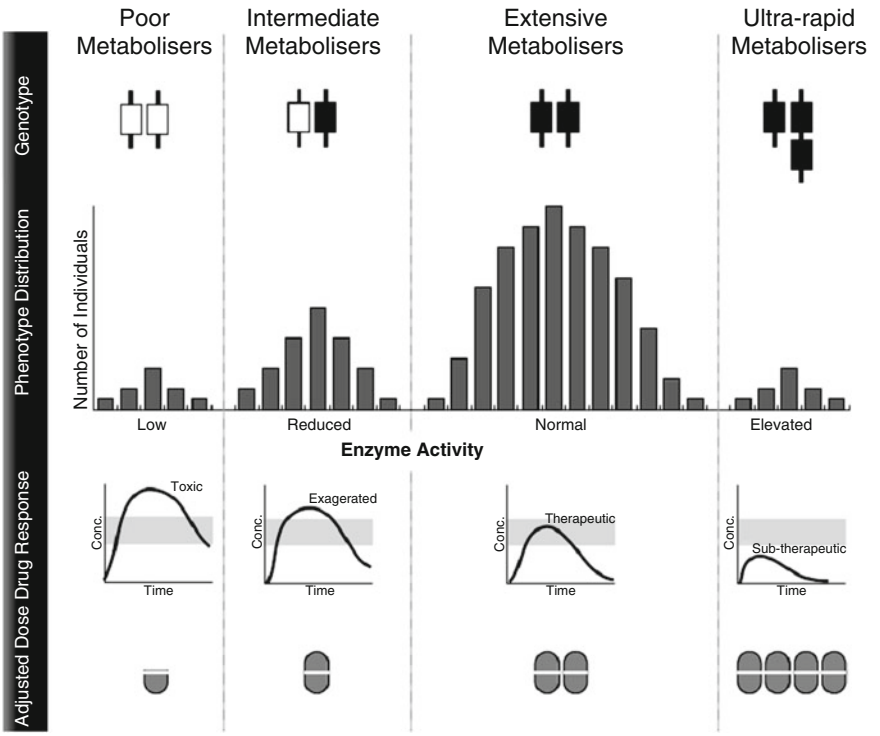

Fig. 3.4 Relationship between genetic variation, enzyme activity, drug response and optimized drug dose. Genetic variation as indicated by genotype (*white boxes* defective allele, *black boxes* functional allele) can produce four different levels of enzyme activity [54] (Reprinted with permission)

concentrations when given a 2D6 inhibitor. Conversely, ultra rapid metabolizers (those with genetic amplification of CYP450 enzymes) will have much lower drug exposure and require increased doses for clinical effect. These genetic polymorphisms are also important in transformation of pro-drugs into the active moiety. For example, poor 2D6 metabolizers are unable to convert codeine into morphine, its pharmacologically active metabolite. Thus they do not experience clinically significant pain relief with codeine and could be labeled as drug seeking patients rather than treated with a more appropriate opiate for their pain [47, 49]. The likelihood of being a poor metabolizer varies between ethnic groups, with 20% of Asians and 3–5% of Caucasians being poor CYP2C19 metabolizers. Conversely, Caucasians are more likely to be poor 2D6 metabolizers (5–10%) than Asians (0–1%). Approximately 29% of black Ethiopians and 1% of Caucasians are CYP450 2D6 ultra-rapid metabolizers [9, 47, 54].

The relationship between psychiatric medications and CYP450 enzymes is bidirectional. While CYP450 enzymes metabolize psychiatric medications, psychiatric medications can also increase (i.e. inducers) or decrease (i.e. inhibitors) the activity of CYP450 enzymes (Table 3.6) [1, 9, 47, 52, 53, 55–58]. Hence medications can be the target and the cause of PK interactions. In addition, a single drug can both be the target and cause of drug interactions. Psychotropic medications are particularly prone to drug interactions since they are commonly CYP450 substrates, often affect the activity of CYP450 enzymes and are frequently used in combination.

Induction. Induction is an increased synthesis of CYP450 enzymes which increases the metabolism of substrates of that CYP450 enzyme, ultimately leading to decreased blood concentrations of the substrate. Due to the need to synthesize new enzymes, the maximal effect of induction takes several weeks to occur. Conversely, when an inducer is discontinued, it takes time for the extra CYP450 enzyme to die off [53]. Thus reversal of induction is dependent on the half-life of the induced CYP450 enzyme and can take up to 4 weeks [53]. This delay between drug initiation or discontinuation and induction is the key to understanding the timing of clinical effects seen with CYP450 enzyme interactions involving induction. For example, carbamazepine is a potent inducer of CYP450 3A4. Since CYP450 3A4 is responsible for carbamazepine's metabolism and maximal induction takes approximately 4 weeks, carbamazepine's dose must be increased 1 month after achieving steady state to maintain a therapeutic concentration. Non-drug induced induction also has the potential to effect metabolism of psychotropic drugs. For example, cigarette smoking induces CYP450 1A2. Therefore, changes in smoking should be factored in when dosing drugs that are predominately metabolized by CYP1A2 (e.g. olanzapine, clozapine). This interaction is due to compounds contained in the cigarette smoke (i.e. polycyclic aromatic hydrocarbons) and not due to the effects of nicotine [55, 56].

Inhibition. Competitive inhibition is the most common mechanism of inhibition and occurs when a drug prevents another drug from binding to a specific CYP450 enzyme [57]. Competitive inhibitors can be but are not always substrates for the inhibited enzyme. For example, bupropion is an inhibitor but not a substrate of CYP450 2D6 while fluvoxamine is both an inhibitor and a substrate for CYP450 1A2 [9, 53]. The clinical significance of inhibition depends on the relative

Table 3.6 CYP450 enzymes commonly involved in drug interactions [1, 9, 47, 52, 53, 55–58]

			Inducer		Inhibitor	
Enzyme	Substrate		Psychotropic	Other	Psychotropic	Other
CYP1A2	Amitriptyline	Haloperidol	Phenobarbital	**Cigarette smoking**	**Fluvoxamine**	Amiodarone
	Caffeine	Imipramine		Insulin		Cimetidine
	Clomipramine	Mirtazapine		Modafinil		**Ciprofloxacin**
	Clozapine	Olanzapine		Omperazole		Fluorquinolones
	Fluvoxamine	Tacrine		Rifampin		
CYP2C9	Amitriptyline		**Phenobarbital**		Fluvoxamine	Amiodarone
	Fluoxetine					Fluconazole
	Phenytoin					Fluvastatin
	Sertraline					Isoniazide
						Lovastatin
						Sulfamethoxazole
						Rifampin
CYP2C19	Amitriptyline	Fluoxetine	Carbamazepine	Prednisone	**Fluvoxamine**	Cimetidine
	Citalopram	Imipramine		Rifampin	Modafinil	Indomethacin
	Clomipramine	Phenytoin				Ketoconazole
	Diazepam	Propranolol				Lansoprazole
	Escitalopram	Sertraline				Modafanil
						Omperazole
						Oxcarbazepine
						Topiramate

CYP2D6	Amitriptyline	Duloxetine		Dexamethasone	Bupropion	Cimetidine
	Amphetamine	Escitalopram		Rifampin	Chlorpromazine	Diphenhydramine
	Aripiprazole	Fluoxetine			Clomipramine	Hydroxyzine
	Atomoxetine	Haloperidol			Duloxetine	Ritonavir
	Chlorpromazine	Imipramine			**Fluoxetine**	
	Citalopram	Mirtazapine			Fluvoxamine	
	Clomipramine	Paroxetine			Methadone	
	Desipramine	Thiordiazine			**Paroxetine**	
		Venlafaxine			**Perphenazine**	
					Thioridazine	
CYP3A4	Alprazolam	Methadone	Barbiturates	Rifabutin	Fluvoxamine	Amiodarone
	Amitriptyline	Mirtazapine	**Carbamazepine**	Rafampin	**Nefazodone**	Cimetidine
	Aripiprazole	Nefazodone	**Oxcarbazepine**		**Paroxetine**	Ciprofloxacin
	Benzodiazepines	Paroxetine	Modafanil			**Clarithromycin**
		Quetiapine				
	Buspirone	Risperidone	**Phenobarbital**			Diltiazem
	Carbamazepine					
	Citalopram	Sertraline	**Phenytoin**			Erythromycin
	Clomipramine	Trazodone				Fluconzaole
	Clozapine	Triazolam				Grapefruit juice
	Diazepam	Venlafaxine				**Protease inhibitors**
	Escitalopram					
	Fluoxetine	Zaleplom				**Itraconazole**
	Haloperidol	Ziprasidone				**Ketoconazole**
	Imipramine	Zolpidem				Macrolide antibiotics
						Norfloxain
						Verapamil

Bolded potent

concentrations, binding affinities and inhibition potency of the drugs involved as well as the degree to which the substrate is metabolized by the CYP450 enzyme [52]. Typically a moderate to high amount of a drug must be metabolized by the inhibited CYP450 enzyme to produce clinically significant effects. Inhibition of CYP450 enzymes is particularly concerning for drugs with narrow therapeutic windows, as small increases in blood concentrations may lead to severe potentially life threatening reactions [53].

Unlike induction, enzyme inhibition usually begins with the first dose of the inhibitor. Since inhibition is dependent on drug concentration, maximal inhibition is typically not seen until a drug reaches steady state [57, 58]. Reversal of inhibition is dependent on the half-life of the drugs involved with full resolution occurring only after five half lives have elapsed since discontinuation of the inhibitor. Less commonly, drugs may irreversibly inhibit a specific CYP450 enzyme and require synthesis of new enzymes, which may take several days [53, 54].

It is important to know which drugs are predominately or moderately metabolized by specific enzymes. Given the large number of drugs involved, memorization of the inducers and inhibitors is time consuming. Therefore it is useful to be aware of the most common, clinically significant interactions and the drug classes most prone to drug interactions. In this way, one is alerted to either a common significant interaction or to a medication that is often involved in drug interactions and should be reviewed.

Excretion. Urinary pH influences the ionization of weak acids and bases and thus affects their reabsorption and excretion. A non-ionized drug more readily diffuses from the glomerular filtrate into the blood. More of an acidic drug is non-ionized in acidic urine than in alkaline urine, where it primarily exists as an ionized salt. Thus, an acidic drug (e.g. a salicylate) diffuses back into the blood from acidic urine, resulting in prolonged and perhaps intensified activity [3]. The risk of a significant interaction is greatest in patients who are taking large doses of salicylates (e.g. for arthritis). Opposite effects are seen for a basic drug like dextroamphetamine. Such interactions are not commonly seen with psychotropic medications.

Some drugs are excreted through the kidney without undergoing significant metabolism. While uncommon for psychotropic medications, lithium and gabapentin, are notable exceptions. Given gabapentin's large therapeutic window, it is not subject to clinically significant elimination interactions. However, lithium excretion is highly sensitive to changes in sodium, hydration status and use of certain medications such as nonsteroidal anti-inflammatory agents and diuretics [47].

Drug Transport. Transport proteins are membrane bound proteins that control the influx of essential nutrients and ions and the efflux of cellular waste and toxins. P-glycoproteins (P-gp) are the most widely studied transport proteins [51]. P-gp is the main transport protein involved in movement of drugs across biological membranes [9, 47, 59]. P-gp is present in many organs associated with drug metabolism, such as the gastrointestinal tract, liver and kidney, but plays no role in a drug's metabolism. P-gp can play an indirect role in the removal of a drug from the body via transport of a drug from the blood into the bile or urine. Alternately, a drug which has already been absorbed into the body may be transported back into the

Table 3.7 P-glycoprotein substrates and inhibitors [9, 39, 59]

Substrates	Inhibitors	Inducers
Bupropion	Carbamazepine	Amitriptyline
Chlorpromazine	Chlorpromazine	Nefazodone
Clozapine	Citalopram	Phenobarbital
Fluoxetine	Nortriptyline	Phenothiazines
Haloperidol	Olanazpine	Phenytoin
Mirtazapine	Paroxetine	Prazosin
	Phenobarbital	St. John's Wort
	Phenytoin	Trazodone
	Quetiapine	
	Risperidone	
	Sertraline	
	Topiramate	
	Trimipramine	
	Venlafaxine	

gastrointestinal tract by P-gps. P-gp transport is important for psychotropic medications as P-gps are located at the blood brain barrier to prevent potentially toxic substances from entering the brain [9, 47, 59].

P-gp binds to a wide range of drugs and there is considerable overlap of substrates of P-gp and CYP450 2D6 and 3A4 [9, 39, 47, 59]. Similar to CYP450 nomenclature, drugs can be classified as substrates, inducers or inhibitors of P-gp (Table 3.7) [9, 39, 59]. Substrates are actively expelled from cells by P-gp, thus limiting a cells' exposure to the substrate. Inhibitors decrease P-gp activity while inducers increase P-gp activity. A drug can be both a substrate and inducer or inhibitor of P-gp.

Drug interactions can occur when two drugs compete for P-gp or when a drug is an inducer or inhibitor of P-gp [39, 47]. Drug interactions with P-gp can have multiple effects depending on the site of action [59]. For example, inhibition of P-gp can prevent a drug's removal from the body via decreased transfer from the blood to the kidney or bile. Alternately, a drug may not be transported back into the gastrointestinal tract due to P-gp inhibition, leading to increased drug concentrations [47].

3.4 Clinical Effects of Drug Interactions

The incidence of life threatening drug interactions is low. Rates of death secondary to drug interactions were reported to be less than 1% in two studies [60, 61]. However, drug interactions reportedly account for up to 20% of adverse drug reactions and can lead to severe adverse drug events [2, 62]. Drug interactions are also implicated in hospital admissions and readmissions [2]. In one retrospective study, 47.7% of avoidable adverse drug reactions were attributed to drug interactions with

Table 3.8 Risk factors for experiencing a drug interaction [60–67]

Patient	Age
	Genetic polymorphism
Drug	Narrow therapeutic window
	Dose
	Major CYP450 substrate
	Strong CYP450 inducer/inhibitor
	Polypharmacy
Other	Number of prescribers

67% reported as life threatening, permanently disabling or requiring transfer for medical care [63]. More commonly, patients may experience increased side effects or lack of benefit secondary to drug interactions. These problems can be incorrectly attributed to drug toxicity or inefficacy [47, 53]. While this may seem relatively minor, particularly with psychotropics that are dosed based on observed effects, it can lead to clinically significant problems. For example, many patients are considered unresponsive to treatment and receive polypharmacy for "treatment resistant" disease. However, if the patient's lack of response was due to drug interactions resulting in low drug concentrations, a patient may be overmedicated or treated with drugs reserved for treatment resistance, which often have significant side effects. Conversely, patients who experience "side effects with all drugs" may be under treated for their illness due to fears of inducing adverse events. For example, a patient who has had severe adverse drug reactions due to drug interactions may be ineffectively treated with sub-therapeutic doses of multiple agents. Therefore, when a patient on more than one drug experiences an extreme or unexpected effect or derives no benefit from adequate doses, drug interactions should be considered.

3.4.1 Risk Factors

The major risk factors for drug interactions are related to patient, drug and other factors (Table 3.8) [60–67]. Patient factors such as age, number of drugs prescribed and concomitant medical illnesses have all been shown to increase the risk of experiencing clinically significant adverse events secondary to a drug interaction. Age related changes in metabolism, excretion and drug sensitivities lead to increased rates of drug interactions in elderly patients. Studies have documented up to 25% of elderly patients experience clinically significant problems due to drug interactions [64, 65].

Risk also increases as the number of prescribed drugs increases. Up to 38% of patients on four drugs and 82% of patients on seven drugs are at risk for a drug interaction [66]. Specific drug characteristics increase the likelihood of clinically significant interactions. For example, narrow therapeutic window drugs such as

lithium and carbamazepine, are more frequently associated with serious events secondary to drug interactions [67]. Drugs that rely primarily on one CYP450 enzyme family for metabolism, such as some antipsychotics, and less selective drugs with activity at multiple receptors and transporters increase the likelihood of experiencing clinically significant interactions [15].

Inhibition and induction of CYP450 enzymes are the most commonly documented cause of significant drug interactions [68]. Specifically CYP450 1, 2, and 3 subfamilies are responsible for the majority of drug metabolism and therefore many drug interactions [49, 53]. Drugs that are strong inducers or inhibitors are more likely to be involved in clinically significant drug interactions. Drugs that are partially metabolized by a specific CYP450 or moderate inhibitors/inducers may be involved interactions but they are less likely to cause serious adverse outcomes [53].

3.5 Drug Interaction Software

While the use of drug interaction software increases the awareness of drug interactions, little is known about their effectiveness in preventing drug related adverse events [69]. Given 80% of computerized drug interaction alerts are over ridden by clinicians, drug interaction software will most likely have limited benefits [70–73]. Patient-specific characteristics, as well as issues with sensitivity and specificity of drug interaction programs, are largely what make our current drug interaction software programs inadequate and justify a strong comprehension of drug interactions by clinicians [47, 73]. As an example, clinicians need to review more than 2,700 alerts to prevent a single serious adverse drug reaction, and at least 4,200 alerts to prevent serious disability or death with most drug interaction software programs. Therefore it is important to develop a system to assess the clinical relevance of drug interactions [73].

3.6 Prevention and Management of Drug Interactions

Initial first steps to decreasing the likelihood of drug interactions are to minimize the number and dose of drugs and, when possible, the duration of drug treatment. Regular review of drugs and discontinuation of drugs with limited or questionable benefit are also important. Prescribers should keep complete medication lists for all patients and update the list regularly. The list should include prescription, over the counter, illicit and herbal drugs and supplements.

A patient's medication taking behavior should be one of the first components assessed. Medication listed in a patient's record does not guarantee the patient is actually ingesting the drug or taking it as prescribed. Also concomitant disease states should also be considered since the risk of potential drug interactions is not

consistent across the population. For instance, the potential for QTc prolongation with citalopram is less worrisome in a young, healthy male than it would be in an older female taking a high dose diuretic.

The individual biology of the patients should also be considered and is often accounted for in clinical practice. For example, if a patient is particularly sensitive to drugs, clinicians may start with lower doses and titrate more slowly. In this way, clinicians can indirectly account for patients who are poor metabolizers of drugs and particularly vulnerable to drug interactions involving inhibition of CYP450 enzymes.

Clinicians should be aware of the psychotropic medications most likely to result in death and permanent disability. In psychiatry these medications include lithium, TCAs, MAOIs and anticonvulsants. Prescribing any of these in combination with other drugs should alert the clinician to pause and assess if the co-prescribed medications could result in a drug interaction.

Certain medications are significantly metabolized by CYP450 enzymes and should trigger a clinician to look for potential drug interactions. Medications which rely on a single CYP450 enzyme for most of its metabolism are more likely to be involved in drug interactions. These medications include antidepressants, antipsychotics and anticonvulsants. Antidepressants and anticonvulsants are also common inducers or inhibitors of CYP450 enzymes. Therefore, prescription of any of the drugs should prompt assessment for drug interactions.

The pharmacologic properties of the suspected drugs should be considered. The time of drug administration, time to onset and elimination half-life should be taken into account. If a drug has metabolites the elimination half-life of the metabolites should be considered as well.

Drugs that have been recently discontinued should be assessed. Fluoxetine's active metabolite norfluoxetine has a longer serum half-life than its parent compound, which has resulted in drug interactions up to 5 weeks after fluoxetine discontinuation [14]. Also, the duration of clinical effects of drugs is important. For example, MAOIs irreversibly inhibit MAO and thus their potential to cause drug interactions is due to the time it takes the body to regenerate MAO, long after the drug has left body [8, 9].

The suspected type of interaction should be considered, as different drug interactions occur at different points in treatment. As an example, induction takes weeks to occur and reverse; leading to the potential for drug interactions well after a medication has been initiated or discontinued.

3.7 Resources for Assessing Drug Interactions

While imperfect, computer software programs can help prevent some potential drug interactions. Consulting with pharmacists, who have extensive training in pharmacodynamics and pharmacokinetics, should be considered. Another important source of useful drug information is the prescribing information or package insert (PI). The PI provides useful information on drug metabolism, elimination and interactions but is often overlooked as a useful clinical tool. Table 3.9 offers guidance in assessing the likelihood of an adverse event is due to a drug interaction [60–67].

Table 3.9 When to suspect a drug interaction [60–67]

	Yes	No
Patient factors		
Is the patient >64 years old		
Are there multiple comorbidities		
Does the patient take over the counter medications or supplements		
Drug factors		
Has a drug recently started, stopped or reached steady state		
Are any of the drugs strong inhibitors or inducers or CYP450 enzymes		
Are any of the drugs strong P-gp inhibitors		
Were there high concentration of the drug		
Did the reaction worsen with increased dose		
Other factors		
Are medications prescribed by >1 clinician		

If the answer is yes to any of the following for a patient on polypharmacy, investigate for potential drug interaction

3.8 Conclusions

Whenever a patient experiences an unexpected adverse drug event or therapeutic failure, drug interactions should be included in the differential diagnosis. Most psychotropic drug interactions are pharmacokinetic involving CYP450 enzymes. Familiarity of high risk medications (e.g. lithium, MAOIs) and drugs involved with significant CYP450 interactions (e.g. antidepressants, antipsychotics, anticonvulsants) can serve as a prompt to investigate potential drug interactions. Minimization of drugs and discontinuation of unnecessary drugs, including over the counter medications and supplements, can also further decrease the risk of drug interactions. Drug interaction software, consults with pharmacists, medical literature review and prescribing information can all help clinicians assess the likelihood of and clinical significance of potential drug interactions.

Appendix. Commonly Encountered Psychotropic Interactions [9, 47, 59, 74]

Drug	Comment
Second generation antipsychotics	
Aripiprazole	Adjust dose with 2D6/3A4 inducers and inhibitors
	Long half life, maximum effects not seen for 3 weeks
Asenapine	Additive QTc prolongation potential
	Adjust dose with 1A2 inducers and inhibitors
Clozapine	Decreased levels in cigarette smokers
	Adjust dose with 1A2 inducers and inhibitors
Iloperidone	Adjust dose with 2D6 inducers and inhibitors
Lurasidone	Adjust dose with 3A4 inducers and inhibitors

(continued)

(continued)

Drug	Comment
Olanzapine	Decreased levels in cigarette smokers
	Adjust dose with 1A2 inducers and inhibitors
	Additive cardiopulmonary depression (IM highest risk)
Paliperidone	Adjust dose in renal impairment
Risperidone	Adjust dose in renal impairment
	Additive QTc prolongation potential
	Adjust dose with 2D6 inducers and inhibitors
Quetiapine	Adjust dose with 3A4 inducers and inhibitors
	Additive QTc prolongation potential
Ziprasidone	Must be taken with food for absorption
	Additive QTc prolongation potential
	Increased risk of QTc prolongation with inhibitors
First generation antipsychotics	
Chlorpromazine	Adjust dose with 2D6 inducers and inhibitors
Fluphenazine	Adjust dose with 2D6 inducers and inhibitors
Haloperidol	Adjust dose with 2D6 and 3A4 inducers and inhibitors
	Additive QTc prolongation potential (IV highest risk)
Perphenazine	Adjust dose with 2D6 inducers and inhibitors
Thioridazine	Additive QTc prolongation potential
	Increases levels of 2D6 substrates
Trifluoperazine	Adjust dose with 1A2 inducers and inhibitors
Anticonvulsants	
Carbamazepine	Decreases levels of 1A2, 2B6, 2C19, 2C9, 2D6, 3A4 substrates
	Decreased oral birth control efficacy
Lamotrigine	Levels significantly increased with valproate
Oxcarbazepine	Decreases levels of 3A4 substrates
Valproate	Significantly increases lamotrigine levels
	Increases TCA levels
Antidepressants	
Bupropion	Inhibits metabolism of 2D6 substrates
Citalopram	Adjust dose with 2C19 and 3A4 inhibitors
	Additive QTc prolongation potential
Duloxetine	Adjust dose with 2D6 inducers and inhibitors
Mirtazapine	Adjust dose with 1A2, 2D6, 3A4 inducers and inhibitors
	May decrease alpha antagonist effect
Nefazodone	Adjust dose with 3A4 and 2D6 inducers and inhibitors
	Increases concentration of 3A4 substrate
MAOIs	Hypertensive crisis
	Serotonin syndrome
SSRIs/SNRIs	Substrates, inducers and inhibitors of CYP450 enzymes (see Table 3.6)
	Increased bleeding with anticoagulants and NSAIDs
TCAs	Substrates, inducers and inhibitors of CYP450 enzymes (see Table 3.6)

(continued)

(continued)

Drug	Comment
Benzodiazepines	
Alprazolam	Adjust dose with 3A4 inducers and inhibitors
Chlordiazepoxide	Adjust dose with 3A4 inducers and inhibitors
Clonazepam	Adjust dose with 3A4 inducers and inhibitors
Diazepam	Adjust dose with 2C19, 3A4 inducers and inhibitors
Traizolam	Adjust dose with 3A4 inducers and inhibitors
Opiates	
Buprenorphine	Adjust dose with 3A4 inducers and inhibitors
Methadone	Significant QTc prolongation Adjust dose with 2B6 and 3A4 inducers/inhibitors

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Chapter 4
Preclinical and Clinical Investigation of Antipsychotic Polypharmacy: What Is the Evidence?

Dimitrios Kontis and Eirini Theochari

Abstract Antipsychotic polypharmacy is a common clinical practice whose implications have not been thoroughly assessed to date. There is a paucity of preclinical studies investigating the effects of antipsychotic combinations on animal models. These models are focusing on the effects of antipsychotic combinations on psychiatric and extrapyramidal symptoms' simulations and on antipsychotic-induced metabolic abnormalities. Although most guidelines favour the use of antipsychotic monotherapy, clinical trials and meta-analyses examining the merits and disadvantages of polypharmacy are contradictory. A recent synthetic approach suggests that antipsychotic polypharmacy could be useful under conditions of acute symptoms' exacerbation non-responsive to monotherapy but not so beneficial in chronic refractory illness. It also recommends that antipsychotic polypharmacy should always have a rational pharmacological basis. The role of antipsychotic combination strategies other than clozapine augmentation in treatment resistant patients needs to be clarified in future research. The specific effects of antipsychotic co-treatment in different symptoms dimensions, its interactions, adverse reactions and associations with medical morbidity and mortality remain to be further examined through rigorously designed clinical trials and prospective epidemiological studies.

Keywords Antipsychotic • Polypharmacy • Preclinical • Clinical

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M.S. Ritsner (ed.), *Polypharmacy in Psychiatry Practice, Volume I: Multiple Medication Use Strategies*, DOI 10.1007/978-94-007-5805-6_4,

4.1 Introduction

Antipsychotic polypharmacy is one of the common secrets in psychiatry. Although a few psychiatrists openly admit that they frequently use more than one antipsychotic in the everyday treatment of their patients or express their support to this practice, antipsychotic polypharmacy continues to be a widely used practice. The prevalence of polypharmacy with antipsychotics varies widely and ranges from 4% to more than 50%, depending on the setting and patient population. However, antipsychotic polypharmacy is a characteristic example of the gap between clinical practice, practice guidelines and clinical trials in schizophrenia [1]. There is even an absence of consensus among the existing guidelines themselves. Although guidelines generally acknowledge that there is a lack of evidence to support the routine use of antipsychotic polypharmacy, their clinical recommendations differ. Some have clearly condemned antipsychotic polypharmacy but others have not. The latter have provided examples of clinical circumstances in which combinations could be justified. Such circumstances are when switching from one antipsychotic to another [2, 3], when augmenting clozapine in treatment-resistant illness [3, 4], and more specifically as a time-limited trial when clozapine treatment has been optimized and this has failed to give adequate symptom control. There are also guidelines which refrained from making recommendations in this area [5].

However, there is limited support of the practice of antipsychotic polypharmacy by rigorous clinical evidence. There are only few blinded, randomized, controlled trials. Similarly, studies that had employed a clinically informative design comprising initial monotherapy, followed by combination therapy and finally returning to monotherapy with adequate dosing and duration of treatment are also few [6]. It therefore appears that the practice of antipsychotic polypharmacy is mostly driven by other factors rather than evidence based medicine. These factors likely include personal preferences and clinical experience of psychiatrists, poor communication between services, family pressure or preferences, pressure of nurses and other health professionals and marketing influences [7]. However, the most important reason seems to be the widely accepted fact that the available pharmacological treatments are still far from meeting all the needs of the management of this complex disorder and therefore psychiatrists are using antipsychotic polypharmacy in an effort to boost treatment outcomes.

In this context, a review of the existing literature in animal models and patients' populations could provide useful information for the clinician. With the aim to help clinical decisions, this chapter will summarize the current preclinical and clinical evidence on the use of antipsychotic polypharmacy. First, it will present the experience deriving from the effects of combinations of antipsychotics in animals. Then it will review findings about the prevalence of antipsychotic polypharmacy in clinical samples and will explore whether this phenomenon is changing with time. Predictors of antipsychotic polypharmacy, or factors associated with its use will be then explored, in addition with older and current findings on the efficacy and side-effects of antipsychotic polypharmacy. The results of initiatives aiming at the reduction of

antipsychotic polypharmacy will also be summarized. Finally, all these data will be critically discussed and topics for future research will be proposed.

4.2 What Is the Preclinical Evidence for Antipsychotic Polypharmacy?

Preclinical studies of antipsychotic drug combinations are sparse. There are only three studies which explored the role of these combinations. One of them examined the effects of the concomitant administration of quetiapine with haloperidol in mice and compared them with those associated with chlorpromazine and risperidone administration and the co-administration of haloperidol with either chlorpromazine or risperidone in simulations of psychosis and extrapyramidal symptoms. Antipsychotic effects were evaluated with the methamphetamine-induced hyperlocomotion test, while the liability to extrapyramidal symptoms was assessed in a catalepsy-induction model. Quetiapine, risperidone, chlorpromazine, and haloperidol dose-dependently reduced methamphetamine-induced hyperlocomotion lending support to their antipsychotic efficacy. In the catalepsy test, quetiapine only weakly induced catalepsy at the highest dose of 100 mg/kg, whereas risperidone, chlorpromazine, and haloperidol dose-dependently induced catalepsy. Interestingly, the combination of quetiapine and haloperidol significantly reduced methamphetamine-induced hyperlocomotion in comparison with haloperidol alone, suggesting that this combination might have an additive beneficial effect on psychotic symptoms. Similarly, both risperidone and chlorpromazine enhanced the effect of haloperidol on hyperlocomotion. The "antipsychotic" effects of drugs were found to be additive and not synergistic and there were no meaningful differences in the magnitude of the protection by any of three drugs combined with haloperidol. With respect to the potential to cause extrapyramidal symptoms, the combination of quetiapine with haloperidol did not augment the cataleptogenic activity of haloperidol. This indicated that, in humans, the co-administration of quetiapine with haloperidol would not worsen extrapyramidal symptoms. In contrast, the concurrent administration of haloperidol with risperidone or chlorpromazine significantly potentiated catalepsy induced by haloperidol alone. The authors reported that 5-HT1A receptors were involved in both "antipsychotic" and "extrapyramidal" effects of the above substances [8]. In summary, this study provided evidence that antipsychotic polypharmacy might increase the antipsychotic efficacy, but it could also be associated with more extrapyramidal side effects. It also raises the possibility that different combinations of antipsychotic medications have similar treatment but different side effects.

In another study of two combined antipsychotic drugs, amperozide, a putatively antipsychotic compound possessing 5-HT_2 antagonistic properties, synergistically increased the effects of antipsychotics in the conditioned avoidance response task and the food-reinforced lever pressing. Given alone, amperozide was almost equipotent to clozapine, but less potent than haloperidol in both test models. However,

the lack of clinically significant antipsychotic properties of amperozide in humans should be taken into account for the interpretation of these findings [9].

The third preclinical study tested the implications of antipsychotic polypharmacy on metabolism. Metabolic effects are common side effects of the atypical antipsychotics. Some atypical agents have been associated with more metabolic effects, such as weight gain than others [10]. Olanzapine belongs to this category and appears to have an increased propensity to cause body weight gain. In contrast, ziprasidone or aripiprazole are known to be weight-neutral. This study tested whether the effect of the co-administration of olanzapine with either ziprasidone or aripiprazole, could attenuate the hyperphagic effect of olanzapine. Female hooded-Lister rats were treated acutely with either vehicle, olanzapine, ziprasidone, aripiprazole or olanzapine in combination with ziprasidone or aripiprazole. They were then placed in automated locomotor activity boxes with pre-weighed palatable mash. Food intake and locomotor activity were measured for 60 min following drug treatment. All olanzapine-treated groups demonstrated significant increases in food intake. However, this effect was attenuated when olanzapine was co-administered with either ziprasidone or aripiprazole. Neither of the latter two drugs affected food intake alone. These findings indicate that aripiprazole and ziprasidone may prevent weight gain when combined with olanzapine [11].

Although only the above three studies have examined the co-administration of two antipsychotic agents in animals, a number of studies have investigated the effects of the combination of antipsychotics with other psychotropic compounds. Using the conditioned avoidance response task as a model of antipsychotic activity, these studies have explored the effects of the co-administration of cholinesterase inhibitors [12], anticonvulsants [13], and selective serotonin (5-HT) 2A receptor antagonists [14] and have produced promising results.

There is also a paucity of preclinical data examining the neurochemical effects of antipsychotic polypharmacy. Although there are no studies exploring the effects of two combined antipsychotic drugs on dopamine or acetylcholine release, M100 907, a serotonin 5-HT2A receptor antagonist and putative antipsychotic, was shown to increase the effects of haloperidol on cortical dopamine release while also inhibiting release of dopamine in the nucleus accumbens [15]. The combination of an atypical antipsychotic with an antidepressant or mood stabilizer has been associated with a potentiation of dopamine increase in brain regions such as hippocampus or medial prefrontal cortex which would predict enhanced efficacy against negative or cognitive symptoms [13, 16, 17].

Based on the apparent lack of preclinical evidence, Honer et al., stressed the need for a more extensive study of antipsychotic polypharmacy combinations that are commonly seen in clinical practice, such as clozapine or olanzapine and risperidone [18]. They suggested that these experiments should employ additional models having high construct and pharmacological validity such as that of prepulse inhibition and should use carefully titrated doses of drugs in a manner that will enable detection of putative synergistic effects.

In summary, the few existing preclinical studies offer promise for understanding the possible mechanisms of action of combinations of antipsychotic drugs for either

efficacy or side effects. Preclinical studies of combinations of other drugs with antipsychotics demonstrate the range of knowledge that can be obtained. Preliminary findings of antipsychotic combinations suggest that the coadministration of atypical antipsychotics with typical ones might have similar additive effects in antipsychotic efficacy but different effects on extrapyramidal symptoms. They also indicate that the addition of a metabolic neutral atypical antipsychotic to an atypical antipsychotic having the propensity to cause a metabolic syndrome might prevent the adverse metabolic effects.

4.3 Antipsychotic Polypharmacy in Clinical Practice

4.3.1 Prevalence of Antipsychotic Polypharmacy

Antipsychotic polypharmacy has been reported to be common in schizophrenia [6]. Relatively high rates (usually more than 20%) of antipsychotic polypharmacy have been reported from all over the world including the United States [19–23], Canada [24–26], Europe [27–40], East Asia [41], Africa [42] and New Zealand [43]. However, there are studies which did not confirm these high rates of antipsychotic polypharmacy [44–53].

4.3.2 Explaining the Differences in Prevalence of Antipsychotic Polypharmacy Among Studies

There are many reasons which could explain discrepancies in prevalence rates among studies. First, different patients' demographic characteristics appear likely to affect the use of antipsychotic polypharmacy. For instance, children and adolescents do not so often receive antipsychotic polypharmacy compared with adults for obvious reasons [45]. Referral issues might also account for the observed differences. People receiving multiple antipsychotics are less likely to be referred to trials which are not specifically designed to directly examine the issue of antipsychotic polypharmacy, e.g. the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial [44]. The inpatient or outpatient status of patients might also influence the prevalence estimation of antipsychotic polypharmacy. Studies which recruited outpatients have generally reported lower rates of antipsychotic polypharmacy [46, 51, 53, 54] compared with those including hospitalized patients [22, 37–39]. Differences in the prevalence of antipsychotic polypharmacy between countries might also account for the differences found in studies. Interestingly, Divac et al. who analyzed the prevalence of antipsychotic polypharmacy at a University Psychiatric Hospital in Serbia found it to be around 70% which is approximately 100% higher than the prevalence observed in other

European countries [55]. A study surveying prescription patterns for patients with schizophrenia admitted for treatment in six East-Asian countries, revealed that Singapore and Japan had the highest rates of antipsychotic polypharmacy [41]. Another study comparing the effect of clozapine on polypharmacy in schizophrenia in Canada versus Singapore found that no patient in the Canadian sample was prescribed another neuroleptic, whereas 28% of Singapore patients were on a second neuroleptic [56]. In a comparative study of the pattern of drug treatment and antipsychotic polypharmacy in inpatients with schizophrenia between three centres in Spain, Sweden, and Estonia, concomitant treatment with at least two neuroleptics (or two different formulations of the same substance) occurred in 76% of patients in Spain, as compared with 59% in Sweden and 56% in Estonia [57]. Finally, an important factor which should also be taken into account in the interpretation of the differences among studies reporting the prevalence of antipsychotic polypharmacy, is the stringency of the criteria for the duration of antipsychotic polypharmacy. The relatively widespread use of antipsychotic polypharmacy identified in cross-sectional surveys reflects not only the addition of a second antipsychotic to boost therapeutic response, but also the use of as-required antipsychotic medication (mainly to treat disturbed behaviour), gradual cross-titration while switching from one antipsychotic to another, and augmentation of clozapine with a second antipsychotic where the illness has failed to respond adequately to an optimized trial of clozapine. The single-day census method which has been used by some studies (e.g. [24, 32, 41]) is unable to distinguish intentional co-prescribing, from medication cross-tapers and per needed medications and so is likely to over-represent the prevalence of antipsychotic combination therapy. Therefore, increasing stringency in the duration criteria for the definition of antipsychotic polypharmacy would be expected to lead to diminished prevalence estimation. For instance, Kreyenbuhl et al. found that the prevalence of antipsychotic polypharmacy in a large sample of patients with schizophrenia was 20.0%, 13.1%, and 9.5% when defined by a ≥30, ≥60, or ≥90-day duration of polypharmacy, respectively [23].

4.3.3 Does the Prevalence of Polypharmacy Depend on the Baseline Antipsychotic Agent?

It would be interesting to know whether the initial administration of a specific antipsychotic is associated with an increased risk of using an additional antipsychotic agent. Several studies have investigated the prevalence of adding a second antipsychotic agent during ongoing treatment with a specific atypical antipsychotic. Andersen et al. examined the day-to-day prescriptions of aripiprazole to an unselected population of 71 psychiatric inpatients. They found that most of patients were on polypharmacy: aripiprazole-antipsychotic combinations were initially prescribed in 75% of patients and 85% of the patients received periods of antipsychotic polypharmacy. Aripiprazole was combined with 17 different antipsychotics. These results

suggest that in practice, aripiprazole is frequently used as part of highly individualized regimens comprising polypharmacy and excessive dosing [58]. A more recent retrospective study described the phenomenon of antipsychotic polypharmacy in 52 patients with schizophrenia discharged with amisulpride from a short-term hospitalization unit. The majority of patients had been receiving at least one antipsychotic in addition to amisulpride. In those treated with two antipsychotics, the most frequently used common combination was with a classic antipsychotic in depot formulation. In patients who were prescribed two antipsychotics in addition to amisulpride, the most common combination was with a second generation antipsychotic, and a classic or depot antipsychotic [59]. In another study which examined the combination of long-acting risperidone with other antipsychotics, using US Medicaid data, polypharmacy with a non-risperidone antipsychotic occurred in 27% of episodes [60]. Finally, in a non-randomized naturalistic observational study which assessed the annual rate and duration of antipsychotic monotherapy and polypharmacy, among schizophrenia patients initiated on commonly used atypical antipsychotic medications, most patients (57.7%) had at least one prolonged period of antipsychotic polypharmacy. The authors found that olanzapine-initiated patients were significantly more likely to be on monotherapy with the initiating antipsychotic during the 1-year post initiation compared to risperidone or quetiapine. The number of monotherapy days was significantly greater for olanzapine than quetiapine, but not for olanzapine versus risperidone, or for risperidone versus quetiapine-initiated patients [20]. Another study found higher rates of polypharmacy with quetiapine than with risperidone [61]. Taken together, the above results indicate that there might be differences in the frequency and duration of antipsychotic polypharmacy use depending on the specific antipsychotic which is initially selected. It is possible that aripiprazole and quetiapine are associated with a higher likelihood of polypharmacy prescription compared with other antipsychotics. However, in order to draw safer conclusions this hypothesis needs to be investigated by well designed head to head, randomized studies.

4.3.4 Prevalence of Polypharmacy: Change Over Time

A number of other studies have examined whether the use of polypharmacy is changing over time. A retrospective study of 853 patients with schizophrenia over 1970–1988 found that there was a reduction in the use of multiple neuroleptics during the interval 1970–83. In particular, the practice of combining oral neuroleptics with depot injections became less common and, when used, a higher proportion of the total dosage was administered by injection. However, during the interval 1983–88 less desirable changes were evident. An increased proportion of patients received two or more neuroleptics (34% versus 23%) with more than a threefold increase in the proportion of patients receiving four or more different drugs (17% versus 5%). The practice of combining a depot injection with an oral neuroleptic of a different type also increased considerably [62]. Similarly, findings from China

suggested that the periods of antipsychotic polypharmacy of inpatients in a psychiatric hospital increased in 1989–1993 compared with 1984–1988 [63].

Edlinger et al. evaluated whether efforts to promote evidence-based guidelines for the psychopharmacological treatment of patients with schizophrenia have led to measurable changes of treatment practice in a Austrian university hospital. Data were collected from all inpatients with schizophrenia in the years 1989, 1995, 1998 and 2011. Data from 1989 to 1998 showed a significant decrease in the use of two or more antipsychotics given simultaneously. Contrary to the initial hypothesis, a significant increase in polypharmacy was found between 1998 and 2001 [64]. In a retrospective cohort study in 31,435 persons with schizophrenia, designed to determine the prevalence, trends, and factors associated with antipsychotic polypharmacy during 1998–2000, the prevalence of atypical antipsychotic polypharmacy was found to be increased between 1998 and 2000 [21]. Similarly, another retrospective study of outpatients in the US which aimed at determining the prevalence of antipsychotic polypharmacy in ambulatory care from 1993 to 2000 reported that the prevalence of polypharmacy increased for each two year period. A visit involving antipsychotic polypharmacy was 2.5 times as likely to occur in 1999–2000 as in 1993–1994. Use of two conventional antipsychotics was predominant in 1995–1996, whereas combining an atypical with a conventional agent or with another atypical agent was more common in 1999–2000. The change in combination patterns likely reflects the increasing availability of several atypical antipsychotics. The rate of antipsychotic polypharmacy appeared to be lower than that among inpatients with serious mental illness. During the observational period, polypharmacy in community practice continued to increase, as did the use of atypical antipsychotics in polypharmacy regimens [54]. The trend towards an increase in the prevalence of antipsychotic polypharmacy was confirmed in a study of Medicaid beneficiaries with schizophrenia in San Diego during 1999–2004. The proportion of patients receiving second-generation antipsychotic polypharmacy increased from 3.3% in 1999 to 13.7% in 2004. This study also found that the availability of antipsychotics could predict the combination pattern of antipsychotic polypharmacy. Among those receiving atypical antipsychotic polypharmacy, the percentage receiving second-generation polypharmacy for 12 months increased from 5.1% to 14.4% [65]. Similarly, McCue et al. conducted a cross-sectional study in two time points (1995, 2000) of inpatients with schizophrenia and reported that although no patients were discharged on treatment with more than one antipsychotic in 1995, in 2000, 15.9% of patients were. The most common antipsychotic combination was haloperidol and olanzapine [66]. An increase in the prevalence of antipsychotic polypharmacy over time was again found by Mojtabai et al. who studied 13,079 visits to office-based psychiatrists in the US during 1996–2006. Prescription for two or more antipsychotics significantly increased across survey years and the odds of receiving two, or more antipsychotics were significantly associated with a diagnosis of schizophrenia [67]. Similarly, in a study of outpatients in Denmark from 1996 to 2005, which investigated treatments and outcomes during the first year after the diagnosis of schizophrenia, there was an increase in the number of patients who received antipsychotic polypharmacy for >4 months [68]. In brief, the above results suggest that

there was a steady increase in the rates of antipsychotic polypharmacy during the nineties and early 2000. The investigation of the factors associated with antipsychotic polypharmacy could help explain this increase.

4.3.5 Predictors of Polypharmacy

Epidemiological studies have found that several factors are linked to antipsychotic polypharmacy. These factors could be divided into two major categories; those who are associated with the patients themselves and those who depend on the treatment setting and the psychiatric team which implements pharmacological treatment (Table 4.1).

4.3.5.1 Patient Factors

The diagnosis of schizophrenia or psychosis is a main factor associated with antipsychotic polypharmacy [22, 39, 52, 67, 69]. Many studies indicate that polypharmacy is selected for patients who suffer from severe mental illness [24, 52, 70], have been hospitalized many times [55] and have less insight into their disease [39]. Not only illness severity but also illness duration has been demonstrated to correlate with antipsychotic polypharmacy. Patients with a longer duration of illness are more likely to be prescribed more than two antipsychotics [41, 71, 72]. Recent inpatient treatment is also associated with the administration of antipsychotic polypharmacy [36, 52]. In addition, the administration of antipsychotic polypharmacy on discharge has been linked with patients' characteristics on admission. Patients who have more positive and manic/hostility symptoms and have received polypharmacy on admission are at increased risk for receiving multiple antipsychotics on their discharge [70]. The latter appears to be late, since antipsychotic polypharmacy correlates with longer hospitalizations [29, 43, 73]. Patients receiving antipsychotic polypharmacy are also less likely to be compliant to treatment [74, 75]. In terms of demographic characteristics, younger age [22, 36, 52, 53, 69] and male gender [52] have been both related with antipsychotic co-prescribing. Patients on polypharmacy are also more likely to be unmarried [69, 76]. Association with ethnicity appears contradictory. There are findings showing that black patients are more likely to receive more than two antipsychotics [77], but this has not been replicated by other studies which found equal prevalence of antipsychotic polypharmacy in blacks and whites in the UK [78, 79] or Maoris versus non-Maoris in New Zealand [43]. Interestingly, Latino and African-American patients in the US have been found to be less likely to have a prescription for polypharmacy [69, 76]. The findings on psychiatric and medical comorbidity in patients who receive antipsychotic polypharmacy versus those on monotherapy are also inconclusive. Most reports suggest that antipsychotic polypharmacy is given to patients with increased psychiatric comorbidity [36, 52, 69], although one study has found the opposite [53]. Patients who are under antipsychotic

Table 4.1 Factors associated with antipsychotic polypharmacy

Factor	Association with polypharmacy	Types of studies	References
Patients' factors			
Psychosis or schizophrenia	+	Cross-sectional, retrospective	[22, 39, 52, 67, 69]
Severe mental illness	+	Cross-sectional, naturalistic, retrospective	[24, 52, 70]
Number of hospitalizations	+	Cross-sectional	[55]
Insight	−	Cross-sectional	[39]
Illness duration	+	Cross-sectional, prospective	[41, 71, 72]
Recent inpatient treatment	+	Cross-sectional, retrospective	[36, 52]
Positive and Manic symptoms at admission	+	Naturalistic	[70]
Polypharmacy at admission	+	Naturalistic	[70]
Longer hospitalization	+	Cross-sectional, case control	[29, 43, 73]
Treatment compliance	−	Retrospective, review	[74, 75]
Younger age	+	Cross-sectional, retrospective	[22, 36, 52, 53, 69]
Male gender	+	Retrospective	[52]
Single marital status	+	Cross-sectional, retrospective	[69, 76]
Ethnicity	±	Cross-sectional, retrospective	[43, 69, 76–79]
Psychiatric comorbidity	±	Cross-sectional, retrospective	[36, 52, 53, 69]

Medical comorbidity	±	Cross-sectional	[43, 69]
Use of Antiparkinsonians	+	Cross-sectional, retrospective	[23, 25, 26, 29, 43, 69, 72, 80, 81]
Additional psychotropics	+	Cross sectional	[26, 69]
Setting and therapists factors			
Knowledge or awareness of treatment guidelines	−	Cross-sectional	[83]
Educational activities of the setting	−	Cross-sectional	[83]
Existence of psychopharmacological unit	−	Cross-sectional	[38]
Recent involvement in research	−	Cross-sectional	[38]
Nurses' beliefs	+	Cross-sectional	[71, 83]
Psychiatrists' beliefs	+	Cross-sectional	[71]
"Inheritance" of polypharmacy cases	+	Cross-sectional	[82]
Living in a facility, foster care	+	Cross sectional	[24, 26]
Other factors			
Mortality	±	Review, retrospective cross-sectional, follow-up study, case control	[86–88, 90]
Increased total antipsychotic dose	±	Review, cross-sectional, retrospective, audit, naturalistic	[27, 32, 41, 43, 48, 69, 70, 91–93]
Increased treatment costs	+	Cross-sectional, retrospective	[65, 94]
Cognitive impairments	±	Cross-sectional	[44, 95–98]

+: positive association; −: negative association; ± inconclusive findings (at least one study with contradictory findings)

polypharmacy regimens have been reported to show less medical comorbidity [69]. However, another study reported an equal prevalence of diabetes type 2 compared to patients receiving monotherapy [43]. Concomitant treatment with antiparkinsonians has also been found to be a predictor of polypharmacy [23, 25, 26, 29, 43, 69, 72, 80, 81], suggesting that these patients may be at increased risk for extrapyramidal side effects possibly due to increased antipsychotic exposure. Finally patients receiving antipsychotic polypharmacy are more likely to receive additional psychotropic agents [26, 69].

4.3.5.2 Setting and Therapists Factors

Besides patients' characteristics, there are also factors associated with therapists which have been shown to impact on the prescription of antipsychotic polypharmacy. One such factor leading to increased antisychotic polypharmacy prescription is psychiatrists' skepticism for the usefulness of treatment algorithms [71]. More clinical experience and the phenomenon of "inheritance" of cases treated with antipsychotic polypharmacy, accompanied by the reluctance to convert polypharmacy to monotherapy could foster the practice of polypharmacy [82]. Another factor associated with polypharmacy could be the lower knowledge or awareness of treatment guidelines by physicians and nurses [83]. This lack of knowledge could be a result of less frequent educational activities [83]. However, it is important to take into account the sources of these activities. Interestingly, psychiatrists who tended to add rather than switch antipsychotics reported more frequent attendance at educational programs sponsored by a pharmaceutical company. It should be noted here that the same psychiatrists paradoxically perceived polypharmacy to be an ineffective strategy for treatment-resistant positive psychotic symptoms [84]. On the contrary, the existence of a psychopharmacological unit inside the psychiatric setting providing access to clinical pharmacology teaching could counteract antipsychotic polypharmacy prescription [38]. The recent involvement of a treatment setting in research might also increase awareness of physicians to the side effects of polypharmacy and decrease its prevalence [83]. Other characteristics of the treatment setting have been also related to antipsychotic polypharmacy. As mentioned above, inpatients appear to be more likely to receive antipsychotic polypharmacy than outpatients. Geriatric patients living in a facility (e.g., assisted living, skilled nursing, long-term care) have been shown to be at increased risk of antipsychotic polypharmacy [85]. Similar findings have been reported in adults with developmental disability [24]. Youths in foster care are also more likely to receive antipsychotics concomitantly and for longer periods of time despite the lack of evidence to support such regimens [26].

The role of nurses on polypharmacy prescription is important. Their belief that polypharmacy is beneficial for patients, their perception of overwhelming work load and time pressure are all associated with increased administration of antipsychotic polypharmacy [71, 83].

4.3.6 Other Factors Associated with Antipsychotic Polypharmacy

There are several published studies which have associated antipsychotic polypharmacy with other factors, such as mortality, increased antipsychotic dose, cost and cognitive impairment.

4.3.6.1 Mortality

First, it should be mentioned that association of antipsychotic polypharmacy with mortality comes from cross-sectional studies and therefore cannot test causality. There is evidence that antipsychotic polypharmacy is indeed associated with increased mortality in patients with schizophrenia [86–89]. However, this was not confirmed in a recent large population-based nested case-control study in Denmark which found that the risk of natural death did not increase with the number of concurrently used antipsychotic agents [90].

4.3.6.2 Increased Total Antipsychotic Dose

Antipsychotic polypharmacy has been shown to be the most powerful predictor of high-dose prescribing for both psychiatric inpatients and outpatients [27, 32, 41, 43, 48, 69, 70, 91, 92]. In a recent review on the benefits and risks of antipsychotic polypharmacy, Barnes and Paton found that combined antipsychotics are indeed a major contributor to high-dose prescribing [93]. This close relationship of antipsychotic polypharmacy with high dosing makes the interpretation of the separate effect of antipsychotic polypharmacy difficult. Indeed, it has been suggested that several correlates of polypharmacy, such as treatment cost and cognitive impairments could be driven by the increased dosage rather than polypharmacy per se.

4.3.6.3 Cost

Antipsychotic polypharmacy has been associated with increased treatment cost. Baandrup et al. investigated the association of antipsychotic polypharmacy in schizophrenia with cost of primary and secondary health service use in a cross-sectional observational study of 736 outpatients. Antipsychotic polypharmacy was associated with significantly higher total health service costs compared with monotherapy when adjusting for potential confounders and risk factors. A subgroup analysis suggested that the excessive costs associated with antipsychotic polypharmacy were partly accounted for by the functional level of the patients [94]. The association of antipsychotic polypharmacy with increased treatment costs has been also confirmed by Gilmer et al. [65].

4.3.6.4 Cognitive Impairment

Antipsychotic polypharmacy has been associated with cognitive impairments in patients with schizophrenia. However, this finding could be interpreted in three ways. The relationship between antipsychotic medication and cognitive function may be due to differential illness severity (e.g., non-standard treatment for severely ill patients who have severe cognitive impairment). Alternatively, poorer cognitive function may be due to polypharmacy or be driven by excessive dosing [95]. In the baseline data of the CATIE trial, the neurocognitive composite score showed a negative association with the use of antipsychotic polypharmacy; patients with lower neurocognitive scores were more likely to be taking two agents [44]. Hori et al. provided evidence for a negative association between the number of antipsychotic medication and cognitive function [95]. Findings from a cross-sectional study in Japan also found that schizophrenia patients in the polypharmacy group had lower composite cognitive cores than those in the second generation antisychotics monotherapy group [96]. However, Elie et al. showed that it is the increased antipsychotic daily dose rather than the number of antipsychotic drugs which is associated with poorer cognitive functioning [97]. In contrast, the negative associations of antipsychotic polypharmacy and high dosing with non-verbal cognitive functions were not detected in a cross-sectional study of patients with schizophrenia which controlled for possible confounding factors such as age, education and anticholinergic burden [98].

4.4 Efficacy of Polypharmacy

The clinical efficacy of the concurrent administration of antipsychotics versus monotherapy remains the most important and controversial issue in antipsychotic polypharmacy. Although it has been examined by meta-analyses and reviews, it appears that the existing data are still confusing [99].

4.4.1 Meta-analyses

There are seven meta-analyses published in English language investigating the efficacy and side-effects of antipsychotic polypharmacy in schizophrenia spectrum disorders (Table 4.2).

Six of them have tested the therapeutic value of adding a second antipsychotic to ongoing clozapine treatment and one reviewed the therapeutic and adverse effects of polypharmacy versus monotherapy in schizophrenia. Taylor et al. examined the effect of adding a second antipsychotic to established clozapine monotherapy in 14 randomized double blind studies and found that augmentation with a second antipsychotic conferred a small benefit over placebo. Meta-regression

Table 4.2 Efficacy and side effects of antipsychotic polypharmacy: findings from meta-analyses

Aim	Efficacy	Side effects	Sample (*N*) or number of studies included	Comment	References
Meta-analyses					
Clozapine augmentation					
To examine using meta-analysis the effect of adding a second antipsychotic to established clozapine monotherapy	+	−	*N=734*	Augmentation with a second antipsychotic is modestly beneficial in patients not responding fully to clozapine. Tolerability seems not to be adversely affected, at least in the short term. Longer studies do not appear to increase the probability of showing positive effects for augmentation	[100]
To evaluate the therapeutic effect of adding an antipsychotic drug to clozapine treatment	+	N/A	*N=522*	In studies lasting up to 16 weeks, the addition of an antipsychotic to clozapine treatment has marginal therapeutic benefit	[101]
To summarize evidence on efficacy of pharmacological augmentation of clozapine treatment in schizophrenia spectrum disorder.	±	±	*N=1,066*	The evidence supporting clozapine augmentation with antipsychotics is sparse. Sulpiride might be useful.	[102]
To evaluate the effects of sulpiride augmentation to clozapine versus monotherapy in schizophrenia.	+	More extrapyramidal effects and prolactin increase, less hypersalivation, less weight gain	*N=221*	Sulpiride plus clozapine is probably more effective than clozapine alone in producing clinical improvement in some people whose illness has been resistant to other antipsychotic drugs including clozapine.	[103]

(continued)

Table 4.2 (continued)

Aim	Efficacy	Side effects	Sample (*N*) or number of studies included	Comment	References
To conduct a meta-analysis of randomized placebo-controlled trials of clozapine augmentation with another antipsychotic drug in patients with schizophrenia who partially respond to clozapine and compare the results with the findings of relevant open studies	+	Extrapyramidal side effects, raised prolactin	*N=166*	Augmentation of clozapine with another antipsychotic drug in patients with schizophrenic illness that has partially responded to clozapine is worthy of an individual clinical trial. This trial may need to be longer than the 4–6 weeks usually recommended for acute antipsychotic monotherapy.	[104]
To determine the efficacy of various clozapine combination strategies with antipsychotics.	±	?	21 studies	The evidence base supporting a second antipsychotic in addition to clozapine in partially responsive patients with schizophrenia is weak. This indicates modest to absent benefit.	[105]
Polypharmacy versus monotherapy					
To evaluate therapeutic and adverse effects of antipsychotic cotreatment versus monotherapy in schizophrenia.	+	±	*N=1,229*	In certain clinical situations, antipsychotic cotreatment may be superior to monotherapy. However, the database is subject to possible publication bias and too heterogeneous to derive firm clinical recommendations	[106]

+: positive findings; −: negative findings; ±: inconclusive findings; ?: not assessed

exploring the effect of length of treatment on effect size showed no relationship. The risk of discontinuing antipsychotic augmentation was no greater than the risk of discontinuing placebo. In conclusion, the authors reported that augmentation with a second antipsychotic is modestly beneficial in patients not responding fully to clozapine. Tolerability seemed not to be adversely affected, at least in the short term [100]. An earlier meta-analysis which had included ten randomized, placebo-controlled studies of antipsychotic augmentation of clozapine treatment had shown that the augmentation group significantly differed from placebo on only one outcome measure examined, the mean effect size for rating scale score (Brief Psychiatric Rating Scale/Positive and Negative Syndrome Scale). On the contrary, antipsychotic augmentation showed no advantage on withdrawals from trials, or on Clinical Global Impression scores. Duration of study was not found to be associated with outcome [101]. It should be mentioned that both meta-analyses failed to reveal evidence for publication bias. Sommer et al. examined the effect of all augmentation strategies to clozapine, including antipsychotics. Available evidence based only on double-blind randomized controlled studies suggests that sulpiride augmentation of clozapine had significant better efficacy than placebo on total, positive and negative symptoms. However, this beneficial effect of sulpiride was based on a single study. The authors drew the general conclusion that evidence for efficacy of clozapine augmentation is currently scarce and that despite their popularity, pharmacological augmentations of clozapine are not demonstrated to be superior to placebo [102]. The beneficial effect of clozapine augmentation with sulpiride was confirmed by Wang et al., who also found evidence for a mixed effect on side effects [103]. In another meta-analysis, Paton et al. reported that the addition of a second antipsychotic in people who partially responded to clozapine is useful, provided that the trial is longer than 4–6 weeks [104]. However a previous meta-analysis examining the efficacy of several clozapine augmentation strategies found weak evidence supporting this practice [105]. A recent meta-analysis examined all randomized controlled trials comparing antipsychotic polypharmacy versus monotherapy. It included 19 trials and showed that antipsychotic co-treatment is superior to monotherapy regarding two a priori defined co-primary outcomes: less study-specific defined inefficacy and all-cause discontinuation. However, the authors reported that specific psychopathology and adverse event data were insufficient to yield meaningful results. In sensitivity analyses, five efficacy moderators were detected: concurrent polypharmacy initiation, clozapine combinations, trial duration >10 weeks, Chinese trials, and combination of second-generation with first-generation antipsychotics. In a meta-regression, similar dose combinations, combinations of first and second-generation antipsychotics and concurrent polypharmacy initiation remained significant. The authors concluded that in certain clinical situations, antipsychotic co-treatment may be superior to monotherapy. In particular, they suggested that benefits may be apparent in acutely exacerbated patients in whom co-treatment is initiated at the beginning of treatment and when the cotreatment is administered for 10 weeks or more. Moreover, benefits of antipsychotic cotreatment did not seem to be simply a function of an increase in antipsychotic dose and resultant

dopamine blockade in the polytherapy group. The authors acknowledged that their database was subject to possible publication bias and too heterogeneous to derive firm clinical recommendations [106].

4.4.2 Reviews

Reviews generally agree that the evidence supporting the efficacy of polypharmacy involves patients with a history of treatment resistance to multiple monotherapy trials, and that positive outcomes are primarily found in studies of clozapine augmented with a second-generation antipsychotic [93, 107–109]. A recent systematic review detected only three studies comparing various combination strategies of clozapine with another antipsychotic and failed to find significant superiority of any particular combination strategy with clozapine [110]. The existing reviews have provided no evidence to support the findings of Correll et al. with respect to the role of concurrent polypharmacy initiation or the duration of 10 weeks of treatment. The existing reviews also revealed the side effects associated with the use of multiple antipsychotics [107, 109] and suggested that prescription for each patient should be individualized with monitoring of the clinical response and adverse effects, and appropriate physical health monitoring, including screening for metabolic syndrome [93]. According to a review by Gardos, studies which examined the side effect burden showed higher rates of anticholinergic and extrapyramidal side effects of antipsychotic polypharmacy compared to monotherapy, but these differences tended to disappear when total dosage was controlled for [109]. Another review including studies from 1976 to 2002 reported that the majority of the double-blind and open-label trials found that combination therapy was effective in reducing symptoms, while less than half of case reports revealed an overall positive outcome [108].

Besides the meta-analyses and the above mentioned reviews, there are also interesting findings from individual studies or case reports providing useful information on the effects of antipsychotic polypharmacy. Interestingly, there are reports showing that the combination of antipsychotics could even worsen psychosis [111, 112]. In contrast, the combination of atypical antipsychotics has been also demonstrated to lead to a reduction in weight or lipid abnormalities which is consistent with the preclinical findings mentioned above [113].

4.4.3 Discontinuation Studies

There is only one randomized trial which addressed the risks and benefits of staying on antipsychotic polypharmacy or switching to monotherapy [114]. This trial found that discontinuing one of two antipsychotics was followed by treatment discontinuation more often and more quickly than when both antipsychotics were continued.

However, there was a successful switch in two-thirds of participants, and switching to monotherapy resulted in weight loss. According to the authors, these results support the reasonableness of prescribing guidelines encouraging trials of antipsychotic monotherapy for individuals receiving antipsychotic polypharmacy, with the caveat that patients should be free to return to polypharmacy if an adequate trial on antipsychotic monotherapy proves unsatisfactory [114]. These findings are in agreement with results of a nonrandomized open-label study of discontinuing polypharmacy in which 44 individuals were tapered from polypharmacy to monotherapy; over half (54%) of the patients remained stable, 23% showed improvement, and 23% worsened [115].

4.5 Management of Antipsychotic Polypharmacy

The high prevalence of antipsychotic polypharmacy in combination with the lack of the adequate evidence has led to initiatives aiming at limiting or eliminating this phenomenon. According to the recent review by Barnes and Paton, practice-based interventions designed to reduce the prevalence of antipsychotic polypharmacy have met with only modest success [93]. This is in agreement with Ananth et al. who suggest that techniques such as experimental ward, peer review, computer information feedback, and comparing different techniques may temporarily reduce polypharmacy but long-term outcome is not affected [75].

Table 4.3 summarizes the studies exploring the efficacy of interventions to reduce polypharmacy.

There were both positive [116–124] and negative results [125, 126]. The types of initiatives comprised web-based tools and policies [127], education and electronic reminders [125], monitoring and education by pharmacists [119], medication-reduction algorithms [120], multi-faceted interventions comprising workbooks, educational visits and reminder systems [122] or combining web tools, leadership approval policies and feedback [127], performance improvement initiatives focusing more on leadership and less on effort [123] and managed care programmes [124].

4.6 Discussing the Evidence

The preclinical evidence for the usefulness of antipsychotic polypharmacy is extremely limited. There are only three studies and, one of these, has used a putative antipsychotic agent whose antipsychotic efficacy in humans is not yet documented.

In terms of the clinical evidence, the existing studies indicate that the prevalence of polypharmacy is relatively high. Its trends are increasing over time and demonstrate variability depending on the country under study. Antipsychotic polypharmacy also appears to be associated with a variety of factors. The “inheritance” of cases

Table 4.3 Interventions to reduce polypharmacy

Reference	Country	Inpatients or outpatients	Type of study	Type of intervention
[116]	Singapore	Inpatients	Prospective with a matched control group for age and gender	The treatment algorithm emphasizes the use of a single antipsychotic agent and short-term use of benzodiazepines for disturbed behaviour early in the treatment rather than increasing the dose of antipsychotic.
[117]	USA	Both inpatients and outpatients	Retrospective	A statewide quality improvement program aimed at reducing polypharmacy
[118]	Singapore	Inpatients	prospective	Using Clinical Practice Improvement Program (CPIP) methodology and using a Plan, Do, Study, Act approach
[119]	Canada	Inpatient and outpatient	Retrospective	A pharmacist monitored prescriptions with antipsychotic polypharmacy and contacted corresponding prescribers to provide education on risks of
[120]	USA	Inpatients	Case control	A medication-reduction algorithm was developed, based on the best available evidence regarding indications for and efficacy of medications and principles of collaborative care
[121]	UK	Medical and nursing staff	Cluster randomized controlled trial	a Cognitive Behavioural Therapy style workbook
[122]	UK	Inpatients	Randomized controlled trial	A multi-faceted intervention comprised: an educational/CBT workbook; an educational visit to consultants; and a reminder system on medication charts

Psychiatric diagnosis	*N*-sample	Aim	Findings/conclusions
first episode psychosis	*N=68* in the comparator group, *N=483* Early Psychosis Intervention Programme patients	To review the prescription patterns in a tertiary mental health institute in Asia and evaluate the impact of a treatment algorithm for patients with first-episode psychosis on the use of polypharmacy	There was a significant reduction in the rate of antipsychotic polypharmacy, prolonged use of benzodiazepines and anticholinergic medication in Early Psychosis Intervention Programme.
Psychiatric diagnoses	*N=51,756*	To study trends in antipsychotic polypharmacy over a 4 year period.	The program did help to reduce the use of antipsychotic polypharmacy.
Schizophrenia	Not Mentioned	To reduce antipsychotic polypharmacy among chronic schizophrenia inpatients at the long-term wards at the Institute of Mental Health, Singapore from 2006 to 2008.	The programme was successful in the reduction of antipsychotic polypharmacy within the geriatric and adult long-term patients.
schizophrenia	2006: *N=648* 2008, *N=778*	The objective was to examine effects of active interventions on physician's prescribing of antipsychotic polypharmacy.	A three-fold decrease in the prevalence of antipsychotic polypharmacy was observed between 2006 (18.3%) and 2008 (6.6%).
Schizophrenia, schizoaffective, bipolar, major depression	*N=24*	To examine the effectiveness of an intervention to reduce medications for patients already receiving polypharmacy during an episode of acute psychiatric hospitalization.	The intervention patients were discharged on significantly fewer medications than controls; symptom reduction and length of stay did not differ significantly.
N/A	*N=193 doctors*, *N=474 nurses*	To examine whether clinicians' beliefs about antipsychotic polypharmacy prescription changed alongside behaviour as a result of a complex intervention, using a questionnaire	There was a significant change in beliefs on antipsychotic Polypharmacy. There was a modest but statistically significant change in antipsychotic polypharmacy prescribing.
Psychiatric disorders	*N=488 patients*	To investigate the effectiveness the intervention in reducing prescribing of antipsychotic polypharmacy on general adult psychiatry wards, compared with guidelines alone.	The intervention reduced levels of polypharmacy prescribing compared to guidelines alone although the effect size was relatively modest.

(continued)

Table 4.3 (continued)

Reference	Country	Inpatients or outpatients	Type of study	Type of intervention
[123]	USA	Inpatients	prospective	An earlier initiative that involve consultation and education & a performance improvement initiative that used a low intensity
[124]	USA	Inpatients and outpatients	Retrospective	Mental health carve-out, managed care plan
[125]	Denmark	Outpatients	Controlled quasi-experimental study performed	The intervention was aimed at psychiatric healthcare providers and consisted of 1 day of didactic lectures, six 3-h educational outreach visits and an electronic reminder during drug prescribing.
[126]	USA	inpatients	Retrospective	Training in the implementation of the Texas medication algorithm
[127]	USA	Inpatients	Prospective	Web based application, approval policies and feedback for polypharmacy prescription

Psychiatric diagnosis	*N*-sample	Aim	Findings/conclusions
all diagnoses	November 2001: *N=492* August 2001: *N=408*	To evaluate initiatives aiming at reducing polypharmacy	Antipsychotic polypharmacy fell significantly—(from 42% to 31%). Higher utilizers of polypharmacy at baseline
At least two diagnoses of schizophrenia, bipolar disorder, major depression	*N=12,810*	To examine prescription drug utilization among Medicaid recipients with the implementation of Prepaid Mental Health Plans in Florida Medicaid.	The implementation of the programme was associated with reduced adherence, polypharmacy and expenditures by the Medicaid agency. There was no change in the likelihood of prescriptions being written within recommended dosage ranges.
Schizophrenia	Baseline: intervention group: *N=232* Control group: *N=351*, and after 1 year of intervention group: *N=216* / Control group, *N=386*.	To evaluate the effect of a multifaceted educational intervention on the frequency of antipsychotic co-prescribing in adult schizophrenia out-patients.	The intervention failed to reduce the frequency of antipsychotic co-prescribing. Future efforts to improve prescribing practice should address organizational barriers to implementation
schizophrenia	*N=60*	Provider's practice behaviors before and after physician and staff training in the use of a schizophrenia medication algorithm and the effects of education on physician adherence to the algorithm were evaluated.	There were no significant differences between the two groups with respect to the frequency and types of antipsychotic polypharmacy.
All diagnoses	*N=4,227*	To study the effect of interventions to decrease antipsychotic polypharmacy in the New York State Office of Mental Health network of psychiatric hospitals.	Antipsychotic polypharmacy decreased significantly and remained low at 6-month follow-up. On long-term follow-up, polypharmacy increased, eventually, but remained well below baseline levels.

already receiving antipsychotic polypharmacy prescriptions for years along with the reluctancy of psychiatrists to convert the treatment of these patients to monotherapy appears to play a major role. The severity of illness could also affect the clinical decision to administer antipsychotic polypharmacy which is usually a practice reserved to the most difficult of patients. Psychiatrists are not likely to prescribe multiple antipsychotics to older patients or children and adolescents, probably because of the risk of adverse effects and interactions. The role of patient's ethnicity on the decision of psychiatrists remains inconclusive. However, it appears that psychiatrists are influenced by the setting in which they are working and nurses' requests and beliefs. As expected, their own beliefs and education also influence their choice, as does their clinical experience. Initiatives which incorporate educational tools and sessions with a higher level control of prescribing seem to lead to reduced prevalence of polypharmacy. Polypharmacy is usually related to increased total antipsychotic dose and increased treatment costs. Its association with mortality and cognitive dysfunction remains to be further investigated. The efficacy and side effects of polypharmacy have been explored by recent meta-analyses and reviews. There is emerging evidence that polypharmacy might be beneficial under certain circumstances. Recent data suggest that it may be mostly useful in acutely exacerbated patients in whom co-treatment is initiated at the beginning of treatment and when the co-treatment is administered for at least 10 weeks. The combination of first with second generation antipsychotics is likely to be the most effective combination and clozapine would be preferable as a baseline antipsychotic.

When polypharmacy is to be used, rational polypharmacy should be the rule. Rational polypharmacy suggests that the treating psychiatrist should avoid using two drugs with similar mechanisms of action, and that the possibility of increased adverse effects should always be borne in mind. Good clinical practice dictates that clinicians use the smallest number of drugs necessary to treat any condition. Sound reasons for antipsychotic polypharmacy administration include the enhancement of dopamine D2 blockade, the achievement of agonism or antagonism of certain receptors implicated in symptoms or side effects, optimization of pharmacokinetic effects, or reduction of adverse effects. Antipsychotic polypharmacy would also be acceptable during cross-tapering of antipsychotics or in an effort to manage particularly challenging symptoms, such as aggression [6]. However, none of these reasons has been adequately tested in animal models or rigorous trials. For instance, the possibility that the addition of small doses of haloperidol to ongoing treatment with atypical antipsychotics offers benefits in antipsychotic efficacy in treatment resistant patients [128], has not been examined in clinical trials. The role of dosage should also be taken into account for the interpretation of study findings which convert monotherapy to polypharmacy or vice-versa. Finally, it is possible that it is the specific drugs and doses of drugs that matters and not polypharmacy per se [129].

In addition to their small number the existing studies on the value of antipsychotic polypharmacy suffer from methodological limitations. For instance it has been observed that the small sample sizes in most reports may introduce greater than 60% Type I error, producing false negative results. Another limitation of these

studies and case reports is the significant differences in the dosages of medications and definitions of clinical improvement that were used, making it difficult to draw safe conclusions [6].

4.7 Conclusions and Future Directions

A synthesis of the existing evidence suggests that, at the preclinical level, antipsychotic polypharmacy could lead to improved antipsychotic effects in models of psychosis, although it would be associated with increased neurologic adverse events. There is preliminary evidence that the administration of antipsychotics with no metabolic effects with others which are associated with weight gain could prevent hyperphagia. The prevalence of antipsychotic polypharmacy ranges according to the country of interest and the different psychiatric settings, while it is steadily increasing. The factors associated with this practice are related to patients, physicians and the treatment context. Several meta-analyses and reviews suggest that antipsychotic polypharmacy is modestly beneficial against treatment resistant symptoms. According to one of them antipsychotic polypharmacy is most effective when it is administered from the beginning and lasts for more than 10 weeks. In addition is also raises the possibility that antipsychotic polypharmacy could be useful under conditions of acute symptoms' exacerbation non-responsive to monotherapy, which contradicts previous views that polypharmacy is only useful in chronic refractory illness. Finally, initiatives to reduce polypharmacy may lead to positive results.

There are a number of issues which remain to be investigated by future research. First, it is probably an oversimplification to consider antipsychotic polypharmacy a unitary concept. Consequently, studies examining the efficacy, interactions and side effects of different combinations of antipsychotics are needed. The specific impact of antipsychotic polypharmacy on different symptoms' dimensions (cognition, aggression, negative symptoms etc.) in schizophrenia also needs to be further explored. Longer term prospective studies assessing the association if antipsychotic polypharmacy with morbidity and mortality could shed more light on this issue and reconcile the contradictory findings. The effects of antipsychotic polypharmacy in disorders other than schizophrenia have not received attention to date. Other important questions which should be addressed by future research are: When one should employ antipsychotic polypharmacy and to which patients? Should antipsychotic polypharmacy be used after many antipsychotic monotherapy trials have failed, or it should be tried from the beginning? Is it an option for treatment resistant patients only, or should it be given during psychotic exacerbation? Is it cost effective? Another topic which has not been investigated to date is whether the time course of separation between antipsychotic polypharmacy from monotherapy is similar or different if clozapine is not part of the polypharmacy regime. Finally, high quality, longer-term, controlled co-treatment and discontinuation studies in patients treated with antipsychotic combinations are also necessary to provide sufficient evidence that could guide clinical practice.

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Chapter 5
Should High Dose or Very Long-Term Antipsychotic Monotherapy Be Considered Before Antipsychotic Polypharmacy?

Stephen M. Stahl and Debbi A. Morrissette

Abstract Standard doses of all antipsychotics target 60–80% occupancy of dopamine D2 receptors. However, many patients do not respond adequately in 2–6 weeks to standard doses of one or more antipsychotics given as sequential monotherapies, as suggested by contemporary treatment guidelines for schizophrenia. The reasons for such inadequate treatment responses are several, and include both pharmacokinetic and pharmacodynamic failures. That is, some patients at standard doses do not attain 60–80% D2 occupancy. Factors accounting for this include not only noncompliance, but also failure to absorb, rapid metabolism, CYP450 2D6 polymorphisms, and others. In addition, some patients at standard doses attain 60–80% D2 occupancy but do not respond adequately to this. Common problems among such patients are hostility, aggression, assaultiveness and violence as well as continued positive symptoms of psychosis. At least two approaches may be considered for such pharmacokinetic and pharmacodynamic failures: namely, high dose monotherapy, and very long treatment times when feasible. High doses of a single agent are actually better studied than antipsychotic polypharmacy with two or more antipsychotics, especially for certain agents, and provides an approach that is potentially simpler, safer and more effective for overcoming both pharmacokinetic and pharmacodynamic treatment failures, and allows a strategy to optimize antipsychotic

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M.S. Ritsner (ed.), *Polypharmacy in Psychiatry Practice, Volume I: Multiple Medication Use Strategies*, DOI 10.1007/978-94-007-5805-6_5,

treatment without polypharmacy. In addition, certain patients have very late onset improvements, measured in months or years, and very long term treatment data for antipsychotics in schizophrenia are beginning to emerge for patients who are not in urgent management situations as an alternative to antipsychotic polypharmacy.

Keywords Monotherapy • High-dose • Pharmacodynamic • Pharmacokinetic • Treatment resistance • Violence

Abbreviations

5HT	Serotonin
D	Dopamine
EPS	Extrapyramidal side effects
H	Histamine
M	Muscarininc
NET	Norepinephrine transporter
SERT	Serotonin transporter

5.1 Introduction

Schizophrenia is the most common form of psychosis, affecting approximately 1% of the population [1]. Based on the dopamine hypothesis of schizophrenia, standard treatment involves the use of antipsychotics to block dopamine D2 receptors. However, a portion of patients with schizophrenia are "treatment-resistant", failing to respond to multiple monotherapy trials of antipsychotics at standard doses. Unfortunately, insufficient treatment of psychosis often manifests as violent and aggressive behaviors that are dangerous to the patient and others and warrant treatment strategies that are not considered first-line, evidence-based practices. Such treatment strategies include both polypharmacy (simultaneous use of two antipsychotics) and high-dose antipsychotic monotherapy. In this chapter, we present an argument for why high-dose monotherapy should be considered for treatment-resistant patients prior to resorting to polypharmacy. Additionally, we discuss how "time" may be a necessary component of the treatment regimen for many patients with schizophrenia.

5.2 Symptoms and Circuits of Schizophrenia

Psychosis can be considered a set of symptoms in which a person's mental capacity, affective response and capacity to recognize reality, communicate, and relate to others is impaired [2]. The domains of schizophrenia include positive symptoms such as

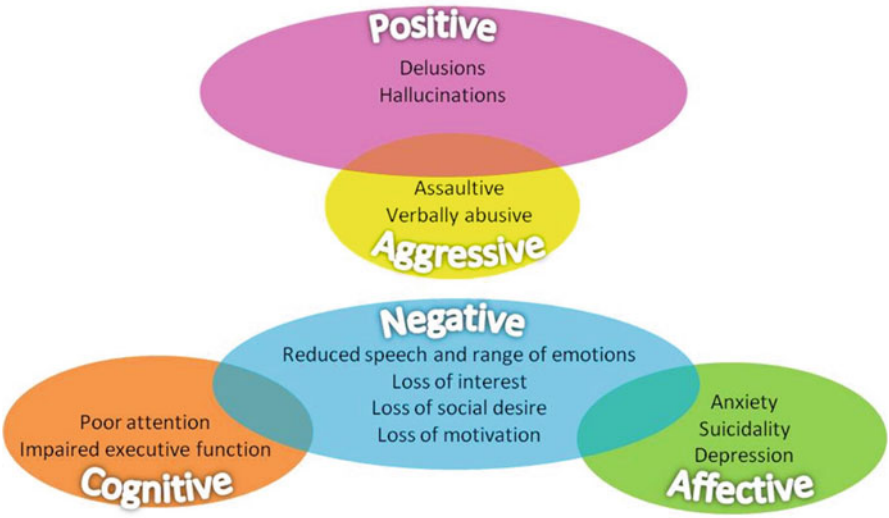

Fig. 5.1 Overlapping symptoms of schizophrenia. The symptom domains of schizophrenia (positive, negative, aggressive, cognitive, and affective) often have overlapping clinical features. It is not surprising that treatments that are effective for one symptom domain (e.g. positive symptoms) may alleviate symptoms from overlapping domains (e.g. aggressive symptoms) (Reprinted with permission from *Stahl's Essential Psychopharmacology* 3rd edition. Copyright Neuroscience Education Institute, 2008)

hallucinations and delusions, negative symptoms including anhedonia, affective symptoms, cognitive symptoms, and aggressive symptoms (Fig. 5.1). In some instances, such as with positive and aggressive symptoms, the domains overlap; thus effective treatments may alleviate symptoms in more than one domain. Each of the symptom domains of schizophrenia is hypothesized to be due to dysfunction in specific neural circuitry (Fig. 5.2). Positive symptoms are thought to be caused by excessive dopamine in mesolimbic pathways; negative symptoms arise with low levels of dopamine in prefrontal cortex, mesocortical circuits, and reward areas, including the nucleus accumbens; cognitive symptoms are associated with hypoactivation of dopamine pathways in the dorsolateral prefrontal cortex; affective symptoms are due to underactivity in ventromedial and prefrontal cortices; and aggressive symptoms stem from excessive reactivity in the amygdala coupled with inadequate prefrontal regulation [2, 3].

5.3 Treating Schizophrenia

Treatment of schizophrenia with antipsychotics is focused on their ability to antagonize dopamine D2 receptors in the mesolimbic pathway. The first-generation antipsychotics were designed to tightly bind D2 receptors (Fig. 5.3). These conventional

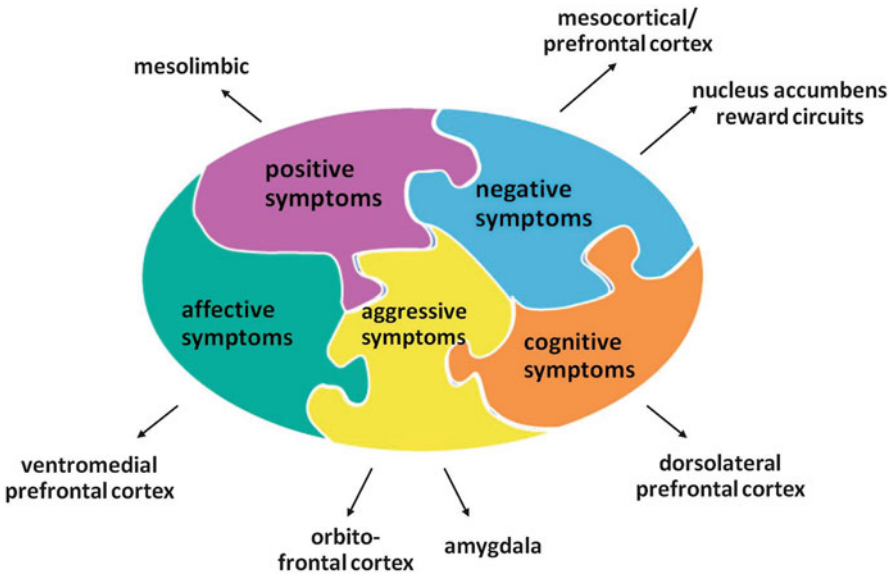

Fig. 5.2 The symptom domains and brain circuits of schizophrenia. Schizophrenia encompasses many different and sometimes overlapping symptom domains including positive, negative, affective, cognitive, and aggressive. Each of these symptom domains is thought to be related to dysfunction in discrete brain circuits. For example, hyperdopaminergia in the mesolimbic system is hypothesized to underlie positive symptoms of schizophrenia (Reprinted with permission from *Stahl's Essential Psychopharmacology* 3rd edition. Copyright Neuroscience Education Institute, 2008)

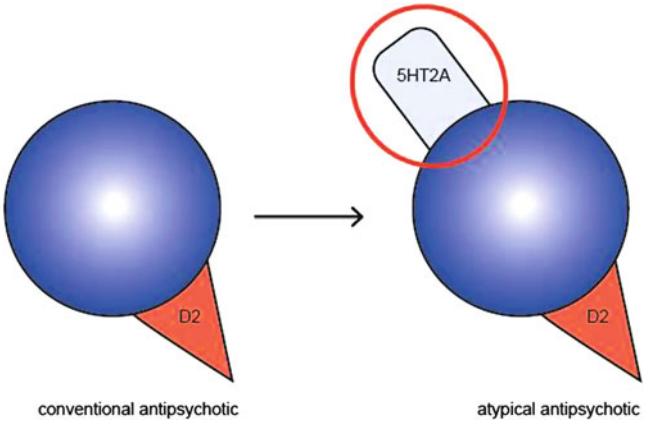

Fig. 5.3 Conventional vs. atypical antipsychotics. Conventional antipsychotics are defined by their antagonism of dopamine D2 receptors. What makes an antipsychotic atypical is the additional property of serotonin 5HT2A antagonism. In addition to D2 and 5HT2A receptor antagonism, individual atypical antipsychotics have a variety of binding affinities for additional receptors that gives each atypical agent a unique binding profile (Reprinted with permission from *Stahl's Essential Psychopharmacology* 3rd edition. Copyright Neuroscience Education Institute, 2008)

antipsychotics are effective at ameliorating positive symptoms for many patients; however, the indiscriminate antagonism of D2 receptors in nigrostriatal as well as mesolimbic pathways often has disturbing motor effects including extrapyramidal symptoms (EPS) and akathisia. Additionally, antagonism of D2 receptors throughout the brain is hypothesized to actually worsen existing cognitive and affective symptoms by further impairing dopamine activity in already hypoactive brain areas (Fig. 5.4).

The second-generation antipsychotics were developed as a means to block D2 receptors while avoiding some of the negative consequences of excessive and indiscriminate D2 receptor antagonism. All atypical antipsychotics bind serotonin 5HT2A as well as D2 receptors. The antagonism of 5HT2A receptors tempers some of the effects of D2 receptor antagonism, potentially preventing the development of EPS (Fig. 5.5). Atypical antipsychotics also binds to other receptors in addition to D2 and 5HT2A; each individual agent has a unique binding profile that lends it additional therapeutic and adverse effects (Table 5.1). Most notably, although the atypical antipsychotics (as a class) have less propensity to cause EPS compared to the conventional antipsychotics, there is increased risk for cardiometabolic issues with the atypical antipsychotics [2].

As aforementioned, the primary focus of schizophrenia treatment is on the amelioration of positive symptoms. Biochemical and imaging studies have shown that blockade of at least 60% of D2 receptors by antipsychotic treatment is necessary in order to reduce psychosis [4]. At greater than 80% occupancy of D2 receptors, the threshold for EPS is reached in many patients. Thus, antipsychotics at standard doses aim to achieve between 60 and 80% D2 receptor occupancy (Fig. 5.6) [4–7].

5.4 When Standard Treatment Fails

Treatment guidelines advocate sequential trials of antipsychotic monotherapies at standard doses (Fig. 5.7) [8]. It is important that each monotherapy trial is continued for an adequate length of time; data indicate that the downstream effects of D2 receptor blockade by an antipsychotic often take more than 6 weeks to manifest [9, 10]. In fact, it may be necessary to treat schizophrenia with an antipsychotic for as long as 1–2 years before a significant improvement in psychotic symptoms is evident [2].

The failure of a patient to respond to standard dose antipsychotic monotherapy of adequate duration may be due to medication nonadherence or to either pharmacokinetic or pharmacodynamic failures [5]. Pharmacokinetic interactions describe the effects of a biological system on a medication and include rapid metabolization, cytochrome P450 polymorphisms, poor absorption (e.g. due to gastric bypass), and interactions with other medications/substances. In the case of pharmacokinetic failure, plasma drug levels do not reach adequate levels (and therefore D2 receptor occupancy is less than 60%) despite standard antipsychotic doses (Fig. 5.8a). Oftentimes, pharmacokinetic failure presents as a lack of both therapeutic and

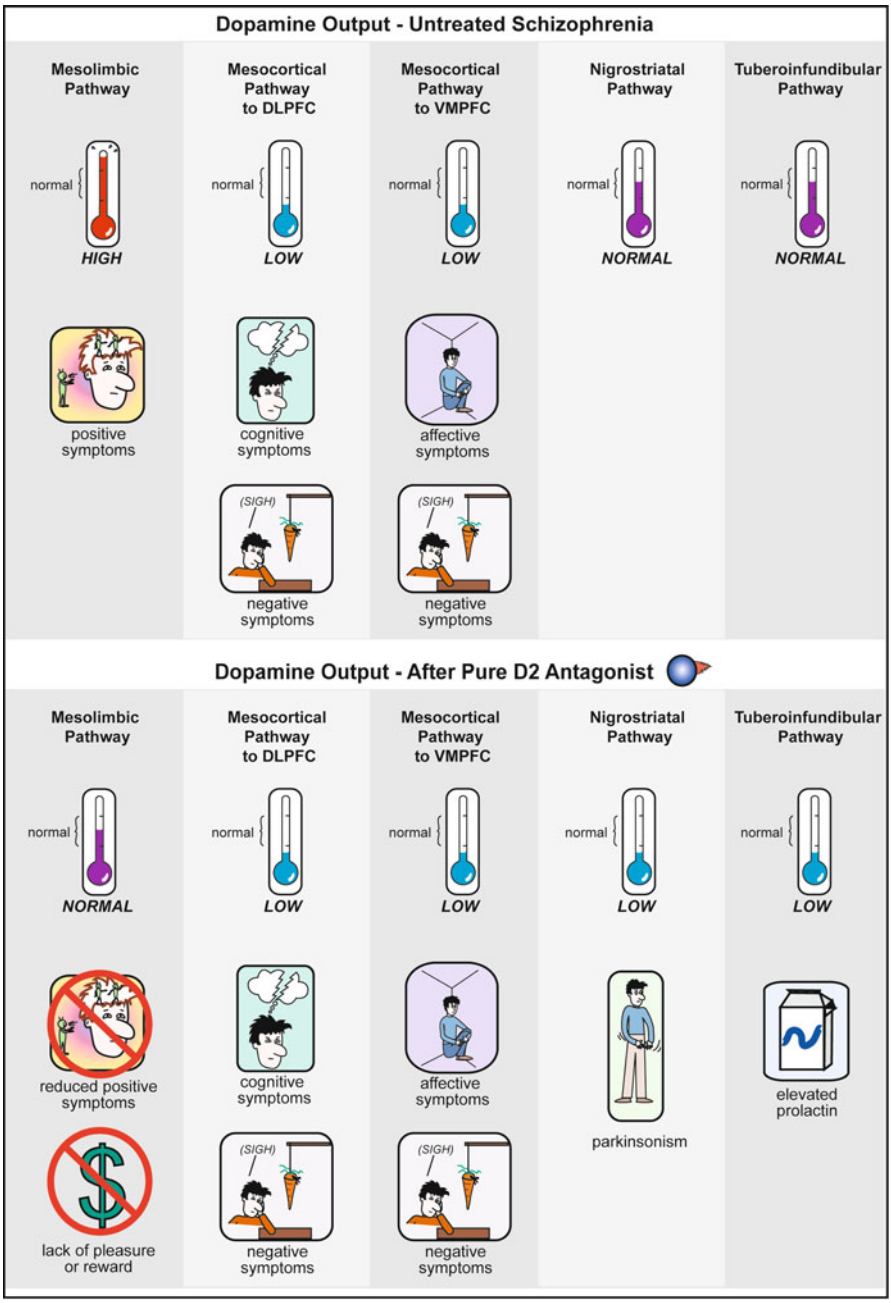

Fig. 5.4 Effect of D2 antagonism on various circuits. Although D2 antagonism in mesolimbic pathways can be an effective treatment for positive and aggressive symptoms of schizophrenia, it may actually exacerbate the cognitive and negative symptoms of schizophrenia. Additionally, blockade of D2 receptors in nigrostriatal and tuberoinfundibular pathways can lead to the development of troubling side effects such as movement disorders and hyperprolactinemia, respectfully (Reprinted with permission from *Stahl's Essential Psychopharmacology* 3rd edition. Copyright Neuroscience Education Institute, 2008)

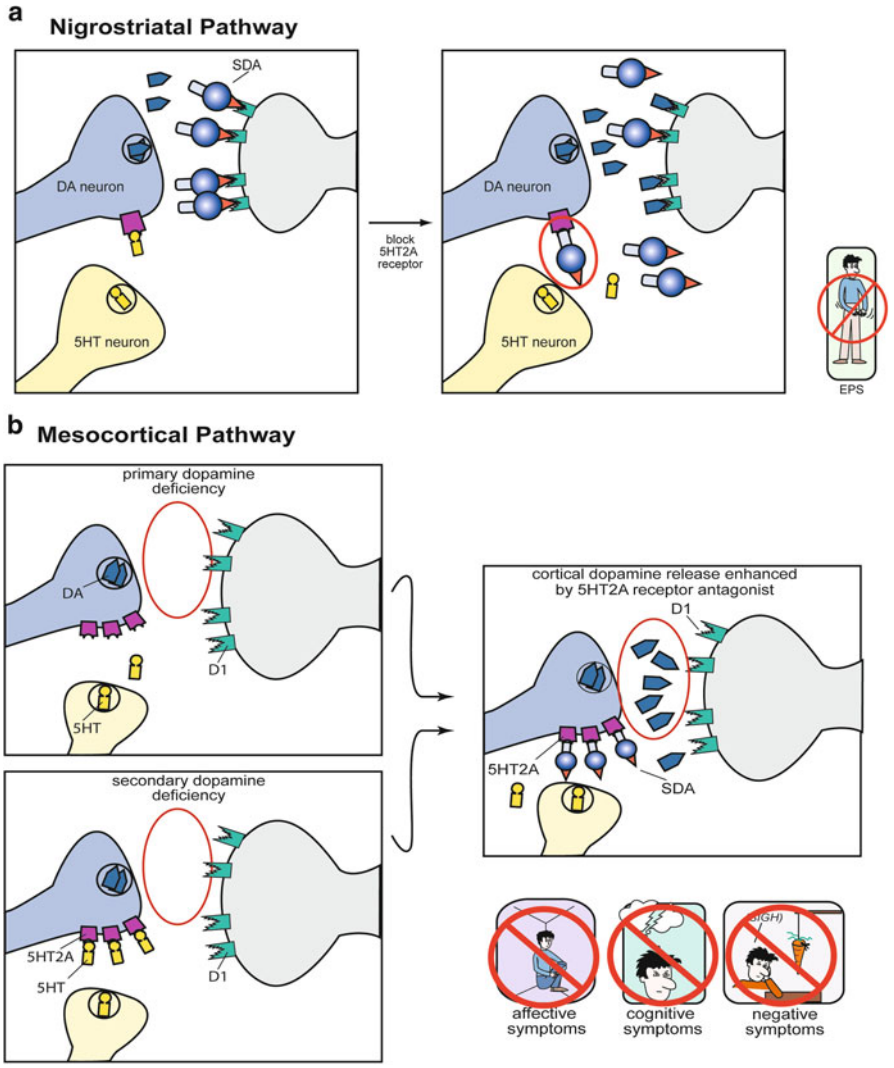

Fig. 5.5 Antagonism at serotonin 5HT2A receptors. **a** Dopamine D2 antagonism in the nigrostriatal pathway can lead to the development of extrapyramidal symptoms (EPS). The additional binding of atypical antipsychotics (i.e. serotonin dopamine antagonists or SDAs) to serotonin 5HT2A receptors found on dopaminergic neurons increases the release of dopamine in the striatum, preventing the development of EPS. **b** In the mesocortical pathway, binding of a SDA to 5HT2A receptors disinhibits cortical release of dopamine preventing further exacerbation of the hyperdopaminergic condition thought to underlie affective, cognitive, and negative symptoms of schizophrenia (Reprinted with permission from *Stahl's Essential Psychopharmacology* 3rd edition. Copyright Neuroscience Education Institute, 2008)

Table 5.1 Vast molecular polypharmacy of atypical antipsychotics

Drug	D2 Antag	D2 PA	D3	5HT1A	5HT2A	5HT2C	5HT7	α1	M1	M3	H1
Aripiprazole		+++	+++	+++	++	++	+++	++			++
Asenapine	+++		+++	++	++++	++++	++++	+++	++	++	+++
Clozapine	+		+	+	++	++	++	+++	+++	++	+++
Iloperidone	+++		++	++	+++	+	++	+++			++
Lurasidone	+++		?	+++	++	+	++++	++			
Olanzapine	++		++		+++	++	+	++	++	++	+++
Paliperidone	+++		+++	+	++++	++	+++	+++			++
Quetiapine	+		+	+*	++*	+*	++*	+++	++*	++*	+++*
Risperidone	+++		+++	+	++++	++	+++	+++			++
Ziprasidone	+++		+++	++	++++	++	+++	++			++
Therapeutic Effects	Reduced positive symptoms	Reduced positive symptoms	Reduced positive symptoms; Reduced negative symptoms; Procognitive; Antidepressant	Reduced EPS; Reduced hyperprolactinemia; Antidepressant; Anxiolytic	Reduced EPS; Reduced hyperprolactinemia	Antidepressant	Reduced circadian rhythm dysfunction; Reduced negative symptoms; Procognitive	Reduced nightmares	Reduced EPS	Reduced EPS	Hypnotic
Side Effects	EPS; Hyperprolactinemia; Increased negative symptoms; Increased cognitive deficits; Sedation	Relatively lower risk of EPS	Unknown	Unknown	Cardiometabolic	Cardiometabolic	Unknown	Dizziness; Sedation; Hypotension	Constipation; Sedation; Dry mouth; Blurred vision	Cardiometabolic; Constipation; Sedation; Dry mouth; Blurred vision	Cardiometabolic; Sedation

+ weak binding affinity (100>Ki<1000)
++ moderate binding affinity (10>Ki<100)
+++ strong binding affinity (1>Ki<10)
++++ very strong binding affinity (Ki<1)
? No data yet available
*Binding property due primarily to the metabolite norquetiapine

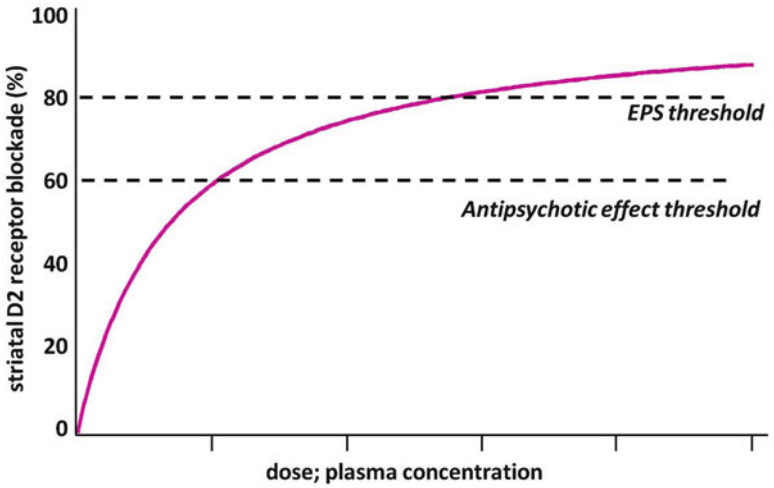

Fig. 5.6 Hypothetical thresholds for antipsychotic drug effects. Blockade of at least 60% of dopamine D2 receptors in the striatum is necessary to ameliorate positive symptoms of schizophrenia. However, when 80% or more of D2 receptors are blocked, extrapyramidal side effects (EPS) are likely to occur. Standard doses of antipsychotics are based on achieving the 60% D2 receptor occupancy without exceeding the 80% EPS threshold. Note that the slope of the curve flattens out with increasing dose; i.e. at higher doses, large increases in dose are needed in order to obtain substantial increases in D2 receptor occupancy (Reprinted with permission from *Stahl's Essential Psychopharmacology* 3rd edition. Copyright Neuroscience Education Institute, 2008)

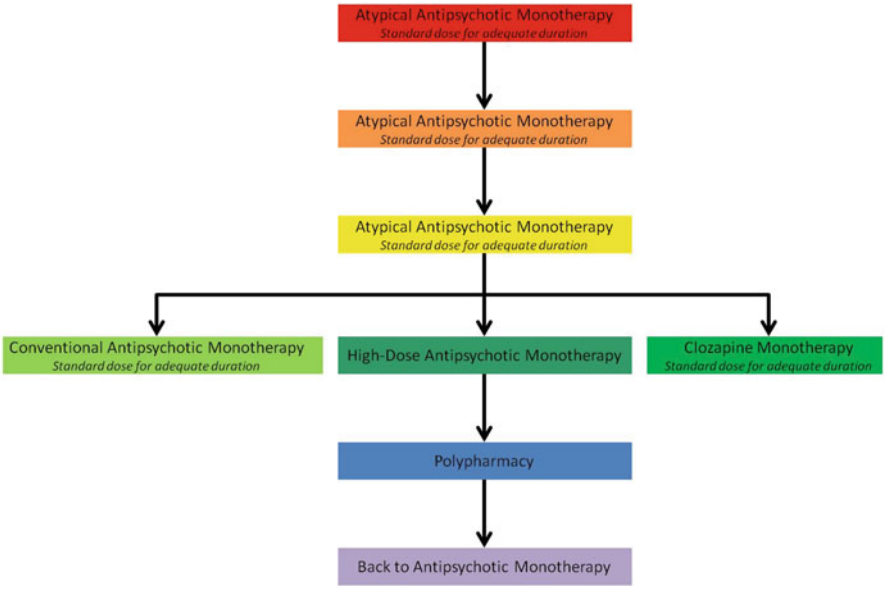

Fig. 5.7 Proposed treatment algorithm for treatment-resistant schizophrenia. Following inadequate response to several different atypical antipsychotic monotherapies, each at standard doses for an adequate length of time, there are several strategies that can be employed. Conventional antipsychotic monotherapy is not a first-line treatment due to the risk for adverse events including movement disorders; however, some patients may respond better to a conventional antipsychotic rather than an atypical one. Clozapine monotherapy is also reserved for treatment-resistant or violent patients due to increased risk for dangerous side effects (e.g. agranulocytosis). High-dose antipsychotic monotherapy also increases the risk for adverse effects but may be necessary in order to overcome pharmacokinetic or pharmacodynamic failures. Antipsychotic polypharmacy (the simultaneous use of two antipsychotics) should be reserved for cases when all other strategies fail. If polypharmacy proves unsuccessful, the patient should be returned to antipsychotic monotherapy (Reprinted with permission from *Stahl's Essential Psychopharmacology* 3rd edition. Copyright Neuroscience Education Institute, 2008)

adverse effects at standard antipsychotic doses. Therapeutic drug monitoring can also sometimes be used to determine if a pharmacokinetic issue underlies treatment nonresponse (as long as nonadherence can be ruled out) [11, 12]. Solutions to pharmacokinetic failure include increasing the antipsychotic dose to achieve sufficient plasma levels (Fig. 5.8a), switching to a different antipsychotic monotherapy (such as one with a sublingual or intramuscular formulation), or simply taking the antipsychotic with food. Pharmacodynamic interactions describe how the medication affects the biological system [5]. With pharmacodynamic failure, there is a lack of therapeutic response despite attaining adequate plasma drug levels (Fig. 5.8b) [5]. This lack of response can be due to inherent issues in D2 receptor density or sensitivity. Data are accumulating to suggest that some patients develop a form of "dopamine supersensitivity" whereby increasing doses of antipsychotics may be necessary in order to reduce psychotic symptoms [13–15]. Interestingly,

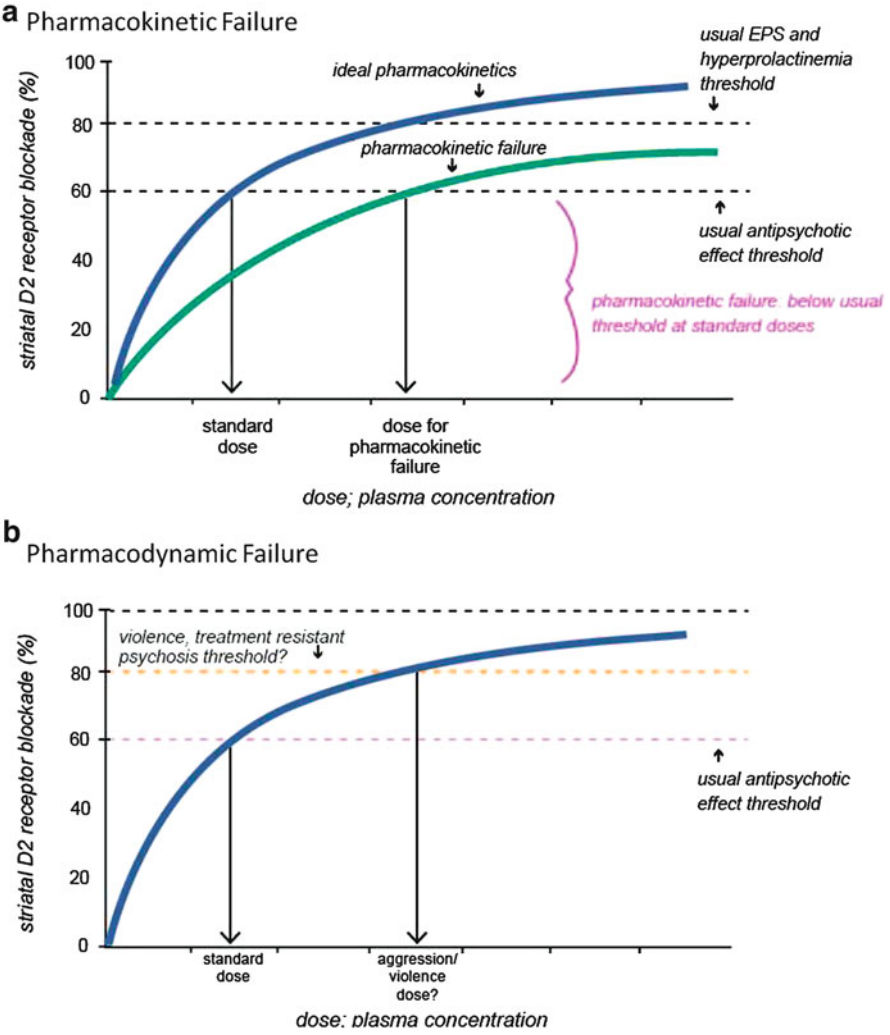

Fig. 5.8 Pharmacodynamic and pharmacokinetic failures. The failure of a patient to respond to antipsychotic treatment may be due to either pharmacokinetic or pharmacodynamic failures. **a** Pharmacokinetic failures describe cases where the therapeutic threshold (~60% D2 receptor occupancy) is not achieved despite dosing at standard therapeutic levels. **b** Pharmacodynamic failures describe cases where occupancy of greater than 80% of D2 receptors by a D2 antagonist maybe required before therapeutic effects are achieved; in other words, pharmacodynamic failures may alter the threshold for therapeutic effects from antipsychotic drugs (Reprinted with permission from *Stahl's Essential Psychopharmacology* 3rd edition. Copyright Neuroscience Education Institute, 2008)

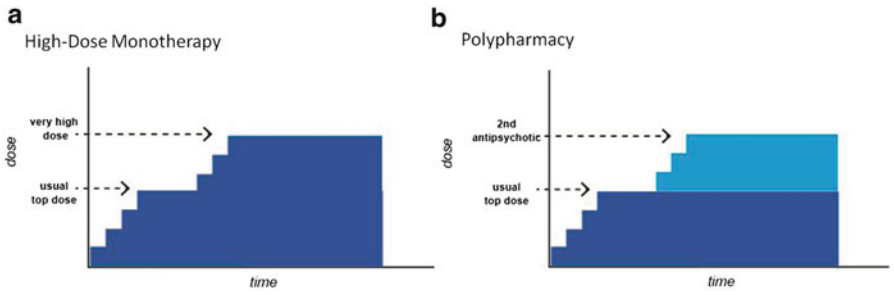

Fig. 5.9 Strategies to increase dopamine D2 receptor occupancy. For patients who are nonresponsive (and possibly violent) despite adequate trials of antipsychotic monotherapies, it may be necessary to employ strategies aimed at overcoming pharmacokinetic or pharmacodynamic failures. **a** High-dose therapy involves increasing an antipsychotic monotherapy beyond standard therapeutic doses using a slow uptitration. **b** For polypharmacy, a second antipsychotic is added to antipsychotic monotherapy, both at standard therapeutic doses (Reprinted with permission from *Stahl's Essential Psychopharmacology* 3rd edition. Copyright Neuroscience Education Institute, 2008)

several factors can increase dopamine supersensitivity, including illicit drug use, social isolation, birth injuries, and genetic polymorphisms [15]. These treatment-resistant patients may present with excessively psychotic symptoms and aggression leading to institutionalization in forensic settings. For these individuals, it may be necessary to use treatment strategies aimed at greater than 80% occupancy in order to relieve psychotic symptoms (Fig. 5.8b).

Unfortunately, the most likely candidates for high-dose or otherwise heroic treatment measures are most often excluded from clinical trials because they are too psychotic, too substance-abusing, too aggressive, or too treatment-resistant to meet inclusion criteria or give informed consent [5, 16, 17]. Likely, these are the patients with pharmacodynamic or pharmacokinetic issues that require dosing to exceed the 80% receptor occupancy threshold (Fig. 5.8a and b). Unfortunately, it may be difficult for the prescribing clinician to know the best strategy for obtaining this high D2 receptor occupancy given the paucity of studies that include the patients who require it.

Essentially, there are two treatment strategies that can increase D2 receptor occupancy beyond the 80% threshold: polypharmacy (the simultaneous use of two antipsychotics) and high-dose antipsychotic monotherapy (Fig. 5.9). Although data supporting the use of antipsychotic polypharmacy are quite limited, this practice is very common in psychiatry; as many as 30% of patients receive antipsychotic polypharmacy [18, 19]. In fact, despite several guidelines recommending that polypharmacy should only be used as a last resort (following failure of several monotherapies and a trial of clozapine), many clinicians attempt polypharmacy as the rule, rather than the exception [12, 20]. Polypharmacy is often employed as a method for increasing dopamine D2 receptor occupancy, but also may be used to recruit additional properties of antipsychotics in order to treat non-positive symptoms such as depression and anxiety [20]. As mentioned previously, atypical antipsychotics

bind to a variety of receptors, some of which are hypothesized to have therapeutic benefit (Table 5.1). Unfortunately, each atypical antipsychotic also binds to receptors associated with increased risk of intolerable effects (e.g. sedation) so using two antipsychotics simultaneously can increase the side effect burden. There is also a risk of drug-drug interactions with antipsychotic polypharmacy that may exacerbate intolerable effects [21]. Simultaneous use of two antipsychotics also further complicates the treatment regimen; both intolerability and complicated treatment regimens are known to negatively impact treatment adherence [22]. On top of antipsychotic polypharmacy, additional drugs (such as anticholinergics) may be required in order to treat the intolerable side effects caused by polypharmacy, thus further increasing the cost and complication of the treatment regimen [8]. There are even some data to suggest that polypharmacy may increase the risk of serious consequences, including diabetes and cardiovascular mortality [23]. A recent study by Langle et al. [18]. also suggested that patients with schizophrenia on antipsychotic polypharmacy have a worse clinical course compare to those on monotherapy.

5.5 Time as a Drug

The downstream effects of D2 receptor blockade may take more than 2–6 weeks to manifest. In such cases, it may be that time itself is a "drug". In a study of 118 patients with first-episode schizophrenia or schizoaffective disorder, it was shown that only approximately 20% of patients had responded to antipsychotic treatment at 4 weeks; however, by week 52, 87% of patients had responded to treatment [10]. Individually, antipsychotic treatments including risperidone, olanzapine, and ziprasidone have shown that continued treatment over the long-term may be needed for some patients. A 12-month study of risperidone showed that the percentage of patients with schizophrenia showing 30% and 60% improvement increased significantly over the duration of the study (Janssen, data on file). Similar data were found in a 7 month study of olanzapine treatment for schizophrenia (Eli Lilly, data on file). Ziprasidone treatment of schizophrenia over 196 weeks also supported continued increases in remission rates and improvement in negative symptoms with time [24, 25].

Oftentimes a second antipsychotic is added to the first when there is inadequate response following only a few weeks of monotherapy; however, response to antipsychotic monotherapy may take as long as 16-weeks to manifest. Adding a second antipsychotic may therefore be superfluous and add only to the monetary and physical cost of treatment without adding any therapeutic benefit [8]. In support of this idea, recent studies have shown that as many as two-thirds of patients treated with antipsychotic polypharmacy can be successfully switched to monotherapy [19, 26]. The Essock et al. [19]. study in particular showed that not only did patients who were switched from polypharmacy to monotherapy have no worsening of symptoms or increased hospitalization, but many had reversal of the metabolic effects that were presumably due to antipsychotic polypharmacy.

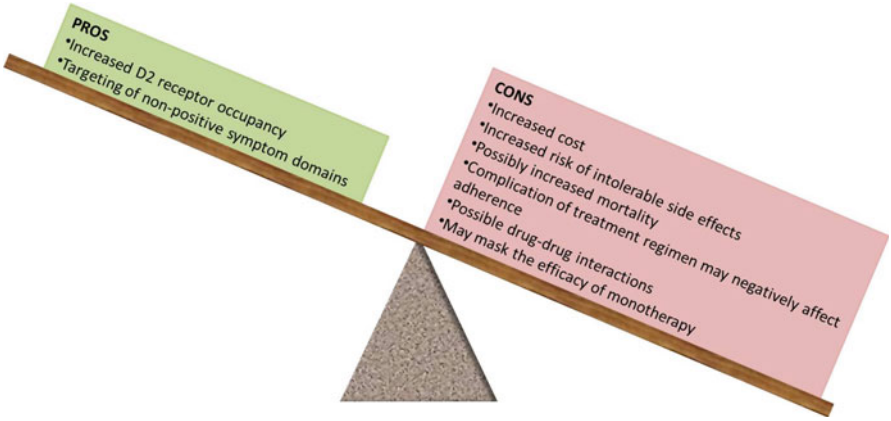

Fig. 5.10 Pros and cons of antipsychotic polypharmacy. The risks inherent with the simultaneous administration of two different antipsychotics far outweigh the possible benefits

5.6 High-Dosing of Atypical Antipsychotics

High-dose monotherapy is another strategy for increasing D2 receptor occupancy. Although this strategy may also increase the risk of intolerable side effects (notably EPS and akathisia) and is also associated with higher costs than standard dose monotherapy, there are significantly fewer disadvantages when compared with antipsychotic polypharmacy (Fig. 5.10). If it is necessary to increase D2 receptor occupancy in order to ameliorate positive symptoms in a particular subset of treatment-resistant, highly psychotic, and/or violent patients, logic would favor the simpler strategy that is associated with fewer adverse consequences.

As with all off-label practices, dosing of antipsychotics above standard therapeutic levels warrants informed consent and increased monitoring of the patient. As the pharmacodynamic and pharmacokinetic characteristics vary from patient to patient, it is virtually impossible to predict what daily dose will be needed in order to achieve an antipsychotic effect [27]. Antipsychotic dosing should be started at the low FDA-approved dose and then titrated upward accordingly until therapeutic efficacy or intolerable side effects occur [28]. The standard dose ranges for atypical antipsychotics and special considerations for high dosing are summarized in Table 5.2. In the following sections, we review the art and science of prescribing each of the FDA-approved atypical antipsychotics at high-doses. As antipsychotics are dosed at a level that blocks 60–80% of D2 receptors (with the exception of clozapine), it is important to note that any receptor binding that is stronger than that of D2 receptors will also be occupied at levels greater than 60% and will likely cause additional therapeutic and adverse effects. It is essential to keep the relative receptor binding affinities in mind when dosing an atypical antipsychotic at higher-than-usual levels to attain >80% occupancy of D2 receptors so that potential effects of binding to receptors other than D2 can be anticipated and monitored.

Table 5.2 Dosing atypical antipsychotics

Medication	Usual dose range (mg/day)[a]	Considerations for high dosing
Clozapine	300–450	Maximum dose is 900 mg/day. Doses above 550 mg/day may require concomitant anticonvulsant administration to reduce the chances of seizure
Risperidone	2–8	FDA-approved up to 16 mg/day. Very high doses usually not tolerated
Paliperidone	3–6	Maximum dose is generally 12 mg/day
Olanzapine	10–20	Some forensic settings up to 90 mg/day
Quetiapine	400–800	Some forensic settings up to 1,800 mg/day
Ziprasidone	40–200	Must be taken with food. PET data support >120 mg/day. Some forensic settings up to 360 mg/day may be appropriate
Aripiprazole	15–30	Higher doses usually not more effective and possibly less effective
Iloperidone	12–24	High dosing not well-studied and may be limited due to risk of orthostatic hypotension
Asenapine	10–20	High dosing not well-studied
Lurasidone	40–160	Must be taken with food. Nightly administration may improve tolerability. High dosing not well-studied but some patients may benefit from doses up to 160 mg/day

[a]Based on oral formulation in adults

5.6.1 Clozapine

Although clozapine is not recommended as a first-line treatment strategy due to the risk for serious adverse effects, most notably agranulocytosis, in patients who have failed several first-line atypical antipsychotic monotherapies a trial of clozapine is recommended. Clozapine has been well-documented for treatment-resistant patients and those who are violent or aggressive and is therefore recommended for such patients [29, 30]. Interestingly, the antiaggressive effects of clozapine are somewhat independent of its ability to improve positive symptoms [31]. Usual doses of clozapine (plasma levels of 400–600 ng/mL) actually bind less than 60–80% of dopamine D2 receptors but clozapine often has antipsychotic effects at 20–67% D2 occupancy suggesting that the antipsychotic effects of clozapine go beyond its ability to block D2 receptors [7]. This is not surprising given the vast binding profile of clozapine. Clozapine has relatively weak affinity for dopamine D2 receptors compared to its affinity for many other receptors including histaminic H1, adrenergic alpha-1, serotonin 5HT2B, and muscrinic M1 receptors, as well as a host of other receptors. Due to these high binding affinities for receptors other than D2, high-dosing of clozapine may cause sedation (due to antagonism of M1, H1, and alpha-1 receptors), hypersalivation and constipation (due to antagonism of M1), cardiometabolic issues (antagonism of H1 and 5HT2C receptors as well as the hypothesized

receptor "X"), and seizures (mechanism unknown) [2]. A meta-analysis by Davis and Chen [16] showed that patients with high plasma levels of clozapine responded more frequently than those with low plasma levels, indicating that doses above 400 mg/day may be required by many patients. Titration of clozapine to high doses should be done by increasing the dose every 5–7 days [5].

5.6.2 Risperidone/Paliperidone

Risperidone and its active metabolite paliperidone have similar receptor binding profiles with relatively strong affinity for dopamine D2 receptors. In the "average" patient, dosing of risperidone at 2–4 mg/day is associated with 70–80% D2 receptor occupancy and is rarely useful at doses above 8 mg/day [2, 6] Both risperidone and paliperidone are associated with increased risk of EPS in a dose-dependent manner, so care must be exercised when increasing the dose of these agents [16]. Titration of risperidone or paliperidone to high doses should be executed by increasing the dose every 5–7 days [5]. One pharmacokinetic difference between paliperidone and risperidone is that paliperidone is not metabolized in the liver so has less chance of drug-drug interactions or effects from cytochrome P450 polymorphisms [2]. Paliperidone may also be more tolerable, with less sedation and fewer EPS and should be dosed higher than risperidone [2]. Both of these agents are also available as long-acting depot formulations so an alternative strategy for achieving high D2 receptor occupancy would be the simultaneously use the depot formulation along with its oral counterpart.

5.6.3 Olanzapine

Olanzapine is perhaps the most well-studied atypical antipsychotic in terms of its use at high doses [8]. The risk of EPS is minimal, even at high doses of olanzapine; however, among the atypical antipsychotics olanzapine carries one of the greatest risk for cardiometabolic effects due to its strong binding affinity for histaminic H1 and serotonin 5HT2C receptors [2]. Doses of olanzapine between 10 and 20 mg/day often correspond to 60–80% D2 receptor occupancy but at plasma levels above 700–800 ng/mL olanzapine is associated with QTc prolongation [2, 7, 11]. Olanzapine has also been shown to improve both cognitive and aggressive behavior in patients with schizophrenia [31]. Several studies have indicated that olanzapine may be most effective at higher doses (40–60 mg/day) and may be useful in treatment-resistant violent patients in forensic settings at doses as high as 90 mg/day [8, 11, 20, 28]. Olanzapine titration to higher doses should take place with dose escalation every 5–7 days [5]. Olanzapine is also available in a long-acting depot formulation that can be supplemented with oral olanzapine to achieve high D2 receptor occupancy.

5.6.4 Quetiapine

Quetiapine is available as both immediate release (IR) and extended release (XR) formulations. Quetiapine binds dopamine D2 receptors with relatively weak affinity; it has far greater affinity for many other receptors including histaminic H1, adrenergic alpha-1, and serotonin 5HT2C receptors, as well as the norepinephrine transporter (NET). Because of this binding profile, high "Papa Bear" doses of at least 800 mg/day are usually required for quetiapine to have antipsychotic effects. Quetiapine has a very low risk of EPS associated with it, even at high doses, but is associated with a moderate risk for sedation and metabolic syndrome due to its high binding affinity for H1 and 5HT2C receptors. Most literature suggests that 1,200 mg/day is no more effective than 600 mg/day but anecdotal use in forensic settings of doses up to 1,800 may be effective in violent patients who tolerate but do not respond to lower doses [2, 16, 28]. Titration of quetiapine usually involves daily dose increases but the dose should be increased at a slower rate when exceeding 800 mg/day [2, 23].

5.6.5 Ziprasidone

Ziprasidone has a fairly high binding affinity for dopamine D2 receptors, surpassed only by its affinity for serotonin 5HT2A and 5HT1B receptors. Ziprasidone is associated with virtually no risk of metabolic effects and earlier concerns about QTc prolongation have not been supported [2]. Importantly, ziprasidone must be taken with food in order to optimize its absorption. There are data to suggest that higher doses of ziprasidone may be most effective and doses as high as 360 mg/day have been reported [2, 11, 20, 28]. For titration of ziprasidone to high doses, daily increases in dose can be done [5].

5.6.6 Aripiprazole

Aripiprazole is a unique member of the approved atypical antipsychotics. Rather than dopamine D2 receptor antagonism, it acts as a partial agonist at D2 receptors. What this partial agonism means is that in the presence of a full D2 receptor agonist (e.g. dopamine), aripiprazole will act as an antagonist at D2 receptors; however, in the presence of a D2 receptor antagonist (e.g. another antipsychotic), aripiprazole will act more as a D2 receptor agonist [2]. Due to this partial agonism and its very high binding affinity for D2 receptors, aripiprazole may actually be less effective for psychosis at higher doses and may reduce the effectiveness of another antipsychotic if an attempt polypharmacy is made [2]. Aripiprazole is not associated with significant risks for sedation, EPS, or metabolic syndrome but may cause akathisia in some

patients. Although the initial titration of aripiprazole can be rapid, dose increases after a steady state has been reached should be done every 10–14 days [5].

5.6.7 Asenapine, Iloperidone, and Lurasidone

Asenapine, iloperidone, and lurasidone are the newest atypical antipsychotics on the market so less is known regarding their use at high doses. When looking to use a high-dose strategy, it would be prudent to first try a high-dose trial of one of the older atypical antipsychotics that have more clinical experience.

Asenapine has moderate binding affinity for dopamine D2 receptors and is usually not associated with increased risk for EPS or metabolic syndrome. Asenapine is available only as a sublingual formulation and therefore may be a good option for patients who have pharmacokinetic failures in response to other antipsychotics due to hepatic metabolism or poor absorption [2]. Doses as high as 30–40 mg/day can be used but must be administered 10 mg at a time given at least 1-h apart. The titration of asenapine should be done by increasing the dose every 5–7 days [5].

Iloperidone is most distinguished by its high binding affinity for adrenergic alpha-1 receptors. Due to this binding property, iloperidone has a high risk of orthostatic hypotension and sedation associated with it, so must be titrated slowly and is not recommended for use at high doses [2].

Lurasidone is the newest antipsychotic approved for use in the United States. It has moderately high binding affinity for dopamine D2 receptors but is most notable for its antagonism of serotonin 5HT7 receptors. Lurasidone is approved up to 80 mg/day but may be more effective in some patients at doses as high as 160 mg/day [2]. Importantly, lurasidone should be taken with food to optimize absorption. Although the original trials on lurasidone suggested that side effect risk increased with higher dosing, recent data indicate that administration of lurasidone in the evening may minimize the risk of adverse side effects [32].

5.7 Conclusions and Future Directions

For many patients with schizophrenia, standard dose antipsychotic monotherapy is ineffective due to pharmacokinetic or pharmacodynamic failures. Often these patients are extremely psychotic and may be excessively violent and aggressive. It is imperative for the safety of both the patient and those with whom the patient interacts that effective treatment strategies are found and utilized. Unfortunately, these difficult-to-treat patients are most often excluded from clinical drug trials leaving a tremendous gap in our understanding of what treatment strategies to employ. Future research that includes treatment-resistant, violent, aggressive patients is needed in order to fill this gap. In the meantime, high-dose antipsychotic monotherapy is supported by both research and a wealth of clinical experience

with treatment-resistant and violent patients, particularly in forensic settings. It is also important that treatment with an antipsychotic monotherapy be given ample time to work as data are accumulating to suggest that many patients require long-term antipsychotic treatment before optimal therapeutic benefits are observed. Another strategy that is commonly employed for the treatment of these resistant patients is the use of antipsychotic polypharmacy. Although the practice of polypharmacy is common (even in not-so-difficult-to-treat patients), there is very little evidence to support its efficacy and many health, monetary, and practical issues should warrant using polypharmacy only as a last resort.

Acknowledgements We wish to acknowledge Nancy Muntner for her work on the illustrations.

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Chapter 6
Multiple Medication Use of Neuropsychiatry in Forensic Psychiatry: Findings from the Central State Forensic Psychiatric Hospital of Saxony-Anhalt

Joachim G. Witzel

Abstract Neuropsychiatric treatment schemes differ considerably in forensic psychiatry compared to daily use in general psychiatric treatment facilities. On one hand, average treatment time usually is dramatically higher and on the other hand, patients dealt with are in danger to recommit serious crimes, if not treated adequately. Hereby, the use of neuropsychiatric polypharmacy might lead to more serious problems in forensic psychiatry, as the impact on risk reduction cannot be easily surveyed. This however, will be a necessary prerequisite of an adequate and as well safe treatment, if we wish to be successful in establishing ensured standards of treatment which will enable us to guarantee a sufficient risk prevention for general society. However, the benefits of the use of multiple medication schemes in terms of neuropsychiatry can be achieved by a very special control of patients and an obligatory ambulant aftercare, when treatment in detention facilities is accomplished.

Keywords Polypharmacy • Forensic psychiatric treatment • Neuroleptics

6.1 Introduction

The most important task of forensic psychiatry concerns the evaluation and treatment of patients whose psychiatric abnormalities have resulted in crimes. Among those who have been committed to forensic psychiatric facilities, we usually find persons suffering from various serious mental illnesses, such as especially schizophrenia. Although not held criminally responsible by the legal system due to their psychiatric status, such individuals often are typically placed in specialized facilities which

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M.S. Ritsner (ed.), *Polypharmacy in Psychiatry Practice, Volume I: Multiple Medication Use Strategies*, DOI 10.1007/978-94-007-5805-6_6,

will enable us to protect general society from the commitment of further crimes as long as the treatment will not be accomplished.

Thus, this aspect of forensic psychiatry can be conceived as a combination of custodial attention, referring to the function of separating dangerous mentally ill individuals from society, as well as an intensive therapeutic care and support to achieve best conditions ever before finally discharging the patient from the hospital as soon as possible—when they finally are judged to no longer pose a significant risk of recommitting future crimes.

The psychiatric abnormalities usually are diagnosed by performing a comprehensive psychiatric evaluation in the course of a criminal prosecution. When this evaluation leads to the conclusion that the person was not fully responsible due to a serious mental disease, he or she will receive treatment to enable resocialization and, eventually, a more or less normal life after discharge.

Clearly then the task of risk assessment is a central question in forensic psychiatry, requiring professional and continuous re-evaluation. At each stage of treatment the question must be answered to what extent risk reduction had been achieved by the therapeutical processes applied. However, the methods used to answer this question are mainly based on psychosocial and subjective criteria only. There is a great need to develop forensic evaluation techniques that are more informed by biological and objective criteria, including the benefits which are connected with medication treatment schemes [1].

Forensic Psychiatry reveals increasing patient numbers throughout previous years and thus is generating a problem, how to deal with a huge number of patients treated there in a way to shorten their average treatment time—without risking increasing redeliquent behavior.

In order to achieve this goal, besides many others, neuropsychiatric treatment strategies are employed very often using multiple medication schemes. So the question is to be answered which schemes might be most successful in fulfilling this task adequately.

In the past we faced in the field of neuroleptics the use of monotherapy referring mostly to the use of conventional neuroleptic substances (FGAs). Indeed, side effects would be found in such patients at least as often as could be seen in those of general psychiatry. Striving for essential risk reduction might have emphasized the wish to neglect such effects. In the light of modern therapy strategies, however, the limitations of such therapy regiments will be looked upon more and more as less convincing and should be left, when ever this might be possible.

As well, the use of depot neuroleptics seemed to be the best way to ensure medical compliance. Indeed, this might be helpful in the large field of medication strategies applied. However, it usually neglects the fact, that best medical compliance as well as risk reduction will be achieved by installing an adequate and professionally driven ambulant aftercare facility for those patients who will be discharged from forensic psychiatry [2]. Under those conditions, the number of strategies in the field of neuropsychiatric treatment can be enriched and will be more precise and working more successfully.

In the past very often conventional treatment strategies were employed, most due to the fact that psychiatrists feared the outcome of poor medical compliance [3, 4]. This is to say, that unreliable administration of medication—for what reason ever—could cause further serious delinquency performed by forensic psychiatric patients in the course of treatment and especially after discharge of such persons.

6.2 Multiple Medication Use

There are few studies having been performed dealing with the results of different therapy schemes in forensic psychiatry, yet. So we assume that the results achieved in daily practice of one of the largest forensic psychiatric hospitals of Germany might shed some light onto this issue.

The Central State Forensic Psychiatric Hospital of Saxony-Anhalt at Stendal is a specialized hospital in Germany offering therapy to 300 patients in the field of forensic psychiatry. It deals with individuals who committed all kinds of crimes, e.g. murder, serious bodily harm, and sexual offences. Besides, all diagnostic groups known from general psychiatry can be found there. The most important groups of diagnoses are represented by schizophrenia and personality disorder.

We proposed the hypothesis that in the course of analogous treatment schemes regarding general psychiatry patients in forensic psychiatric facilities should benefit from such widely established therapy regimens as well.

Of course, we know today that in many cases it will not meet the gold standard of neuropsychiatric treatment, if we will avoid a medication using a combination of various neuroleptic substances. However, we face the difficulties, that such therapeutic standards cannot be administered as depot medication alone. So we will have to leave conventional therapeutic strategies, if we will allow the use of modern regimens.

In the past we feared to give way to further delinquent behavior of forensic psychiatric patients using medication schemes not consisting of depot formulations alone. This is due to the estimation that we hoped to ensure the administration of neuroleptic substances by prescribing predominantly depot neuroleptics resulting in constant plasma levels of the substance administered. There is no doubt, that we will usually face a higher risk of poor medical compliance using oral substances, as in this case we usually will be dependent on cooperative behavior of our patients who hopefully will reliably swallow the prescribed medication.

Thus, we face a dilemma which consists of the need to establish modern therapy schemes introducing the use of multiple predominantly orally administered substances on one hand—and the risk of redelinquent behavior eventually resulting in serious crimes which might be related to the use of such strategies due to poor medical compliance. It might be assumed as an unsolvable problem, thus telling us that it would be better to use conventional depot medication and neglect the benefits of modern multiple medication use in the field of forensic psychiatry rather than to risk further crimes committed by mentally ill patients.

Indeed, if we just think twice, we will realize that continuous medication even in the case of applying depot formulations can be assured to a sufficient extent only, if we will be able to control it regularly. After patients having been discharged from forensic psychiatric facilities, however, it will be the task of aftercare units to ensure this. So the dilemma referred to before usually can be avoided by introducing a professional aftercare which will control patients and the way they cooperatively use the prescribed medications. In this case, it is no longer a decisive aspect of such treatment, if medication was administered by depot or oral medication schemes. Meanwhile, we have gold standards of controlling such persons by analyzing plasma regarding the levels of previously prescribed medication.

All in all, we may conclude that even in the case of forensic psychiatric patients the use of multiple substances which are administered orally should be at least as effective as conventional treatment schemes. Especially by avoiding side effects such as neurologic symptoms of neuroleptic therapy, we could enhance the cooperative ability of individuals when having been discharged from forensic psychiatric facilities. Moreover, it seems more likely that modern therapy schemes might be more promising regarding medical compliance, when the period of forensic psychiatric aftercare will come to an end. During this time discharged patients will not be obliged anymore to take any drug prescribed. So we will be dependent on professional psychoeducational schemes applied before, which will enable the patients to understand, how important was the use of the prescribed medication. It is probable that this might be more successful in case of using modern neuroleptics which cause much less side effects than conventional ones.

Especially the use of polypharmacy will need such professional aftercare to control side effects [5, 6]. Using various substances the risk to introduce side effects such as e.g. extrapyramidal effects on motor control, sexual dysfunction, tardive dyskinesia, weight gain, and gynecomastia is increased. The occurrence of such side effect unfortunately will lead to poor medical compliance. So the aftercare units of forensic psychiatry should not deal only with the problem to avoid further commitment of crimes by judging the mere risk in any individual. The way to successful risk reduction in contrast should start at a much earlier stage in controlling negative effects on medical compliance.

Successfully applied polypharmacy will enable doctors to prescribe substances which will not cause dramatic side effects—and thus supporting the patient's ability to maintain the prescribed medication. For this reason, it might be necessary to judge the risk of introducing side effects before medication will be prescribed. As well, there should be an opportunity to change, if those side effects will occur in the course of the treatment. If we will not neglect such positive aspects of modern neuroleptic treatment regiments, it will be possible to use polypharmacy to reduce risk of discharged patients of forensic psychiatry by supporting their compliance. We know for sure, that many patients having been discharged from forensic psychiatry will recommit crimes due to their unability to show continuously cooperative behaviour. So we should try to support the ability to cooperate by using modern medication schemes and by avoiding side effect where ever possible.

At the same time and in the same way, this will be proceeded, it will be possible to control medical compliance by tests. Thus, there will be no negative effects on

medical compliance by prescribing modern neuroleptic substances—or combinations of orally administered substances [7].

6.3 Epidemiologic Aspects

The percentage of schizophrenic patients in forensic psychiatry has been steadily increasing during the past years and reaches now more than 50% of patients sent to our hospital by the court at present.

Most of these patients are treated due to very serious crimes committed such as murder, serious bodily harm, sexual offences, and arson. As well, multimorbidity of such patients is astonishingly high reaching more than 70%. Especially, they are suffering from additional drug addiction which will make medical treatment even more complex.

Average treatment time increased during previous years and reached meanwhile about 7 years, thus reflecting difficulties in performing risk reduction [8].

As unsufficient treatment of such individuals will result in the commitment of further serious crimes, we are due to establish treatment schemes to ensure reliable risk reduction to protect general society from this [9]. This includes modern medical strategies referring to polypharmacy, if needed, to enhance the prognosis of patients.

6.4 Combinations

In our hospital we found that the use of second-generation-antipsychotics (SGAs) was a common treatment strategy. These substances were often administered as oral medication (Fig. 6.1).

When those substances were combined, we usually found the combination of risperidone and quetiapine the most common one (Fig. 6.2). Thus, we were able to avoid serious side effects, such as extrapyramidal-motoric side effects or even tardive dyskinesia [10–13].

The impact of neuroleptic treatment, however, can be supported by using mood stabilizers as valproinate or carbamazepine in order to reduce aggression or impulsivity of forensic psychiatric patients, mostly used in combination with SGAs [4, 14].

6.5 Conclusions and Future Directions

There is evidence to be found that a high percentage of patients treated in general psychiatry will receive a combination therapy. In scientific articles there are various percentages indicated ranging from 20 to 50% [15–17]. Besides, we face an increasing use of combinations regarding antipsychotics and antidepressants or mood stabilizer [18].

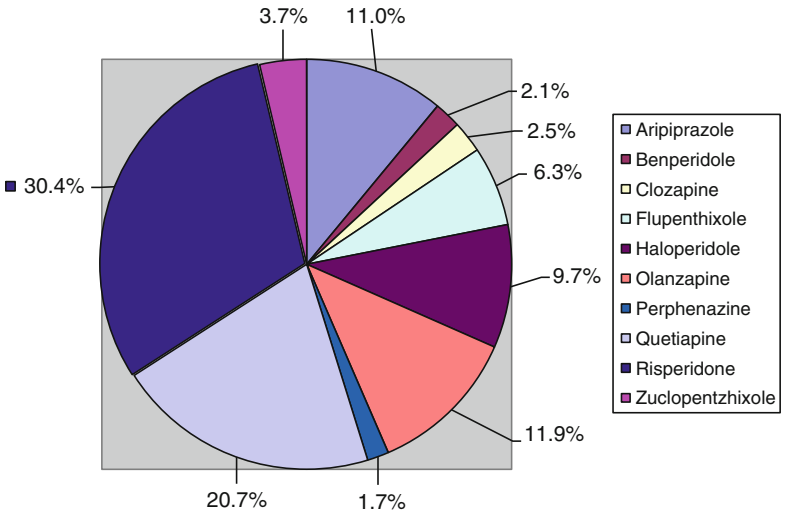

Fig. 6.1 Polypharmaceutic prescriptions of neuroleptic substances (N = 599) in the Central State Forensic Psychiatric Hospital of Saxony-Anhalt, Stendal, Germany in 2005–2007

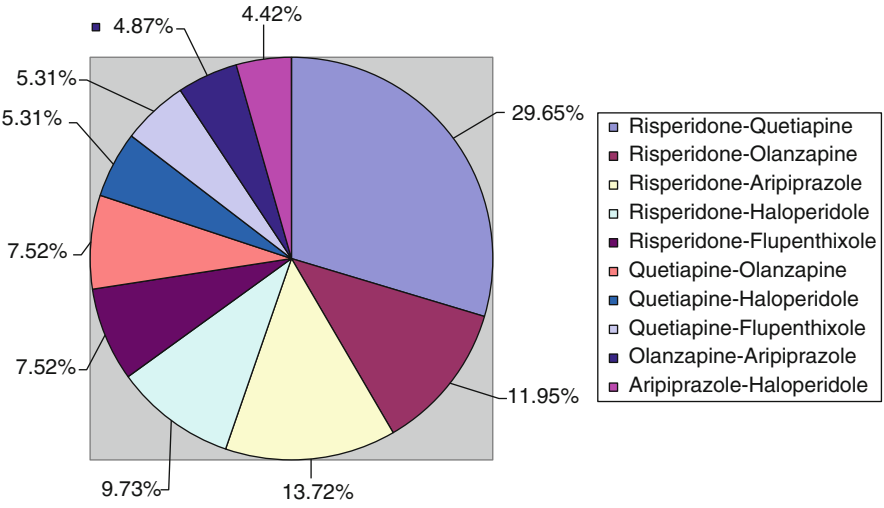

Fig. 6.2 Percentage of combinations regarding polypharmaceutic prescriptions of neuroleptic substances (N = 303) in the Central State Forensic Psychiatric Hospital of Saxony-Anhalt, Stendal, Germany in 2005–2007

In our hospital we found 20% out of the group of patients treated by antipsychotics to receive a combination therapy. These results are paralleled by the findings of Megna who reported 22.2% of patients to be administered a combination therapy in general psychiatry [7].

The use of neuroleptic substances now is extended to various diseases besides antipsychotic treatment and opens the door for highly interesting new medical therapy strategies which might be very promising in the field of forensic psychiatry as well [19–25]. Using such combination therapies in the field of neuroleptic treatment, we should be aware of the fact that it need to be of reliable benefit for the patients [26–29].

Finally, we should take into consideration that the process of resocialisation of forensic psychiatric patients is a most challenging task for the patients who were treated for many years, thus being detented in facilities which often did not allow them to cope with the needs of daily life. They will need to learn, how to come back to society and how to restore a common daily life. It is easy to understand that they will face numerous stereotypes—and every single redelinquency of any patient will enhance this process for all of them. We may conclude from this that patients will need medication schemes which will support their cognitive abilities and will not introduce negative symptoms as this will exclude them from society and will impair or even make resocialisation process nearly impossible [30].

Besides advanced therapeutic strategies in the field of psychopharmacotherapy, we will be due to install a system using modern diagnostic methods [31] to enable our patients to profit as much as possible from the treatment in forensic psychiatry for the sake of general society as only applying best treatment strategies can protect us from the commitment of further crimes after patients have been discharged.

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Part II
Augmentation Strategies

Chapter 7
Antipsychotic Treatment Within a Naturalistic Trial—How Are We Treating Schizophrenia Patients in the "Real-World"?

Rebecca Schennach, Michael Obermeier, Florian Seemüller, Daniela Krause, Richard Musil, Ilja Spellmann, Hans-Jürgen Möller, and Michael Riedel

Abstract Current treatment guidelines recommend antipsychotic monotherapy in schizophrenia patients. However, in contrast several researchers find a high prevalence of polypharmacy in schizophrenia patients either to enhance antipsychotic efficacy or when specific syndromes (e.g. anxiety, depression) are present. It has been reported that clinicians are aware of guideline recommendations, yet not basing their treatment decisions on them. But understanding treatment decisions in everyday care has important implications by mirroring the patients' needs, the clinicians' challenges which in turn can influence treatment guidelines, research projects and health politics. A way of better understanding such treatment decisions is by analyzing data of naturalistic trials. Therefore, in order to shed more light on the "real-world" prescribing pattern in patients suffering from a schizophrenia spectrum disorder the pharmacological profile of patients treated within a naturalistic multicenter study by the German Research Network on Schizophrenia was evaluated in terms of the antipsychotic compounds and treatment regimes applied. Two hundred fifty two patients were examined within the present analysis. At discharge, 81.7% of the patients received one antipsychotic compound with mainly atypical antipsychotics being prescribed. In terms of antipsychotic combination treatment, the concurrent

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M.S. Ritsner (ed.), *Polypharmacy in Psychiatry Practice, Volume I: Multiple Medication Use Strategies*, DOI 10.1007/978-94-007-5805-6_7,

prescription of an atypical and typical was the most frequent strategy. The most common prescribed compounds at discharge were risperidone, amisulpride, olanzapine and clozapine. Despite the high number of patients receiving only one antipsychotic, a considerable proportion of patients was also treated with psychotropic drugs besides antipsychotics (42% of the patients). 15.9% of the patients were additionally treated with antidepressants, 13.5% with anticholinergics, 13.1% with mood stabilizers, and 12.7% of the cases with tranquilizers/hypnotics. Generally, polypharmacy was associated with greater risk of side effects. On the background of the naturalistic design of this study we are not able to draw any causal conclusion in terms of the clinicians' rationale resulting in the observed prescribing profile. In agreement with other studies we found around 40% of the patients to be discharged receiving more than one psychotropic drug suggesting that in everyday care polypharmacy is believed to be effective. Future studies are warranted in order to help indentifying patients who might profit form polypharmaceutical treatment regimes on the background of gaining evidence that in the "real-world" monotherapy might not be effective enough in a considerable number of patients suffering from schizophrenia.

Keywords Schizophrenia • Antipsychotic treatment • Real-world • Polypharmacy

Abbreviations

APA	American Psychiatric Association
BMBF	German Federal Ministry of Education and Research
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
DDD	Defined daily doses
DGPPN	German Society of Psychiatry Psychotherapy and Nervous Diseases
FES	First-episode schizophrenia
IC-SOHO	Intercontinental Schizophrenia Outpatient Health Outcomes
NICE	National Institute for Health and Clinical Excellence
PORT	Schizophrenia Patient Outcomes Research Team
RCT	Randomized controlled trials
TMAP	Texas Medication Algorithm Project
UKU	Udvalg for Kliniske Undersogelser—Side Effect Rating Scale
WFSBP	World Federation of Societies of Biological Psychiatry

7.1 Introduction

The first-line psychopharmacological treatment of schizophrenia is the application of antipsychotic drugs [1], however, antipsychotics are only partially effective resulting in residual symptoms of schizophrenia in a number of patients [2]. As a consequence, clinicians either increase the antipsychotic dosage, switch the antipsychotic compound or start combination approaches and polypharmacy. Generally, combination of

substances from the same class or augmentation strategies can be differentiated. By combining e.g. two antipsychotics it is believed that antipsychotic efficacy is enhanced concurrently applying lower dosages for the single antipsychotics hoping to reduce the occurrence of side effects [3, 4]. In a cross-sectional study performed between 2004 and 2006, examining 200 community based patients with schizophrenia it was reported that 42.5% of the patients received more than one antipsychotic compounds and 70% of the patients were treated with an antipsychotic and another drug class leaving antipsychotic monotherapy to 25.5% [5]. The general prevalence of antipsychotic polypharmacy ranges between 10 and 30% with studies examining prescribing practices over time showing a trend towards an increasing use of antipsychotic polypharmacy [6, 7].

However, despite the widespread use of polypharmaceutical strategies, this strategy bears several drawbacks and its efficacy is not yet proven [8]. Miller and Craig mention several arguments against using a combination of antipsychotics in their discussion on pros and cons of antipsychotic polypharmacy such as the lack of evidence supporting this practice except for clozapine, an increased likelihood of problematic side effects as well as pharmacokinetic and pharmacodynamic interactions or greater costs [8]. Also, current treatment guidelines principally omit the prescription of more than one antipsychotic medication other than in combination with clozapine [9]. Only in the Texas Medication Algorithm Project (TMAP) dated from the year 2003, antipsychotic polypharmacy is listed as a last resort [10]. Stahl highlights this controversy by stating that using two antipsychotics at the same time is the most expensive, most widely practiced, yet least evidence-based therapeutic option in psychiatry today [11]. How come then, that despite guidelines recommending monotherapy polypharmacy is increasing?

Generally, it has been reported that clinicians quite frequently do not adhere to treatment guidelines [12, 13]. In a survey of psychiatrists on their attitude towards guidelines Healy et al. reported that most clinicians were aware of the guideline (in this case the TMAP), but did not consult on them in order to make their treatment decisions [14]. When trying to identify factors influencing the clinician's choice of treatment applied to schizophrenia patients within a prospective naturalistic study Edlinger et al. found that most illness-related and sociodemographic variables did not have any influence on the choice of medication, but that side effects largely affected the choice of antipsychotics [15].

Understanding what treatment decisions are made by clinicians in every-day care has important implications for the revision and development of further treatment guidelines, warranted research projects and also for health politics. A way of better understanding such treatment decisions is by analyzing data of naturalistic trials. As Sebastian et al. emphasize in their report of naturalistic studies of atypical antipsychotics in the treatment of schizophrenia, naturalistic studies are studies in clinical practice of drug effects and less rigorous in the design than controlled trials [16]. Due to the broad patient selection they address the "real-world" practice and patient issues [16]. Therefore, it can be assumed that on the background of shared decision making, results of naturalistic studies also mirror the patients' attitude towards the treatment recommended and applied which is essential when trying to understand treatment-related medical decisions.

Therefore, in order to shed more light on the "real-world" prescribing pattern in patients suffering from a schizophrenia spectrum disorder the pharmacological profile of patients treated within a naturalistic multicenter study by the German Research Network on Schizophrenia were evaluated in terms of the antipsychotic compounds and treatment regimes at the time-point of discharge. Within this evaluation, the "real-world" practice was set into comparison to current guideline recommendations.

7.2 Antipsychotic Treatment Within the "Real-World"—Results from a Naturalistic Study Performed by the Competence Network on Schizophrenia

More than 10 years ago the German Research Network on Schizophrenia has been funded as a network of about 25 interrelated research studies and projects by the German Federal Ministry of Education and Research (BMBF). The aim was bringing together the leading research institutions with qualified routine facilities to optimize preventive strategies, the acute- and long-term treatment, and rehabilitation of patients suffering from schizophrenia [17]. Within this network a multicenter observational, naturalistic follow-up programme was performed at 11 psychiatric university hospitals (Aachen, Berlin, Bonn, Cologne, Düsseldorf, Essen, Göttingen, Hamburg, Mainz, Munich, Tübingen) and three psychiatric district hospitals (Augsburg, Inn-Salzach-Klinikum, Isar-Amper-Klinikum Munich) between January 2001 and December 2004. Even though in terms of judging treatment benefits randomized controlled trials (RCT) are the "gold standard" [18], observational studies aiming to represent the "real" clinical situation are believed to be of high importance in complementing results of RCTs [19]. Therefore, present results on the naturalistic antipsychotic treatment of schizophrenia spectrum disorder patients provide the opportunity to follow the prescribed treatment and concurrently the course of the illness and outcome.

All inpatients with a DSM-IV diagnosis of a schizophrenia spectrum disorder aged between 18 and 65 years were eligible for inclusion. Exclusion criteria were an involuntary hospitalization, a head injury, a history of major medical illness and alcohol or drug dependency. Within this naturalistic study patients were treated following current treatment guidelines for schizophrenia spectrum disorder using defined daily doses for the respective drugs. Combination and augmentation strategies were applied when considered to be indicated and helpful by the clinician in charge. In the entire multicenter study 474 patients were enrolled, yet this analysis is based on 252 patients with completed psychopathological as well as medical and pharmacological data. Of these, 54% were male and 35% suffering from their first illness episode with a mean age of 35.7 years (±11.37) and a mean duration of illness of 6.8 years (±8.94). 82% were diagnosed with schizophrenia, 12% with schizoaffective disorder and 6% with a brief psychotic disorder. The mean duration of inpatient stay was 62.1 days (±44.56).

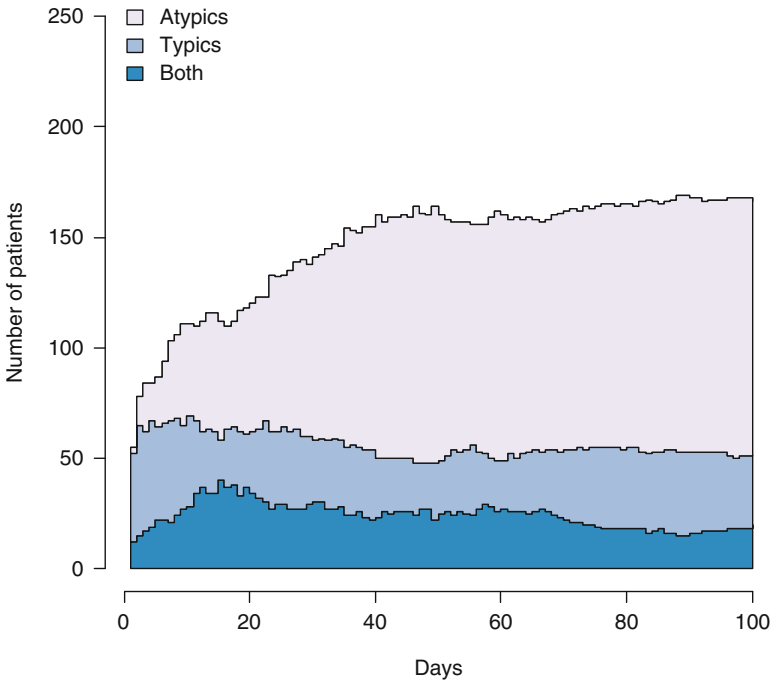

Fig. 7.1 Course of antipsychotic treatment during inpatient stay using LOCF

During the study patients were treated under naturalistic conditions as follows: 81% of the patients received typical antipsychotics, 80% of patients atypical antipsychotics and 64% of the patients were treated with typical as well as atypical compounds (Fig. 7.1). 79% of the patients were augmented with tranquilizers, 27% with antidepressants, 30% with anticholinergics, and 16% of the patients with mood stabilizers. In the following, the antipsychotic treatment regimes at discharge using monotherapy (one antipsychotic), polypharmacy (two or more antipsychotics) and augmentation strategies (at least one antipsychotic and another psychotropic drug) at the time-point of discharge will be displayed and discussed.

7.2.1 Antipsychotic Therapy at Discharge

At discharge, 82% of the patients received one antipsychotic, 18% two antipsychotics and less than 1% of the patients were treated with three antipsychotics in this study (Fig. 7.2) which is in agreement with current treatment guidelines [9]. The majority of patients on antipsychotic monotherapy received atypical antipsychotics (70%) (Fig. 7.3) and in terms of antipsychotic polypharmacy mainly atypical and typical antipsychotics were combined (10%) followed by combination treatment of atypical

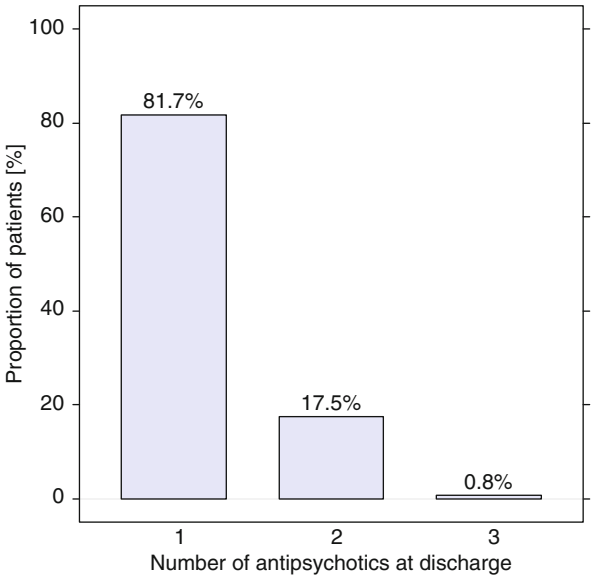

Fig. 7.2 Number of antipsychotics at discharge (not differentiating between atypical and typical compounds)

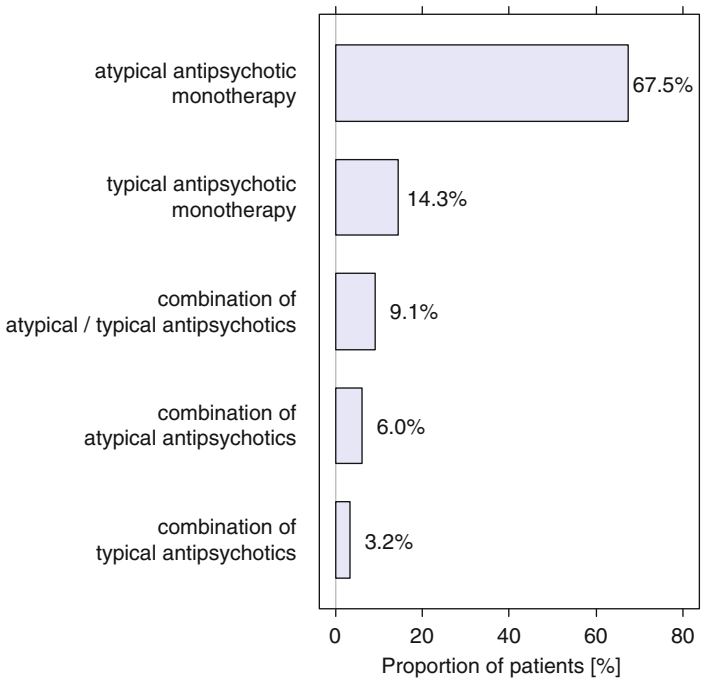

Fig. 7.3 Antipsychotic monotherapy and polypharmacy at discharge

compounds (6%). The mean antipsychotic dosage for the patients at discharge in defined daily doses was 1.80 (±4.94). Only one patient received depot antipsychotic treatment which is why depot antipsychotics are not separately listed in the following. Generally, when following current treatment guidelines oral administration of antipsychotics is preferred and depot or long-acting injectable antipsychotics should be chosen when it is the patient's preference or in case of adherence problems [20].

7.2.1.1 Atypical Versus Typical Antipsychotics in the Acute Naturalistic Treatment of Schizophrenia Spectrum Disorder

More than 80% of the patients were prescribed atypical antipsychotic treatment when discharged from the hospital after the acute treatment of psychosis which is in line with other observational reports [21, 22]. Generally, all treatment guidelines emphasize the importance of an individualized drug selection including the patient's prior treatment response and side effect experience, adherence level, relevant medication history, personal preferences, the drug's side effect profile, and the long-term treatment planning [23]. The guidelines' preference in terms of the class of antipsychotic compound is an area with discrepancies as discussed by Gaebel et al. in his recent review on schizophrenia treatment guidelines [20]. Following the "older" guidelines (e.g. American Psychiatric Association (APA), German Society of Psychiatry, Psychotherapy and Nervous Diseases (DGPPN)) the first-line drug choice is treatment with an atypical antipsychotic, whereas newer ones (National Institute for Health and Clinical Excellence (NICE), Schizophrenia Patient Outcomes Research Team (PORT)) do not distinguish between drug classes anymore, but recommend antipsychotics in general [20]. Also, in the very recent update of the guidelines on the acute treatment of schizophrenia by the World Federation of Societies of Biological Psychiatry (WFSBP) there is no general recommendation in terms of the antipsychotic class, finding the separation into atypical and typical antipsychotics considered to be arbitrary [24]. What should be kept in mind when discussing the choice of antipsychotic drug in the present study in the context of guideline suggestions is the time-point of when the study was performed, which was from 2001 to 2004. The revision of some of the newer guidelines has been performed years later on the background of evidence from studies comparing atypical and typical compounds finding no significant advantages for the atypical drugs concurrently identifying some serious side effects [1]. Besides, the considerable costs associated with the treatment of atypical antipsychotics is further fueling this critical debate [25, 26]. Surprisingly, also in first-episode schizophrenia (FES) patients the prescription of atypical compounds is not the first-line anymore when following the newer guidelines. This is in contrast to the positive clinical experiences that FES patients are more vulnerable for developing side effects and treatment with atypical compounds has consistently been associated with significantly less side effects compared to typical antipsychotics [27, 28]. In turn, the more

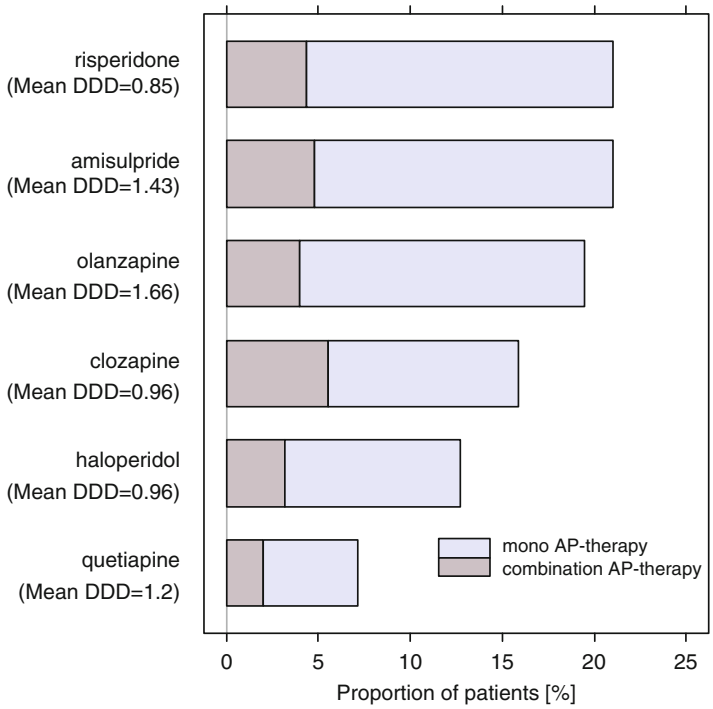

Fig. 7.4 The most frequently prescribed antipsychotic compounds and the proportion of monotherapy or antipsychotic polypharmacy at discharge (combination referring only to combination of antipsychotic compounds)

favorable tolerability profile resolves in a lower discontinuation rate and therefore in a lower risk for relapse.

The single antipsychotics prescribed most frequently in our study were risperidone and amisulpride, followed by olanzapine, clozapine and haloperidol (Fig. 7.4). As stated by Edlinger et al. in their 12 year observation on the pharmacological treatment of schizophrenia patients, risperidone was the most commonly prescribed novel antipsychotic in 1995, losing this position to clozapine and olanzapine [21]. Also, Diatta et al. found risperidone and olanzapine to be the most frequently prescribed atypical antipsychotics in their cross-sectional national survey in 2003 [29]. Interestingly, in the present study the second most often prescribed drug was not olanzapine as in many comparative studies, but amisulpride. Given that this was a multicenter trial the result cannot be explained by one center preferably prescribing this compound. Possibly, this phenomenon can rather be explained by health service properties as amisulpride is not licensed by the Food and Drug Administration so that comparative studies from the United States must differ in their prescribing patterns in terms of amisulpride. It has also been reported that there is little randomized evidence comparing amisulpride

with other second-generation antipsychotics possibly contributing to the limited evidence of its prescription pattern [30]. In a recent meta-analysis comparing atypical and typical compounds, amisulpride was found to be similarly efficacious than clozapine, olanzapine, and risperidone and all of these compounds were more efficacious in the overall symptom change than typical comparators [31]. In many comparative studies amisulpride is used as an adjunctive antipsychotic given its highly selective D2/D3 dopaminergic receptor antagonism [32], especially in combination with clozapine [33, 34]. Combining amisulpride to clozapine was in addition found to reduce clozapine-induced sialorrhea [35]. Another rather surprising finding in the present study was that even though most guidelines recommend treatment with atypical antipsychotics more than 10% of the patients were prescribed typical compounds with a considerable proportion of those patients receiving haloperidol monotherapy. Possibly these patients did well on haloperidol with only few or no side effects leaving them on this effective antipsychotic monotherapy.

Treatment guidelines provide detailed antipsychotic dosing tables, which can be very informative, but for some compounds the upper ranges are not clearly indicated. In the naturalistic study at hand the mean antipsychotic dosage at discharge was analysed using defined daily doses (DDD). The DDD is defined by the WHO Collaborating Centre for Drug Statistics and Methodology as the assumed average maintenance adult dose per day for the main indication of the respective drug. The mean DDD of the frequently prescribed antipsychotics were similar to the recommended mean DDD by the WHO. It has been reported that doses tend to increase with the duration of prescription which might reflect the development of increased tolerance with time [36], a result which cannot be commented on by the present study due to the fact that the antipsychotic treatment and dosage were examined only at discharge.

7.2.1.2 Mono- Versus Polypharmacy in the Acute Naturalistic Treatment of Schizophrenia Spectrum Disorder

In this study the majority of patients was discharged with one antipsychotic prescribed, and in turn the majority with an atypical antipsychotic monotherapy (Fig. 7.3) mirroring treatment guidelines at the time-point of when this study was performed on the background of a hypothesized broader pharmacological activity profile of atypical compounds [29]. In the patients receiving polypharmacy, a combination of an atypical and typical antipsychotic was most prevalent. Generally, in case of polypharmacy an atypical plus typical antipsychotic has been reported to be the most common combination [7, 37]. Some authors believe that the primary rationale for this strategy is that while switching from a typical to an atypical compound, the atypical agent is added to the typical drug with some patients being stuck on this combination [4].

In terms of the single antipsychotic compounds applied which are shown in Fig. 7.4, clozapine was the antipsychotic most often prescribed in combination with

another antipsychotic compound which is in agreement with other study reports [21]. The combination with clozapine is furthermore among the agents best studied in terms of polypharmaceutical treatment [38] and clozapine combination with other typical compounds is among the very few combination recommendations in case of non-response recommended by treatment guidelines [20]. On the background of reports stating that maximal antipsychotic efficacy occurs with D2 occupancy of 70% or greater and clozapine binding too loosely to achieve sustained D2 occupancy above 70% the combination of clozapine with a more "tightly bound" antipsychotic (e.g. haloperidol, risperidone) would be expected to increase D2 receptor occupancy [39]. Kapur et al. were able to show that the addition of haloperidol to clozapine increased D2 occupancy in five schizophrenia patients [40]. The authors also found elevated serum prolactin concentrations underlining previous literature reports linking polypharmacy to the presence of significantly more side effects compared to monotherapy [40]. In the present study, patients receiving polypharmacy were found to worsen in terms of side effects whereas the monotherapy patients improved (change in the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale [41] for monotherapy patients: −0.92 (±5.23); polypharmacy: 0.26 (±5.92) $p=0.0127$). However, a benefit from combining clozapine with another antipsychotic was not shown in all studies [42, 43]. In terms of the other single antipsychotic compounds, quetiapine is found to be more often prescribed in combination compared to e.g. olanzapine and risperidone with the lowest rate of polypharmacy for olanzapine [44, 45]. We only found a slightly lower rate of polypharmacy treatment at discharge for risperidone and a very low rate for quetiapine which might be explained by the generally rather low prescribing frequency of quetiapine possibly due to the fact that it was only licensed shortly before study initiation.

In terms of the frequency of polypharmacy, less than 20% were discharged with more than 1 antipsychotic prescribed which is somewhat in contrast to research reports stating that in up to 40% of schizophrenia patients multiple antipsychotics are prescribed [46]. Besides, some experts claim that "real-world" symptom-orientated strategies often result in polypharmacy [47] also challenging present results. However, it should be pointed out that the current time-point of antipsychotic treatment evaluation was the patients' discharge and does therefore not mirror the prescription profile during the acute treatment and hospitalization, but might rather reflect the patients' long-term treatment regimen. This hypothesis is underlined by the results in Fig. 7.1 on the course of antipsychotic treatment during hospitalization showing that the proportion of mono- and polypharmacy changes with considerably more patients receiving antipsychotic polypharmacy during inpatient stay compared to discharge. From a clinical point this phenomenon can be explained very well. In the acute treatment where a rapid response is warranted cross-titration when switching from one drug to another can be the best tolerated. Also, in inpatient settings, the adjunctive treatment with some typical antipsychotic compounds to atypical antipsychotics is viewed as temporarily useful in treating an acute exacerbation of schizophrenia [48].

In terms of comparative studies it is sometimes hard to distinguish whether short- or long-term treatment has been evaluated. For example, in a study by Diatta et al.

on the patterns and frequency of atypical antipsychotic prescribing in psychiatric medical centers the authors identified that 70% of the patients were treated with single-drug atypical antipsychotics yet not explicitly mentioning how many assessment time-points had been performed including renewal or first treatment contacts [29]. Ganguly et al. in turn particularly evaluated the use of antipsychotic polypharmacy based on the duration (long-term polypharmacy defined as lasting >2 months) in a retrospective study cohort of 31,435 patients with schizophrenia treated between 1998 and 2000 [49]. They found that 40% of the patients received polypharmacy in total, and 23% in the long-term again underlining that the use of polypharmacy seems to decrease in the long-term [49]. Similarly, Covell et al. characterized the prescribing pattern of outpatients within the public health system of Connecticut and found that during the 2-year observational period 35% of the patients had at least one prescription for concurrent antipsychotic medications with 10% of the patients receiving long-term polypharmacy [44]. The authors found a significant overlap between polypharmacy and medication changes suggesting that most of polypharmacy treatment was initiated during the course of a medication chance [44]. Still, also in terms of long-term treatment data on the use of antipsychotic polypharmacy vary. Faries et al. examined a large prospective naturalistic study of patients treated for schizophrenia during a 1-year period reporting that only a third (35.7%) of the patients were treated predominantly with monotherapy (>300 days) [50]. And when evaluating antipsychotic medication use patterns for individuals in schizophrenia Loosbrock et al. used data on outpatient antipsychotic medications as well as other health services during 1997 finding 52% of the patients to be prescribed only one antipsychotic, 13% switching medication, 7% receiving augmenting antipsychotic treatment, 2% being on more than one antipsychotic at baseline and 26% receiving no antipsychotics at all [51].

So what might be the rationale for long-term polypharmacy? Miller and Craig discuss several potential explanations such as that all reasonable monotherapies failed or have been refused by the patient, that a combination is used to partially deal with a particular problem of monotherapy or that polypharmacy has been started because of a monotherapy's lack of efficacy [8]. Yet adding a second drug was not found to improve psychosis symptoms beyond the expected 20–30% improvement in the "median" patient as Stahl cites in his editorial on antipsychotic polypharmacy despite the wish to reach for more efficacy [52]. He believes that the shift observed towards more polypharmacy might be due to the growing gap between evidence-based practice and practice-based evidence, at least for certain patient populations [52]. Generally, polypharmacy has been found to be associated with variables mirroring a more chronic course of schizophrenia such as a longer duration of illness or a higher number of prior inpatient treatment [6, 53]. Biancosino et al. concluded in their study on determinants of antipsychotic polypharmacy that clinicians reserve antipsychotic polypharmacy for severe, persistent and difficult-to-treat patients supporting Stahl's statement that clinicians caring for difficult patients find polypharmacy a beneficial strategy [6]. Still, recent evidence suggests that a satisfying amount of patients originally stable on polypharmacy can be successfully switched to monotherapy mirroring that long-term polypharmacy might not be

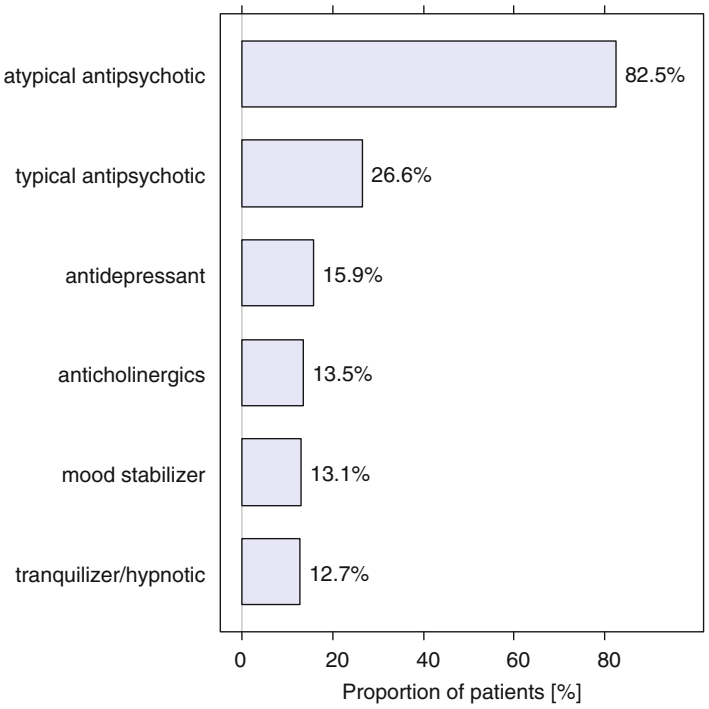

Fig. 7.5 Overview of the different psychotropic drug classes prescribed at discharge

indicated in that many patients [54]. Therefore, it seems necessary to determine who might profit from and should get polypharmacy more than demonizing polypharmacy. As a consequence, more studies identifying patient characteristics and subpopulations suitable for polypharmacy are desperately warranted so that expert consensus and treatment guidelines can give recommendations on antipsychotic polypharmacy strategies changing the paradigm back from practice-based evidence to evidence-based practice [52].

7.2.2 Antipsychotic Therapy and Adjunctive Treatment Strategies at Discharge

Within this naturalistic trial adjunctive treatment could be observed (Fig. 7.5) with antidepressants being prescribed in 15.9% of the patients, followed by anticholinergics (13.5%), mood stabilizers (13.1%) and tranquilizers/hypnotics (12.7%). When taking these adjunctive psychotropic drugs into account, the proportion of patients on an "antipsychotic monotherapy" decreases from the above mentioned 81% (considering only antipsychotics) to 58%. A detailed analyses of the different

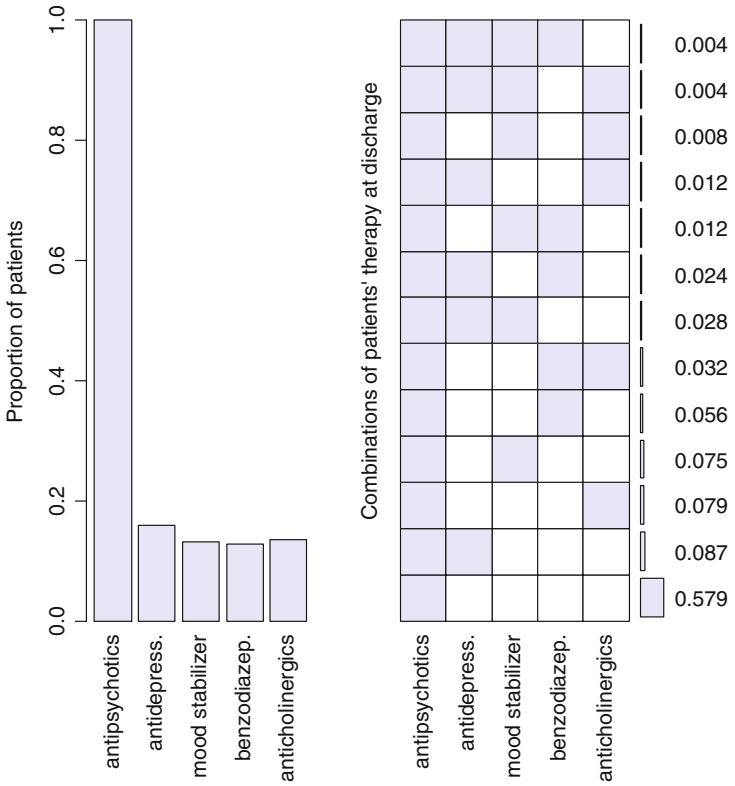

Fig. 7.6 Analysis of the different combination strategies at discharge

combination strategies is shown in Fig. 7.6. This suggests that patients are more likely prescribed an antipsychotic and an adjunctive psychotropic drug than a combination of two antipsychotics. Interestingly, this phenomenon is mirrored by results of the Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) study finding around 1/5 of the patients to be prescribed more than one antipsychotic, but almost 1/2 of the patients to receive augmentation treatment [55]. In some comparative studies the percentage of patients receiving a psychotropic drug besides an antipsychotic is even higher. Pickar et al., for example, examined the pharmacotherapy of 200 community based schizophrenia outpatients within a cross-sectional study finding 70% of the patients to receive an antipsychotic and another drug class with the most common drug class combination being antipsychotics and a mood stabilizer [5]. And a retrospective cohort study in schizophrenia patients lasting 1 year (1995) showed that almost 90% of the examined patients received a concomitant drug during the year [56]. As Bitter et al. state, concomitant psychotropic drugs such as antidepressants or mood stabilizer are frequently prescribed to augment antipsychotic response [55, 57, 58] or to address specific syndromes such

as depression or anxiety [59]. Within this article we are not able to provide detailed information on the rationale of the prescribing pattern and observational studies principally do not allow conclusions in terms of causality [60].

7.2.2.1 Antidepressants

The combination of an antipsychotic with an antidepressant has been discussed as a beneficial strategy in case of therapy resistance [61], but is most often performed and recommended when a comorbid depressive syndrome is present [62] or in case of negative symptoms. A very similar number of patients than in the present analysis on adjunctive antidepressants has been reported in the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) study (14.6%) with the patients receiving antidepressants being more likely to have a SCID diagnosis of comorbid depression and experiencing more depressive baseline symptoms [63]. In agreement, within the SOHO trial, antidepressant prescription was also linked to the presence of depressive symptoms at baseline [55]. However, similar to the ongoing debate about the benefit of antipsychotic polypharmacy, the application of adjunctive antidepressants is not as robust as one might expect due to its commonness [64, 65]. As Möller states in his review on the drug treatment of depressive symptoms in schizophrenia patients there are inconsistent results regarding the efficacy of antidepressants in this patient population, at least partially due to methodological problems, yet with the clinical experience of this treatment strategy being more positive [66]. Possibly this clinical experience might have been the underlying rationale of the observed antidepressant prescription profile in the present study.

7.2.2.2 Mood Stabilizers

The augmentation of antipsychotics with mood stabilizers is generally the most common add-on strategy in schizophrenia [47] and prevalence rates range up to almost 26% [5] indicating that in the present analysis a rather lower proportion of patients received mood stabilizers. The administration of mood stabilizers has been associated with a longer duration of illness which might be a marker of illness chronicity [67, 68] possibly explaining the presently found discrepant results. Because around one-third of the patients in this naturalistic sample had their first illness episode and a general mean duration of illness of less than 7 years suggesting if anything only little illness chronicity keeping clinicians possibly from prescribing adjunctive mood stabilizer. Besides, in a study on the adjunctive prescription of mood stabilizers in hospitalized schizophrenia patients Sim et al. found mood stabilizer use amongst others being significantly and independently associated with aggressive behaviour [67]. Significant aggressive behaviour was not documented for the proportion of patients in the present study which might be in relation to the fact that e.g. involuntary admissions or similar procedures associated with aggression were excluded from this study.

Similar to the prescription of antidepressants the clinical rationale of mood stabilizers is to enhance antipsychotic efficacy in patients with partial response or in cases of aggression or significant mood symptoms [69]. And also in agreement to the augmentation of antipsychotics with antidepressants, compelling evidence for the effect of adjunctive mood stabilizers in schizophrenia is still pending [70]. For the most commonly used mood stabilizer, it has been stated in a very recent revision of the treatment guidelines by the World Federation of Societies of Biological Psychiatry (WFSBP) that there is negative/no general evidence for the usage of carbamazepine and valproate in the general treatment of schizophrenia [24]. Both drugs but might have an effect when especially targeting aggression and hostility. Also, current evidence for lamotrigine is inconsistent and if anything, lithium might be effective in patients with mood symptoms or with schizoaffective patients [24].

7.2.2.3 Tranquilizer/Hypnotics

The proportion of patients being treated with additional tranquilizers/hypnotics at the time-point of discharge was 12.7% which is dramatically lower as during the acute inpatient time (79% as mentioned above). In principle, in the acute treatment tranquilizers are prescribed in case of e.g. anxiety, agitation, or catatonia. In a review on benzodiazepines in schizophrenia Gaillard et al. discussed that the use of benzodiazepines might permit a reduction in the antipsychotic dose and increase the plasma concentration of antipsychotics possibly acting on the mesoprefrontocortical regions where there are fewer dopaminergic auto receptors [71]. Jaspert and Ebert examined two patients with acute schizophrenia or schizo-affective psychosis being treated with benzodiazepine-monotherapy finding sufficient antipsychotic efficacy of the benzodiazepine treatment hypothesizing that the effects observed are probably caused by an activation of inhibitory GABA-ergic neurons by benzodiazepines. In the long-term treatment, the prescription of tranquilizers/hypnotics has been associated with sleeping disturbances often complained of by clinically stable schizophrenia patients on antipsychotic medication [72]. A very similar number of patients (13.7%) as in our own study received sedatives/hypnotics within the CATIE trial finding the prescription of these drugs to be predicted by higher depression baseline scores and SCID Axis I Anxiety Disorders [63]. Both, depression and anxiety have been consistently linked to sleeping disturbances letting Chakos et al. hypothesize that insomnia might be a residual symptom of these disorders possibly mirroring a trait marker for these conditions [63].

7.2.2.4 Anticholinergics

Several combination strategies in the treatment of schizophrenia are supposed to relieve the patient from drug-induced side effects and it is a very established and efficacious strategy to administer anticholinergic agents when extrapyramidal

symptoms are present [73]. A rather small number of patients (13.5%) received anticholinergic agents in the present naturalistic trial which might be due to the fact that the majority of patients received atypical antipsychotics which are known to cause considerably less extrapyramidal side effects [74, 75] in turn reducing the need of anticholinergics. Besides, antipsychotic polypharmacy has been associated with the administration of anticholinergic medication [76, 77], and since the majority of the patients in the present study received antipsychotic monotherapy the prescription of anticholinergics seems to be less required. On the background of study reports finding an association between peripherally measured anticholinergic drug and impaired learning during cognitive remediation [78] Gallego et al. critically question the benefits of treating patients with polypharmacy above the threshold for extrapyramidal symptoms resulting in the application of anticholingerics [79].

7.3 Conclusions and Future Directions

In the present study the antipsychotic prescribing pattern of patients discharged from hospital within a naturalistic treatment trial was examined. A considerably high number of patients received antipsychotic monotherapy with an atypical antipsychotic mirroring most of the established guideline recommendations. However, the adjunctive prescription of another drug class besides antipsychotics was common with antidepressants being the most frequent augmentation strategy followed by anticholinergics, mood stabilizers and tranquilizers/hypnotics. This suggests that residual syndromes might persist after the acute treatment in which the prescription of specific compounds becomes mandatory. Also, such augmentation strategies might have been started to enhance antipsychotic efficacy or both. Anyhow, present results suggest that in clinical daily practice many patients cannot sufficiently be treated with antipsychotic monotherapy asking for future trials helping to identify suitable patients that might profit from polypharmaceutical strategies. This might help to establish the best fitting treatment for the individual patients earlier in the course of treatment possibly positively influencing the course of treatment and with it the course and outcome of schizophrenia.

Acknowledgements The study was performed within the framework of the German Research Network on Schizophrenia which is funded by the German Federal Ministry for Education and research BMBF (grant 01 GI 0233). The authors thank all those who were involved in the study, especially the colleagues at the psychiatric hospitals the study was conducted at.

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Chapter 8
A Multi-Target Drug Treatment in Schizophrenia and Schizoaffective Disorder Using Adjunctive Agents with Non-D_2 Mechanisms of Action

Michael S. Ritsner

Abstract Pharmacologic actions to reduce neurotransmission through the D_2 receptor have been the only proven therapeutic mechanism for schizophrenia (SZ) and schizoaffective (SA) disorder. However, in view of the multifactorial genesis and pathogenesis of these psychoses, it is unlikely that any antipsychotic drug would work equally well against all symptoms and behavioral disturbances. The absence of a single therapeutic target for SZ/SA disorder has prompted the use of *polypharmacy strategies* including *multi-target pharmacotherapy*, consisting of various *add-on medications and supplements*. Multi-target polypharmacy strategies include the off-label prescription of adjunctive agents such as antidepressants, mood stabilizers, and benzodiazepines already in use, and novel potential adjunctive agents (newer molecules or compounds) based on several non-dopaminergic hypotheses (serotonergic, noradrenergic, glutamatergic, gamma-aminobutyric acid related, and cholinergic neurotransmission, neuroprotective mechanisms and brain neuroplasticity). This chapter is an overview of the current state of evidence for the augmentation of antipsychotics with antidepressants, lithium, antiepileptic agents, benzodiazepines, and new molecules and compounds for the treatment of people with SZ/SA disorder with a special focus on research data published within the past 5–7 years. Using these agents for the augmentation of antipsychotics based on a *multi-target drug treatment approach* entails the combination of two or more drugs/agents with different mechanisms of action on the central nervous system in an attempt to enhance efficacy.

Keywords Augmentation • Antidepressants • Mood stabilizers • Lithium • Antiepileptic drugs • Benzodiazepines • Schizophrenia • Schizoaffective disorder • Hormones • Supplements

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M.S. Ritsner (ed.), *Polypharmacy in Psychiatry Practice, Volume I: Multiple Medication Use Strategies*, DOI 10.1007/978-94-007-5805-6_8,

Abbreviations

AMPA	DL-α-NH_2-2,3-dihydro-5-methyl-3-oxo-4-isoxazolepropanoic acid
BDNF	Brain-derived neurotrophic factor
BZD	Benzodiazepines
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CNS	Central nervous system
COX	Cyclo-oxygenase
DA	Dopamine
DHEA	Dehydroepiandrosterone
DHEA(S)	Both DHEA and DHEAS
DHEAS	Dehydroepiandrosterone sulfate
EPA	Eicosapentaenoic acid
FGAs	First generation antipsychotics
GABA	γ-amino-butyric acid
GSK	Glycogen synthase kinase
HPA	Hypothalamic-pituitary-adrenal axis
NMDA	*N*-methyl-D-aspartate
PANSS	Positive and Negative Symptom Scale
PREG	Pregnenolone
PREG(S)	Both PREG and PREGS
PREG(S)/DHEA(S)	Both PREG(S) and DHEA(S)
PREGS	Pregnenolone sulfate
SAMe	S-adenosyl L-methionine
SANS	Scale for the Assessment of Negative Symptoms
SGAs	Second generation antipsychotics
SSRI	Selective serotonin re-uptake inhibitor
SZ/SA	Schizophrenia and schizoaffective disorder

8.1 Introduction

Schizophrenia (SZ) and schizoaffective (SA) disorder are pervasive and debilitating conditions. The biological mechanisms underlying these disorders are not fully understood.

The *dopamine hypothesis* states that there is over activity in the dopamine systems. The hypothesis stems from the finding that all effective anti-psychotic medications block dopamine brain receptors, and that their potency correlates with the strength of binding to dopamine D_2 receptors in the brain. However, the idea that the symptoms of psychosis are caused by the overactivity of dopamine is not supported by currently available evidence [1].

Dopamine (DA) D_2 receptor antagonism is a unifying property of all antipsychotic drugs, while often effective at ameliorating psychosis, these drugs are largely

ineffective in the treatment of negative and cognitive symptoms. In recent years, a variety of new experimental pharmacological approaches have emerged, including compounds that act on targets other than the dopamine D_2 receptor. However, there is still an ongoing debate as to whether drugs selective for singe molecular targets (that is, 'magic bullets') or drugs selectively non-selective for several molecular targets (that is, 'magic shotguns') will lead to more effective new medications for schizophrenia [2]. This has prompted *multifactorial approaches* to the development of new therapeutics, such as polypharmacy and an augmentative strategy known as "*intramolecular polypharmacy*", in which a single drug has the capacity to affect multiple receptor types [3]. These multi-target agents (also called '*multifunctional drugs*' [4]) with more than one putative therapeutic mechanism of action may lead to the development of selective drugs for the treatment of SZ/SA disorder.

The concurrent use of more than one drug to treat syndromes and diseases is common in internal medicine [5, 6]. Wald and Law [7] postulated that using a combination of well known, inexpensive medications in one pill (the "*polypill*") would be a particularly effective treatment against cardiovascular disease. They presented a statistical model which suggested that widespread use of the polypill could reduce mortality due to heart disease and strokes by up to 80%. The treatment is potentially inexpensive, with few side effects (in perhaps 10–15% of recipients) and the research was based on data from many trials relating to the individual components. Increasingly, combined antihypertensive agents are being used in practice to enhance control and improve compliance. In some cases, a combination of relatively low doses has resulted in superior efficacy not only to the components administered alone but to higher doses of the individual components [8]. Systematic reviews and meta-analyses have confirmed that there is evidence that low-dose combination products could provide equal or enhanced efficacy with a potentially reduced adverse effect burden [9]. Mahmud and Feely [10] report a prospective study using a capsule containing four different antihypertensive drug classes, each given in a dose one quarter of the usual dose of the preparation: patients received amlodipine (5 mg), atenolol (50 mg), bendroflumethiazide (2.5 mg), and captopril (50 mg twice daily) or a capsule containing each of the four above at one-quarter dosage in a parallel group design for 4 weeks. This randomized trial indicates that the capsule containing four agents of different classes at a quarter of the usual dose was more effective at lowering blood pressure than any of the individual drugs alone in the usual dose. There is clearly a lot of work to be done before any product could be registered for use in hypertension, but this preliminary report confirms the theoretical basis of the polypill concept and suggests that other multiple drug therapy approaches using low doses may be able to realize benefits at least as great as those predicted from the controlled trials [5]. Thus, a range of combination therapies utilizing medications with differing mechanisms of action have been shown to provide superior blood pressure-lowering efficacy than monotherapy with individual components.

Although the international guidelines recommend antipsychotic monotherapy as the treatment of choice, many of SZ/SA patients receive two or more antipsychotics in clinical practice (antipsychotic polypharmacy). The term "combination" includes virtually all the ways in which one medication may be added to another. The other commonly used

terms are "augmentation" which implies an additive effect of a second medicine added to the initial prescribed drug, an "add on" which implies adding on to an existing, possibly effective treatment which, for one reason or another, cannot or should not be stopped [11]. Experts recommend polypharmacy in a few special clinical situations [12]:

- For augmentation when a patient fails to respond to adequate antipsychotic trials,
- In some instances of failed cross-taper of antipsychotics, and
- Adding an FGA to a SGA for agitation during acute treatment of psychosis.

Interestingly, a myelin-centered model of human brain function suggests that widely used psychotropic treatments share complex signaling pathways such as Akt and glycogen synthase kinase-3 (GSK_3) that affect myelination, its plasticity, and repair [13, 14]. Independent lines of research involving biochemical and behavioral approaches in normal and/or genetically modified mice provide converging evidence for an involvement of the signaling molecules Akt and GSK_3 in the regulation of behavior by DA and 5-HT (5-hydroxytryptamine, serotonin) neurotransmissions [15]. It may also provide a link between the action of these neurotransmitters and gene products, such as those disrupted in schizophrenia one (DISC1) and neuregulin (NRG), that are associated with increased risk for mental disorders [16]. These signaling pathways respond to neurotransmitters, neurotrophins, hormones, and nutrition, underlie intricate neuroglial communications, and may substantially contribute to the mechanisms of action and wide spectra of efficacy of current therapeutics by promoting myelination [17].

The trend of antipsychotic polypharmacy has increased considerably, especially since the introduction of second generation antipsychotics (SGAs) [11, 12]. Pickar and associates [18] reported that only 25% of 200 schizophrenia patients are treated with antipsychotics alone. Nielsen and co-authors [19] using a cohort study of newly diagnosed patients with schizophrenia in Denmark (n = 13,600) reported that between 1996 and 2005 there was increased use and dosing of antipsychotics and antidepressants, as well as more antipsychotic polypharmacy. In contrast, antipsychotic monotherapy of Japanese inpatients with schizophrenia increased from 31.6% in 2007 to 33.8% in 2009 [20].

There are current updates and critical reviews of the pharmacology and clinical profiles of current antipsychotic drugs and preparations that act on novel targets and have the potential to be therapeutic agents in the future [2, 21–26]. This chapter is an overview the current state of evidence of the augmentation of antipsychotics with antidepressants, lithium, antiepileptic agents, benzodiazepines, and new molecules and compounds for the treatment of SZ/SA disorder (Fig. 8.1).

8.2 A Multi-Target Drug Treatment

The aim of augmenting antipsychotics, *multi-target drug treatment approach,* is to combine two or more drugs/agents with different mechanisms of action on the central nervous system in an attempt to enhance efficacy and/or tolerability. There are

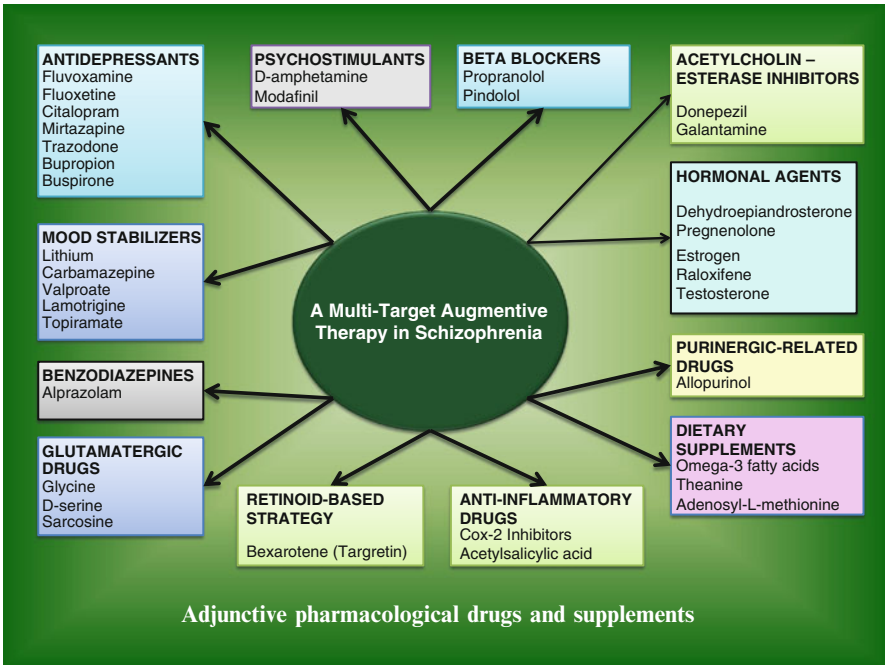

Fig. 8.1 Adjunctive pharmacological drugs and supplements (© M.S. Ritsner (2012) and used by permission)

several possible rationales for a *multi-target drug treatment approach* that is more likely to alleviate core and comorbid symptoms.

- The multifactorial genesis, genetic heterogeneity and pathogenesis of schizophrenia and other functional psychoses/disorders cannot be attributed to any single cause, see, e.g. [27, 28], and Fig. 8.2 [40].
- In light of the clinical polymorphism of these conditions, it is unlikely that any antipsychotic drug would work equally well against positive, negative, and mood symptoms, cognitive, functional and quality of life deficits, and against behavioral disturbances in all patients. Indeed, although clinical guidelines recommend the routine use of a single antipsychotic drug in a standard dose [41, 42], prescriptions for high-dose and combined antipsychotics are common in clinical practice [43].
- Poor treatment response of patients with SZ/SA is a compelling clinical problem. In addition to the poor response of about one-third of SZ/SA patients [44], antipsychotic monotherapy is often inadequate in the management of particularly challenging symptoms such as negative and cognitive disturbances, affective instability, anxiety or insomnia, persistent aggression, functional and quality of life impairments.

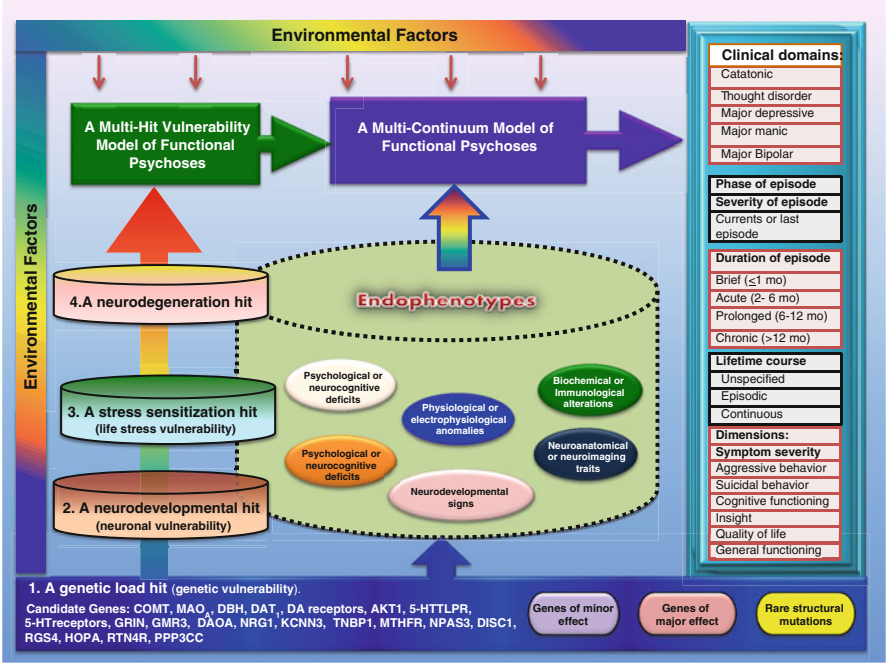

Fig. 8.2 Multidimensional continuum model of functional psychoses for research purposes (Version 1.1) (© M.S. Ritsner [26] and used by permission)

- In addition to dopaminergic, serotonergic, noradrenergic, and glutamatergic pathways, γ-amino-butyric acid (GABA) and acetylcholine dysregulation have also been implicated in the pathogenesis of SZ/SA disorder [45–48].
- Multiple lines of evidence have linked degenerative abnormalities in both post-mortem and brain imaging studies to the pathophysiology of SZ/SA disorder [49]. These changes include ventricle enlargement, volumetric reduction, and atrophy or loss of neurons and glial cells in selective cortical and limbic brain regions [25, 26, 50, 51].
- *Neurotrophic effects* can be considered a therapeutic strategy intended to augment proliferation, differentiation, growth, and regeneration, whereas *neuroprotective effects* slow or halt the progression of neuronal atrophy or cell death following the onset of disease or clinical decline [52]. Available data suggest that psychotropic treatment needs to target brain protective mechanisms [14, 29].
- Antipsychotic agents might be enhanced by co-administration with antidepressants, mood stabilizers, benzodiazepines, and others compounds that act via other, non-dopaminergic mechanisms (e.g., serotonergic, glutamatergic, adrenergic receptors, and others) [23–26].

Thus, elucidation of the contribution of multiple signaling pathways to the action of psychotropic drugs might lead to more efficient *multi-target drug* therapeutics for

SZ/SA disorder, especially for the associated cognitive impairments, negative and mood symptoms.

8.3 Augmentation in the "Real World"

Adjunctive pharmacological agents are extensively used in the treatment of patients with schizophrenia. There are two types of adjunctive agents:

- Off-label prescription of adjunctive agents, such as antidepressants, lithium, antiepileptic drugs, and benzodiazepines that are already in use; and
- Newer molecules or compounds based on several non-dopaminergic hypotheses that are currently being examined.

There are established practices in "real world" pharmacotherapy. Pickar et al. [18] reported that 70% of 200 schizophrenia patients received an antipsychotic together with medication from another drug class: the most common drug class combinations were antipsychotics and mood stabilizers. A total of 42.5% of patients received more than one antipsychotic drug.

Cascade et al. [53] found that 43% of patients receive one additional class to supplement their antipsychotic medication, and 10% of patients are prescribed two or more classes of drugs in addition to an antipsychotic agent. The most common classes used to supplement antipsychotic medications in the management of schizophrenia include antidepressants (28%), mood stabilizers (18%), sleep aids (5%), and agents to treat extrapyramidal symptoms (7%), according to Dussias et al. [54]—20%, 15%, 7%, and 6%, respectively.

Längle et al. [55] evaluated the effects of different types of psychotropic polypharmacy on clinical outcomes and quality of life in 374 patients with SZ/SA disorder in routine care before discharge and after 6, 12, 18, and 24 months. At baseline 22% of the participants received antipsychotic monotherapy (quetiapine, olanzapine, or risperidone), 20% received more than one antipsychotic drug, 16% received antipsychotics combined with antidepressants, 16% antipsychotics plus benzodiazepines, 11.5% had antipsychotics and mood stabilizers, and 16% received psychotropic drugs from three or more subclasses.

Shinfuku et al. [56] based on a systematic chart review of 300 patients (100 of whom were psychotropic-free prior to their first visit) during a 2-year period, reported that polypharmacy occurred in 79% of the patients, with 2-year rates of the use of hypnotics (56.7%), benzodiazepine derivative anxiolytics (49.7%), anticholinergic drugs (38.3%), antidepressants (21.3%), and mood stabilizers (14.0%). *Once polypharmacy had started, it was continued until their final visit in >70% of the patients*. Himelhoch et al. [57] estimated the receipt of prevalent and incident antidepressant medications in the fiscal year 2007 among 2,412 veterans who received treatment for schizophrenia. They found that 37.4% also received an antidepressant prescription.

In order to determine the frequency of off-label prescriptions for mood stabilizers a cross-sectional survey of inpatients aged 18–65 years at St Andrew's Hospital

(Northampton, UK) was carried out [58]. Thirty percent (75/249) patients were administered one or more *mood stabilizers*, of which 71 were off-label. Sim et al. [59] examined the frequency of mood-stabilizer use and its clinical correlates among hospitalized patients diagnosed with schizophrenia in 2001–2008 in nine Asian regions (China, Hong Kong, India, Korea, Japan, Malaysia, Taiwan, Thailand, and Singapore). Overall, mood stabilizers were given to 20.4% ($n = 1{,}377/6{,}761$) of hospitalized schizophrenia patients, with increased usage over time. Xiang et al. [60] surveyed the use of adjunctive *mood stabilizers* in older Asian schizophrenia patients aged 55 years or more that were extracted from a database that included 1,452 patients from nine Asian countries and territories. The frequency of prescription of *mood stabilizers* was 26.7% in the pooled sample, with 25.5% in 2001, 26.9% in 2004 and 27.7% in 2009. Multiple logistic regression analysis of the whole sample revealed that patients on *mood stabilizers* were younger and more likely to be men and to have extrapyramidal side effects (EPS) and a longer duration of illness.

Guidelines for the prescription of benzodiazepines (BZD) recommend that their use be limited to the short-term relief of severe anxiety or insomnia. However, clinical experience suggests that in psychiatry these drugs might be more broadly prescribed. Haw and Stubbs [61] investigated benzodiazepine prescribing in a specialist UK psychiatric hospital using a structured interview with consultant psychiatrists. Of 412 inpatients, 77 (18.7%) received 90 BZD prescriptions for psychiatric indications. Most prescriptions were for anxiety (45/90; 50.0%), aggression (23/90; 25.6%) and agitation (13/90; 14.4%). Use was commonest for acquired brain injury, schizophrenia (26/77; 33.8%) and personality disorders. Much usage was chronic (only 4.4% prescriptions had been initiated within the previous 4 weeks) and off-label (94.4%). In psychiatry BZD are quite frequently used in the management of a number of groups of difficult-to-treat patients.

The frequency of BZD prescription in nine Asian countries and territories was 20.7% in the pooled sample, with 20.2% in 2001, 18.4% in 2004 and 23.1% in 2009 (the sample included 1,452 hospitalized schizophrenia patients aged 55 years or more). Compared to patients in China, their Korean and Singaporean counterparts were more likely to be on BZD [60]. Use of psychotropic medications (antidepressant, anxiolytic, and sedative/hypnotics) by 1,449 participants in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study was documented at each study visit: initiation of new adjunctive agents post baseline period was moderately frequent, 14.6% of patients received antidepressants, 13.7% received anxiolytics, and 11.2% received sedative/hypnotics [62].

Thus, substantial proportions of patients with SZ/SA disorder do not achieve acceptable levels of response with antipsychotic therapy alone, which commonly leads clinical psychiatrists to use augmentive agents. Differences in the use of adjunctive medications may be due to true differences in the frequency of ancillary symptom complexes. For instance, among patients with recognized ancillary symptom complexes, black patients may also be less likely than white patients to receive treatment. This may be due to racial differences in accessibility of mental health care, physician perceptions of patients, and patient beliefs and preferences [63]. Further research is needed to clarify the underlying biases and behaviors that affect use of adjunctive medications among patients with schizophrenia.

8.4 Antidepressants

Depressive symptoms in patients with schizophrenia may be secondary to negative symptoms [64], medications, or neuroleptic-induced movement disorders [65], or a core component of various stages of SZ/SA disorder [66, 67]. At the same time, depressive symptoms are common in older patients with schizophrenia [68]. The most prevalent symptoms cut across several domains of the depressive syndrome: psychological (e.g., depressed mood, depressed appearance, psychic anxiety); cognitive (e.g., guilt, hopelessness, self depreciation, loss of insight); somatic (insomnia, anorexia, loss of libido, somatic anxiety); psychomotor (e.g., retardation and agitation) and functional (diminished work and activities) [69].

Lako et al. [70] investigated the prescribing patterns of antidepressants in relation to the course of depressive symptoms in a cohort of 214 Dutch patients with psychotic disorder patients. Depressive symptoms were prevalent among 43% of the patients. Antidepressants were prescribed for 40% of the patients and the majority (83%) continued this therapy after 1 year.

8.4.1 Mechanism of Action

A common mechanism of action of antidepressant drugs has not been found. Antidepressants are usually classified according to structure (e.g., tricyclic antidepressants, TCAs) or function (e.g., monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, SSRIs). However, it may be more useful to classify them according to the acute pharmacologic effects that are presumed to trigger behavioral improvement. If this is done, the antidepressants can be grouped in four categories [71]:

- Selective blockade of norepinephrine reuptake: desipramine, nortriptyline, amoxapine, maprotiline reboxetine
- Selective blockade of serotonin reuptake (SSRIs): citalopram, fluoxetine, paroxetine, sertraline
- Nonselective enhancement of norepinephrine and 5-HT transmission: imipramine, amitriptyline, phenelzine, tranylcypromine, venlafaxine, mirtazapine
- Unknown potent stimulatory effects on norepinephrine and 5-HT: trimipramine, bupropion, nefazodone, trazodone

The molecular mechanisms underlying the augmentation are unclear. There is increasing evidence suggesting that symptoms of depression and anxiety may be associated with serotonergic dysfunction in schizophrenic patients; significant progress has been made, pointing to some candidate systems which may be involved in SSRI-antipsychotic synergism. While as yet limited in scope, the evidence suggests definable molecular targets which may be implicated in drug development based on SSRI-antipsychotic synergistic actions [72]. Laboratory investigations into the mechanism of this synergism showed that co-administration of SSRIs and

antipsychotics produces changes in the $GABA_A$ receptor and related systems, which differ from the effects of each drug alone. SSRI augmentation of antipsychotics alters the expression of the $GABA_A$ receptor and related genes in peripheral mononuclear cells of schizophrenia patients [73].

8.4.2 Clinical Studies

The antidepressants that are most frequently assessed in clinical trials are those that are specifically targeted to treat persistent negative symptoms [30, 74–78].

8.4.2.1 Fluvoxamine

Published reports of clinical trials revealed that fluvoxamine improved negative symptoms and cognitive deficits in treated chronic schizophrenia [79–81]. Fluvoxamine at dosages up to 100 mg/day is not associated with clinically significant changes in plasma risperidone concentrations. However, higher doses of fluvoxamine may elevate plasma levels. Fluvoxamine increases plasma haloperidol and risperidone concentrations in a dose-dependent manner [82, 83].

8.4.2.2 Fluoxetine

Current evidence indicates that fluoxetine can ameliorate primary negative symptoms in chronic schizophrenic patients treated with first-generation antipsychotics [84]. The combination is well-tolerated, although as antipsychotic drug concentrations may rise, close monitoring of drug doses and possibly drug concentrations is needed.

8.4.2.3 Citalopram

There is contradictory evidence that add-on citalopram to antipsychotic drugs may improve the psychopathological and/or cognitive symptoms in schizophrenia [85–87]. Kasckow et al. [86] conducted a 10-week single-blind trial of citalopram (20–40 mg/day) vs no citalopram augmentation in 19 middle-aged and elderly patients with schizophrenia hospitalized for more than six of the past 12 months. Patients in both groups improved on positive and negative symptoms, but the citalopram group revealed significantly greater improvement in the Hamilton Depression Rating (HAM-D) scale and Clinical Global Impression Scale scores than the control group. Citalopram (40 mg/d) adjunctive treatment to atypical antipsychotics produced no significant cognitive improvement in patients with schizophrenia after 12 weeks of treatment [87]. Citalopram augmentation of antipsychotic treatment in middle aged and older patients with schizophrenia and subsyndromal depression

appears to improve social and mental health functioning as well as quality of life. Among 55 participants with schizophrenia or schizoaffective disorder and baseline suicidal ideation, citalopram reduced suicidal ideation, especially in those whose depressive symptoms responded to treatment [88]. Iancu et al. [75] evaluated the efficacy of escitalopram for the treatment of negative symptoms in patients with schizophrenia. Under double-blind conditions, 40 patients with chronic schizophrenia were randomized to add-on treatment with escitalopram (up to 20 mg) or placebo for 10 weeks. Escitalopram was well tolerated, but was not more effective than placebo in the treatment of negative symptoms in patients with chronic schizophrenia. A double-blind, crossover study demonstrated *anti-aggressive effects* of adjunctive citalopram in chronic schizophrenia [89].

8.4.2.4 Mirtazapine

Evidence that the combination of mirtazapine (remeron), and antipsychotic drugs may improve negative and/or cognitive symptoms in schizophrenia is contradictory [90–98]. Berk et al. [92] using a 6 week, double-blind design, recruited schizophrenia patients that were treated with SGAs plus mirtazapine (30 mg/day) or placebo, and did not find significant differences between mirtazapine and placebo treated participants in Positive and Negative Syndrome Scale (PANSS) scores or any of the secondary outcome measures. Abbasi et al. [93] investigated the effect of mirtazapine (30 mg/day) added to risperidone (6 mg/day) as augmentation therapy in 40 inpatients during the active phase of chronic schizophrenia and prominent negative symptoms in a double-blind randomized clinical trial. The mirtazapine group showed significantly greater improvement in negative symptoms and PANSS total scores over the 8-week trial. Mirtazapine was well tolerated and no clinically important side effects were observed. Other clinical trials suggest that augmentation with mirtazapine can effectively improve both negative and/or cognitive symptoms of schizophrenia [96, 97].

Overall, six randomized, double-blind, placebo-controlled trials assessed add-on mirtazapine to SGAs (four trials), and to first generation antipsychotics (FGAs, two trials). Five of the six trials supported the use of mirtazapine for negative symptoms of schizophrenia [98]. An open-label extension phase to a randomized controlled trial showed that mirtazapine continued to produce significant improvement in negative symptoms over a longer duration of time, when added to FGAs [95]. Mirtazapine appears to be well tolerated and associated with few drug interactions. Although adjunct mirtazapine to antipsychotics has been shown to be effective at doses of 30 mg/day in most of the trials, limitations of these studies include short study duration and small sample sizes.

8.4.2.5 Trazodone

Trazodone used in conjunction with neuroleptics, mildly reduced the severity of negative symptoms in residual schizophrenia (47 patients with an average age of

60 years) and did not exacerbate florid psychosis during a 6-week trial [99]. This conclusion was confirmed by Hayashi et al. [100] in double-blind, placebo-controlled small study (n = 12) with the dose gradually increased from trazodone 50 mg/day to 200 mg/day. Results also indicated a possible beneficial effect of trazodone in the treatment of tardive dyskinesia.

8.4.2.6 Bupropion

Bupropion affects the uptake of the neurotransmitters norepinephrine and dopamine. Englisch et al. [101] reported on a consecutive series of depressed patients with psychotic spectrum lifetime diagnoses who received bupropion extended release for a period of 6 weeks in addition to stable doses of antipsychotic agents. All patients experienced significant improvements of their major depressive episodes. Psychotic positive symptoms remained stably absent, and both negative symptoms and global psychopathology considerably improved. The treatment was generally well tolerated; however, subtle electroencephalographic deteriorations were observed. This case series suggests safe and effective antidepressive treatment with bupropion in SZ patients, if stable antipsychotic medication and electroencephalographic-monitoring are provided. Further randomized studies involving a control group are necessary.

8.4.2.7 Buspirone

Buspirone is a partial agonist at 5-HT_{1A} receptors, and is approved by the US Food and Drug Administration as an anxiolytic. It was tested for use in depression, panic disorder, obsessive-compulsive disorder, and schizophrenia as well [102]. Randomized controlled trials produced mixed results concerning the efficacy of buspirone in the augmentation of antipsychotic drugs [103–105]. For instance, 73 patients with schizophrenia, who had been treated with SGAs for at least 3 months, were randomly assigned to receive either buspirone (30 mg/day), or matching placebo. Attention, verbal fluency, verbal learning and memory, verbal working memory, and executive function, as well as psychopathology, were assessed at baseline, 6 weeks, and 3 and 6 months after baseline. A significant time by group interaction effect was noted on the Digit Symbol Substitution Test, a measure of attention/speed motor performance, with better performance of the buspirone group compared to the placebo group at 3 months [103]. On the contrary, in a 6-week, double-blind, placebo-controlled, independent group study, 18 subjects (14 males, four females) received in random order either placebo or buspirone (15–30 mg/day). There were no statistically significant differences between placebo and buspirone treatments on either of the cognitive function measures or symptom ratings [104]. Another small trial with 23 schizophrenia patients [risperidone (6 mg/day) plus buspirone (60 mg/day)] and 20 patients treated with risperidone plus placebo showed that the buspirone group had significantly greater improvement in the negative symptom and positive general

psychopathology subscales and PANSS total scores over the 8-week trial. Therapy with 60 mg of buspirone per day was well tolerated, and no clinically important adverse effects were observed [105].

8.4.2.8 Meta-analysis

Sepehry et al. [31] performed a meta-analysis of *11 studies* that assessed SSRI add-on therapy for the negative symptoms of schizophrenia. Studies were retained if

- SSRI add-on therapy was compared with antipsychotic monotherapy among schizophrenia spectrum disorder patients;
- The clinical trial was randomized, double-blind, placebo-controlled with a parallel-arm design;
- Negative symptoms were assessed with the Scale for the Assessment of Negative Symptoms or the PANSS-Negative subscale.

When studies were divided according to severity of illness, a moderate and significant effect size emerged for the studies involving so-called "chronic patients" (n = 274). *This meta-analysis provides support for augmentation with antidepressants for the treatment of negative and affective symptoms in schizophrenia.*

Singh et al. [32] published a systematic review and meta-analysis of *23 randomised controlled trials* of antidepressant augmentation that included 819 patients with chronic schizophrenia treated with SSRIs (mirtazapine, reboxetine, mianserin, trazodone, and ritanserin). Across the included studies there was a moderate pooled standardized mean difference with an effect size of 0.48. In specific subgroup analyses *fluoxetine, trazodone, and ritanserin* led to significantly greater response rates than placebo.

Watanabe [106] also concluded that fluoxetine, trazodone and ritanserin are more effective than placebo when used as add-on therapies for negative symptoms of schizophrenia. There was no evidence that antidepressant treatment induced a deterioration of psychotic symptoms. Further research is required to address the potential benefits and risks of chronic administration of antidepressants to patients with schizophrenia. Predictors of antidepressant initiation (14.6% of group) in the CATIE study were female gender or white skin color, and a prior diagnosis of depression or symptoms of depression at baseline. Patients with higher positive symptom scores and younger patients were started on antidepressants sooner. Duration of antidepressant treatment was longer in patients with less education and in those with a history of alcohol abuse/dependence [62].

Recently, Tiihonen et al. [107] showed that antidepressant use is associated with decreased suicide deaths among patients with schizophrenia in Finland.

Thus, clinical studies have shown that negative symptoms of schizophrenia unresponsive to antipsychotic monotherapy can improve after augmentation with some antidepressants. Possible explanations for inconsistencies in study findings include small sample sizes, variable duration of treatment, a range of concomitant antipsychotic regimens, and the nature of the inclusion criteria and outcome measures used [108].

8.5 Mood Stabilizers

The term "mood stabilizer" does not describe a mechanism, but rather an effect. Lithium, carbamazepine, valproate, and lamotrigine are recognized mood stabilizers.

8.5.1 Lithium

Lithium, the first mood-stabilizing medication approved by the U.S. Food and Drug Administration for treatment of mania, is often very effective in controlling mania and preventing the recurrence of both manic and depressive episodes.

8.5.1.1 Mechanism of Action

Lithium, affecting each neurotransmitter system within complex interactive neuronal networks, is suggested to restore the balance among aberrant signaling pathways in critical regions of the brain. Evidence from both in vitro and in vivo studies has demonstrated that lithium exerts multiple effects on neurotransmitter/receptor-mediated signaling, ion transport, signal transduction cascades, hormonal and circadian regulation, and profoundly alters gene expression patterns (see, e.g., reviews [109, 110]). Recent molecular studies have revealed the action of lithium on signal transduction mechanisms, such as phosphoinositide hydrolysis, adenylyl cyclase, G protein, glycogen synthase kinase-3beta, protein kinase C, and its substrate myristoylated alanine-rich C kinase substrate [111]. Lithium's main mechanisms of action appear to stem from its ability to inhibit glycogen synthase kinase-3 activity and also to induce signaling mediated by brain-derived neurotrophic factor. Lithium has emerged as a *neuroprotective agent* efficacious in preventing apoptosis-dependent cellular death. Lithium neuroprotection is provided through multiple, intersecting mechanisms; for instance, lithium increases cell survival by inducing brain-derived neurotrophic factor and thereby stimulating activity in anti-apoptotic pathways, including the phosphatidylinositol 3-kinase/Akt and the mitogen-activated protein kinase pathways [112]. Furthermore, there is evidence that demonstrates the action of lithium on cyclic adenosine monophosphate (cAMP)-mediated signal transduction, cAMP response element binding activation, increased expression of brain-derived neurotrophic factor, the phosphatidylinositide cascade, protein kinase C inhibition, glycogen synthase kinase 3 inhibition, and B-cell lymphoma 2 expression [113].

8.5.1.2 Clinical Studies

Lithium has been the subject of more double-blind studies than any other adjunctive treatment. Patients originally treated with placebo added to neuroleptics did not have significantly greater improvement when they received open-label adjunctive

lithium [114]. Findings from another research suggests that lithium might benefit only schizoaffective patients. However, the methodological shortcomings of the trials analyzed limit the impact of the evidence provided [115]. Based on a review of 20 studies with 611 participants, Leucht, Kissling, and McGrath [116] found:

- Three studies that compared lithium with placebo as the sole treatment showed no difference in any of the outcomes;
- In eight studies comparing lithium with antipsychotic drugs as the sole treatment, more participants in the lithium group left the studies early (n = 270);
- Eleven studies examined whether the augmentation of antipsychotic drugs with lithium salts is more effective than antipsychotic drugs alone. More participants who received lithium augmentation had a clinically significant response (n = 244). However, statistical significance became borderline when participants with schizoaffective disorders were excluded in a sensitivity analysis (n = 120, p = 0.07);
- No superior efficacy of lithium augmentation in any specific aspect of the mental state was found; and
- There were no differences between groups for adverse events.

Authors concluded that despite some evidence in favor of lithium augmentation, the overall results are inconclusive. A large trial of lithium augmentation of antipsychotic medications is required in order to detect a benefit of small effect size in patients with schizophrenia but with no affective symptoms.

8.5.2 Anticonvulsants

Anticonvulsant drugs are widely used for psychiatric indications. This includes alcohol and benzodiazepine withdrawal symptoms, panic and anxiety disorders, dementia, schizophrenia, and to some extent personality disorders. Besides pain syndromes, their main domain aside from epilepsy, however, is bipolar disorder [117].

8.5.2.1 Mechanism of Action

When hyper-function of glutamatergic pathways in the frontal cortex of schizophrenic patients was proposed [45], clinical studies provided evidence for glutamate abnormalities in schizophrenia. The majority of antiepileptic drugs have more than one mechanism of action [71]. Antiepileptic drugs are divided by mechanisms of action into the following groups [118]:

- Antiepileptics which block sustained repetitive firing in individual neurons, this effect is mainly due to the blockade of voltage-dependent sodium or calcium channels: carbamazepine, lamotrigine, oxcarbazepine, topiramate, valproate;
- Drugs that enhance inhibitory events mediated by gama-aminobutyric acid (GABA): gabapentin, phenobarbital, topiramate, and valproate;

- The third group practically consists of one drug which blocks T-type calcium channels and is active against absences (ethosuximide); and
- Antiepileptic drugs that reduce events that are mediated by excitatory amino acids: glutamate, phenobarbital, and topiramate [119].

Lamotrigine's anticonvulsant action has been attributed to the increase in GABA release and also antagonism of voltage-gated sodium channels leading to a reduction in glutamate release [120–122]. There is also a glutamatergic hypo-function hypothesis of schizophrenia based on the ability of the non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, phencyclidine, to induce psycho-mimetic effects in healthy human volunteers indistinguishable from schizophrenia. Phencyclidine mimics the positive and negative symptoms and cognitive dysfunction as well as formal thought disorders and even auditory hallucinations. It could exacerbate psychosis in schizophrenic patients [123, 124]. The two opposing glutamatergic hypo-function and hyper-function theories have been reconciled by the fact that phencyclidine has a glutamate release increasing potential beside its NMDA associated channels blocking properties [46]. Therefore, the psychotic symptoms of phencyclidine could be due to glutamate release potentiation and not due to the reduction of glutamate activity.

Topiramate is an anticonvulsant drug with alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor antagonist properties and a GABA potentiating action [123, 124]. Because of these properties, topiramate could be chosen as a novel medication to address downstream consequences of NMDA receptor hypo-function, which are potentiation of GABAergic neurotransmission and antagonism of the excitotoxic actions of glutamate at the AMPA classes of glutamate-gated channels [125, 126].

Thus, conventional antiepileptics generally inhibit sodium currents (carbamazepine, phenobarbital, phenytoin, and valproate) or enhance GABA-ergic inhibition (valproate). Novel antiepileptic drugs mainly associated with an inhibition of voltage-dependent sodium channels are lamotrigine and oxcarbazepine [127].

8.5.2.2 Clinical Studies

Add-on carbamazepine, valproate, lamotrigine and several other antiepileptic drugs to antipsychotic agents have been prescribed with diverging or inconclusive results in SZ/SA disorder [128].

Carbamazepine (Tegretol)

Although the findings of the various clinical trials are very difficult to compare, the results generally indicate beneficial effects particularly if carbamazepine is used as an adjunct to antipsychotic medication [129]. Recently conducted clinical trials indicated that carbamazepine augmentation may be effective for patients with schizophrenia treated with aripiprazole, although carbamazepine dramatically decreases plasma concentrations of aripiprazole [130].

Leucht and associates [131] evaluated the effects of carbamazepine and its derivatives for the treatment of schizophrenia and related psychoses (ten studies, 258 participants). A favorable effect of carbamazepine was found when those who received the antipsychotic (perphenazine) had Parkinsonism. There were no between group differences between the add-on carbamazepine and the add-on placebo groups, regarding acceptability or early termination of study. Carbamazepine augmentation was superior compared with antipsychotics alone in terms of overall global improvement. No data were available for the effects of carbamazepine on subgroups of people with schizophrenia and aggressive behavior, negative symptoms or EEG abnormalities or with schizoaffective disorder. Based on currently available randomized trial-derived evidence, carbamazepine cannot be recommended for routine clinical use for treatment or augmentation of antipsychotic treatment of schizophrenia.

Valproate

There is only limited evidence to support the use of augmentation therapy with valproate *(divalproex sodium)*, including a single small study that revealed less agitation in the valproate augmentation group versus the antipsychotic monotherapy group. A Cochrane review and meta-analysis of only seven randomized studies with 519 participants found no significant benefit of valproate augmentation [132]. A clinical trial with 249 patients hospitalized for acute exacerbation of schizophrenia, in which valproate (a maximum dosage of 30 mg/kg/day) or placebo was added to risperidone (6 mg/day) or olanzapine (15 mg/day), showed improvement from baseline throughout the 28-day treatment period in the two combination therapy and the two antipsychotic monotherapy groups. There were statistically significant treatment differences favoring combination therapy as soon as day 3 for PANSS total score, derived Brief Psychiatric Rating Scale (BPRS) total score, as well as PANSS and BPRS subscales. Treatment with divalproex in combination with an atypical antipsychotic agent resulted in earlier improvement in a range of psychotic symptoms among hospitalized patients with acute schizophrenia [133]. A recent 12-week, randomized, double-blind, parallel-group, multi-center trial with 402 patients failed to show an advantage of valproate augmentation at any of the time points [134].

Citrome et al. [135] compared the specific anti hostility effects of SGAs monotherapy (olanzapine or risperidone) with that of combination treatment with divalproex sodium among 249 inpatients with schizophrenia in a double-blind, 28-day multicenter trial. Combination treatment with risperidone or olanzapine plus divalproex had a significantly greater anti hostility effect at days 3 and 7 than monotherapy. The effect on hostility appears to be statistically independent of antipsychotic effect on other PANSS items reflecting delusional thinking, a formal thought disorder, or hallucinations. Thus, divalproex sodium may be useful as an adjunctive agent in specifically reducing hostility in the first week of treatment with risperidone or olanzapine among schizophrenia patients who are experiencing an acute psychotic episode.

Lamotrigine

A double-blind, placebo-controlled 14 week trial with a cross-over design, assessed the addition of lamotrigine to ongoing clozapine treatment in 34 treatment resistant patients. Lamotrigine was shown to be more effective than placebo in reducing positive symptoms and 'general psychopathological symptoms' measured by the PANSS, but had no significant benefit on negative symptoms [136]. Two multicenter, randomized, double-blind, 12-week, parallel-group trials were conducted to compare flexibly dosed lamotrigine (100–400 mg/d) with placebo as add-on treatment in 429 schizophrenia patients with stable, residual psychotic symptoms. The primary end point was the change in PANSS total score at week 12 [137]. Results from these two studies do not support the use of lamotrigine as an adjunct to atypical antipsychotics in patients with refractory psychosis. It is unclear why positive results from previous lamotrigine trials were not replicated. The positive effect of lamotrigine on cognition in one trial, while of uncertain significance, may merit further study.

Fifty-one treatment-resistant schizophrenic patients treated with clozapine received, either up to 200 mg/day of lamotrigine or placebo in a double-blind design for 24 weeks, [138]. Lamotrigine added to stable clozapine treatment showed a beneficial effect on negative, positive and general psychopathological symptomatology. Regarding cognitive functions, improvement was observed in attentional resistance to interference, verbal fluency and executive functioning. The findings provide evidence that lamotrigine augmentation of clozapine treatment is well tolerated and may be proposed as an effective therapeutic strategy to improve outcome in treatment-resistant schizophrenia.

Glick et al. [139] compared the efficacy of mood stabilizer augmentation of an antipsychotic for patients with schizophrenia who are both stabilized and partially responsive. Adult patients with SZ/SA disorder were enrolled in a 12-week, double-blind randomized trial. They were randomly assigned to one of three adjunctive treatments: (1) lamotrigine, (2) divalproex sodium, or (3) placebo. There were no differences in global outcomes, positive, negative and depressive symptoms, quality of life, or demoralization among the three groups.

A Cochrane review and meta-analysis of five lamotrigine augmentation studies and 537 participants revealed some efficacy on positive and negative symptoms, though results were mixed and not robust [140]. However, in another more recent meta-analysis data were restricted to lamotrigine add-on therapy to clozapine, with clozapine as a proxy for highly likely treatment resistance. In this meta-analysis of five trials and 161 participants a significant effect in favor of lamotrigine was observed [33]. This meta-analysis drew between two and 30 patients for the clozapine and placebo groups from individual trials in which a mixture of baseline antipsychotics was allowed and in which clozapine treatment was not used as a stratification factor. This means that the included patients were not truly randomly assigned to clozapine or placebo, rendering a suggestive analysis. Nevertheless, overall lamotrigine still seems to hold some promise but more studies are needed.

Topiramate

Clinical results suggest that treatment with topiramate may improve negative symptoms and cognitive dysfunction in schizophrenia when added to a stable dose of antipsychotic medication [141–143]; however much of this information is based on open-label studies, case reports and case series [144]. In a randomized, double-blind, placebo-controlled study of SZ patients, the addition of topiramate resulted in a reduction of both positive and negative symptoms compared with patients on antipsychotic monotherapy [143]. A 12-week naturalistic, open study was carried out to examine the potential benefits of topiramate in clozapine-treated schizophrenia patients who exhibited a suboptimal clinical response (20 subjects were enrolled, and 16 completed the study). Topiramate augmentation led to a 14% improvement in total Brief Psychiatric Rating Scale scores ($p=0.0003$), a 2.5% decrease in body weight ($p=0.015$), and was generally well tolerated; paraesthesia was the most common side effect [145]. These findings support topiramate as a viable augmentation strategy in clozapine partial responders.

8.5.2.3 Aggressive Behavior

Antiepileptic drugs may reduce aggression by acting on the CNS to reduce neuronal hyper-excitability associated with aggression. Huband et al. [146] reviewed 14 studies of five different antiepileptic drugs with data from 672 participants. Four antiepileptics (carbamazepine, valproate/divalproex, oxcarbazepine and phenytoin) were effective, compared to placebo, in reducing aggression in at least one study, although for three drugs (valproate, carbamazepine and phenytoin) at least one other study showed no statistically significant difference between treatment and control conditions. The authors considered that the body of evidence summarized in this review was insufficient to allow any firm conclusion to be drawn about the use of antiepileptic medication in the treatment of aggression and associated impulsivity.

Mood-stabilizer use was significantly and independently associated in multivariate logistic modelling with: aggressive behavior, disorganized speech, multiple hospitalizations, less negative symptoms, younger age, and revealed regional variation [59]. Further research is warranted.

8.6 Benzodiazepines

The use of benzodiazepines (BZDs) in schizophrenia was mainly for symptoms such as insomnia, anxiety, agitation, aggression, and psychotic excitement in general and control of florid psychotic symptoms such as hallucinations and delusions in particular [147, 148]. BZDs were further found to be useful in the reduction of neuroleptic-induced side effects such as akathisia or tardive dyskinesia [149].

8.6.1 Mechanism of Action

Benzodiazepines bind to the $GABA_A$ receptor, reducing the quantity of GABA required to open the chloride channel, hyperpolarize the neuron and inhibit neurotransmission [150]. Benzodiazepines also have an effect on the mesoprefrontocortical regions where neuroleptics may be less efficient [151].

8.6.2 Clinical Studies

The use of various types of BZDs as adjunct therapy to neuroleptics in the treatment of symptoms such as agitation and psychotic excitement in general and control of florid psychotic symptoms such as hallucinations and delusions in particular is well known [152–155]. For instance, about half of the 48 alprazolam-treated patients with schizophrenia demonstrated clinically significant improvement in both positive and negative symptoms [154]. The positive symptoms appear to be significantly reduced by BZDs in some but not all studies [156]. These suggest that there could be a group of patients who respond to BZDs. Diazepam was reported to be effective in treating prodromal and early signs of schizophrenia [155].

Multivariate logistic regression and multivariate linear regression analyses were performed to assess predictors of benzodiazepine use and dose, respectively, in Asian patients with schizophrenia [157]. Overall, 54% of the patients received adjunctive BZDs at an average daily dose equivalent to 30.3 mg diazepam, with minor changes over the years sampled. Benzodiazepine use was highest in Taiwan and Japan, lowest in Thailand and China, and was associated with shorter duration of illness, presence of delusions, hallucinations, disorganized speech, social or occupational dysfunction, and use of mood stabilizers, anti-parkinsonian or antidepressant drugs, and lower doses of antipsychotics.

As reviewed by Volz et al. [158], a meta-analysis of 31 randomized studies with 2,454 participants did not reveal significant superiority for BZDs compared with placebo. Nevertheless, a number of methodological problems such as insufficient data or the use of different outcome criteria hampered the meta-analytic process. The sedative effects of benzodiazepines in schizophrenia could be shown, but there is much room for randomized studies on the decisive question whether BZDs improve or at least hasten the amelioration of positive symptoms.

Tiihonen et al. [107] using national databases of mortality and medication prescriptions among a complete nationwide cohort of 2,588 patients hospitalized in Finland investigated if the use of benzodiazepines, antidepressants, or multiple concomitant antipsychotics is associated with increased mortality among patients with schizophrenia. Authors concluded that BZD use was associated with a marked increase in mortality among patients with schizophrenia, whereas the use of an antidepressant or several concomitant antipsychotics was not.

Predictors of anxiolytic initiation (13.7% of group) in the CATIE study were not being African-American, younger age, higher body mass index, and akathisia. Time to anxiolytic initiation was shorter in patients who were separated or divorced and

in patients with better neurocognitive functioning. Duration of anxiolytic treatment was shorter for African Americans and longer in patients with better instrumental role functioning. Predictors of sedative/hypnotic use (11.2% of group) were depressive symptoms and prior diagnosis of an anxiety disorder. Time to initiation of sedative/hypnotics was longer for those with depressive symptoms and shorter for those with a history of alcohol abuse or dependence [62].

Thus, BZDs, in conventional doses, can enhance the antipsychotic effect of neuroleptics in schizophrenics who did not respond satisfactorily to neuroleptics alone. This effect is more conspicuous regarding hallucinations, and improvement has also been observed for delusions, thought disturbances, some negative symptoms, anxiety and tension. Some BZDs may be more effective than others in schizophrenia, but this has not been clearly determined. Benzodiazepines combined with clozapine clearly increases the frequency of cardiovascular and respiratory accidents [151].

8.7 Glutamatergic Drugs

8.7.1 Mechanism of Action

NMDA receptors are a major subtype of glutamate receptors and mediate slow excitatory postsynaptic potentials. The glutamate hypothesis of schizophrenia is based on the ability of NMDA receptor antagonists to induce schizophrenia-like symptoms. There are strong lines of evidence indicating that dysfunction of NMDA receptors may explain the pathophysiology of schizophrenia [107, 159, 160]. Research over the past two decades has highlighted promising new targets for drug development based on potential pre- and postsynaptic, and glial mechanisms leading to NMDA receptor dysfunction. Reduced NMDA receptor activity on inhibitory neurons leads to disinhibition of glutamate neurons increasing synaptic activity of glutamate, especially in the prefrontal cortex [161].

8.7.2 Clinical Studies

Presently, glutamatergic drugs are not available for clinical use [162].

Much interest has surrounded the use of agonists at the NMDA-glycine site (D-serine, glycine, D-alanine and D-cycloserine) and glycine transporter-1 (GlyT-1) inhibitor (sarcosine) in order to improve the symptoms of stable chronic schizophrenia patients receiving concurrent antipsychotics.

8.7.2.1 Glycine

This therapeutic approach for the treatment of schizophrenia aimed to increase synaptic glycine levels with add-on oral glycine to antipsychotic agents. Clinical trials provided clinical support for this approach. For instance, in a double-blind,

placebo-controlled fashion 14 medicated patients with chronic schizophrenia were treated with glycine. Significant improvement in negative symptoms occurred in the group given glycine but not in the group given placebo, suggesting that potentiation of NMDA-receptor-mediated neurotransmission may represent an effective treatment for neuroleptic-resistant negative symptoms in schizophrenia [163]. High glycine dose studies replicated and extended initial findings by demonstrating improvements in positive, negative, and cognitive symptoms of the disorder [164–166]. High variability of clinical efficacy of glycine adjuvant therapy (ranging from 20 to 70%) should be noted.

8.7.2.2 D-cycloserine

Thirty eight stable adult schizophrenia outpatients (87% completed the trial) treated with any antipsychotic except clozapine were randomized to a double-blind, 8-week add-on trial of d-cycloserine 50 mg or placebo. Once-weekly dosing with d-cycloserine for 8 weeks produced persistent improvement of negative symptoms compared to placebo, although statistical significance was, in part, the result of worsening of negative symptoms with placebo [167]. These results must be considered preliminary since a number of outcomes were examined without correction for multiple tests. Preliminary studies with once-weekly administration of D-cycloserine supported its benefit on negative symptoms, memory consolidation, and facilitation of cognitive behavioral therapy for delusions [168].

8.7.2.3 D-serine

The mammalian brain contains unusually high levels of D-serine. In the last few years, studies from several groups have demonstrated that D-serine is a physiological co-agonist of the NMDA type of glutamate receptor—a key excitatory neurotransmitter receptor in the brain [169, 170]. Heresco-Levy et al. [171] assessed the efficacy and safety of D-serine adjuvant treatment for 39 schizophrenia patients treated with SGAs (risperidone- or olanzapine) using a double-blind, placebo-controlled, 6-week crossover trial with 30 mg/kg/day D-serine. D-serine administration induced increased serine serum levels ($p<0.001$) and resulted in significant ($p<0.001$) improvement in negative, positive, cognitive, and depression symptoms, as measured by the PANSS. D-serine was well tolerated, and no detrimental changes in clinical laboratory parameters were noted. These findings indicate that risperidone and olanzapine efficacy might be augmented with D-serine adjuvant treatment, and confirm D-serine efficacy against main schizophrenia symptom domains.

Kantrowitz et al. [172] performed a 4-week, open-label trial of adjunctive D-serine (30, 60 or 120 mg/kg/day) with 42 antipsychotic-stabilized patients with SZ/SA disorder. On the PANSS, improvement was observed for positive ($p=0.006$; $d=0.46$), negative ($p<0.001$; $d=0.68$), general psychopathology ($p=0.001$; $d=0.53$), and total ($p<0.0001$; $d=0.74$) symptoms. Furthermore, increases in

plasma levels correlated with improved symptomatic and neuropsychological function. Thus, findings support a double-blind investigation of D-serine at doses 60 mg/kg/d, and suggest effectiveness in treatment of both persistent symptoms and neurocognitive dysfunction. However, when Lane et al. [173] compared D-serine, and sarcosine with placebo in the treatment of 60 patients using a double-blind, placebo-controlled design, D-serine did not differ significantly from placebo on any measure (symptoms, functioning, and quality of life).

8.7.2.4 Sarcosine

A glycine transporter-I inhibitor is a small molecule that enhances the NMDA neurotransmission and has been shown to be beneficial as adjuvant therapy for schizophrenia. In one study, 65 risperidone-treated in-patients with acute exacerbations of schizophrenia were given adjuvant sarcosine (a glycine transporter inhibitor) 2 g/day, DSR 2 g/day, or placebo in a 6-week, randomized, double-blind trial. The sarcosine group showed significantly more symptom improvement than the other two groups [174]. In a 6-week, controlled trial with chronic schizophrenia patients, sarcosine 2 g/day adjuvant treatment led to 17% ($P<0.0001$), 14% ($P<0.0001$), and 13% ($P<0.0001$) reductions in positive, negative, and cognitive symptoms, respectively, without inducing any significant side effects [174]

Lane, Huang, Wu et al. [175] examined the effects of sarcosine adjuvant therapy for schizophrenic patients among 20 schizophrenic inpatients enrolled in a 6-week double-blind, placebo-controlled trial of sarcosine (2 g/day) which was added to their stable doses of clozapine. Sarcosine produced no greater improvement when co-administered with clozapine than placebo plus clozapine at weeks 2, 4, and 6. Sarcosine was well tolerated and no significant side-effects were noted. Thus, unlike patients treated with other antipsychotics, patients who received clozapine exhibited no improvement with the addition of sarcosine or agonists at the NMDA-glycine site. In a replication study sarcosine was shown to be superior to placebo on all four outcome measures of PANSS total score ($p=0.005$), Scale for the Assessment of Negative Symptoms (SANS) ($p=0.021$), Quality of Life (QOL) ($p=0.025$), and Global Assessment of Functioning (GAF) ($p=0.042$) [173].

8.7.2.5 Meta-analysis

Tiihonen and Wahlbeck [176] analysed 18 short-term trials with 358 randomised participants. All trials were short-term trials with a maximum duration of 12 weeks. In all of these trials, glycine, D-serine, and D-cycloserine was used to augment the effect of antipsychotic drugs. D-cycloserine, a partial agonist of NMDA receptors' glycine site, seemed ineffective towards the symptoms of schizophrenia. NMDA receptor co-agonists glycine and D-serine showed some effects in reducing the negative symptoms of schizophrenia ($n=132$, $p=0.0004$), but the magnitude of the effect was moderate. In general, all glutamatergic drugs appeared to be ineffective in

further reducing positive symptoms of the disease when added to the ongoing antipsychotic treatment. Glycine and D-serine may somewhat improve negative symptoms when added to regular antipsychotic medication, but the results were not fully consistent and data are too few to allow any firm conclusions. Many participants in the included trials were treatment-resistant which may have reduced treatment response. Additional research on glutamatergic mechanisms of schizophrenia is needed.

In a meta-analysis Tsai and Lin [34] included about 800 subjects from 26 studies. Overall, the NMDA-enhancing molecules were effective in most schizophrenic symptom domains with an effect size of total psychopathology of 0.40. Glycine, D-serine, and sarcosine treatments significantly improved multiple symptom domains, whereas D-cycloserine did not improve any symptom domain. Moderator analysis revealed that glycine, D-serine and sarcosine were better than D-cycloserine in improving overall psychopathology. Patients that received risperidone or olanzapine, but not clozapine, improved. No significant side effect or safety concern was noted.

Another meta-analysis was based on 29 trials with 1,253 participants [35]. Subgroup analysis revealed medium effect sizes for D-serine and N-acetyl-cysteine for negative and total symptoms, and for glycine and sarcosine for total symptoms. When added to clozapine, none of the drugs demonstrated therapeutic potential, and addition of glycine worsened positive symptoms. Taking into consideration the number of trials and sample sizes in subgroup analyses, D-serine, N-acetyl-cysteine and sarcosine as adjuncts to non-clozapine antipsychotics revealed therapeutic benefit in the treatment of negative and total symptoms of chronic schizophrenia.

Recently de Bartolomeis et al. [177] critically updated preclinical and clinical data on the modulation of glutamate NMDA receptor activity by NMDA-receptors co-agonists, glycine transporters inhibitors, AMPAkines, mGluR5 agonists, NMDA-receptors partial agonists. Though promising preclinical findings have been reported for virtually all compounds, clinical efficacy has not been confirmed for D-cycloserine. Contrasting evidence has been reported for glycine and D-serine that may however have a role as add-on agents. More promising results in humans have been reported for glycine transporter inhibitors.

Thus, although hypofunction of NMDA receptor-mediated neurotransmission is proposed to play an important role in the pathophysiology of schizophrenia, results of clinical trials of small molecules that enhance the NMDA function are inconsistent.

8.8 Hormonal Agents

It is a well-established fact that schizophrenia, and related psychoses may have a significant hormonal, mainly neuroprotective, component in the pathogenesis of the disease. Findings from the current literature support the role of neurosteroids and the estrogen protection hypotheses.

8.8.1 Neurosteroids

Neurosteroids such as dehydroepiandrosterone (DHEA), pregnenolone (PREG), and their sulfates (DHEAS and PREGS) display multiple effects on the central nervous system.

After discovering that PREG and DHEA are produced in the brain Baulieu [178] introduced the term "neurosteroids". Current knowledge concerning PREG and DHEA metabolism, the enzymes mediating these reactions, and their localization was recently summarized [179, 180]. Clinical studies revealed low levels of PREG in individuals with major depression [181], generalized anxiety disorder [182], generalized social phobia [183], and chronic medicated schizophrenia patients [184]. Comparisons of the values of blood DHEA and DHEAS levels of schizophrenia patients with healthy controls were found to differ among studies, ranging from normal, to low, and to high levels [185–193]. A meta-analysis of differences in mean concentrations of serum DHEA(S) between schizophrenia patients and control subjects shows a significant non-zero effect ($p<0.001$), and significant heterogeneity of data ($p<0.001$; [194]).

Alterations in PREG(S) and DHEA(S) in schizophrenia may be associated with impaired stress-response. Several lines of evidence have shown that a variety of stressors result in a shift in the balance of cortisol and DHEA(S), in that there is an increase in cortisol synthesis and a decrease in androgen synthesis. During acute psychological stress, stimulation of adrenal steroid release is accompanied by a shift towards DHEA release [195]. Furthermore, DHEA(S) were shown as mediators of the HPA axis adaptation to extreme stress and the psychiatric symptoms associated with posttraumatic stress disorder [196]. PREG is increased in rodent brain and plasma after HPA activation by acute stress or ethanol administration [197]. The antiglucocorticoid properties of DHEA [198] and neuromodulatory effects of DHEA(S) on GABA, NMDA and sigma receptors in the brain [199–201] may contribute to symptom severity, including behavioral functions such as response to stress, anxiety, aggressive behavior, learning and memory [202]. This, in turn, may lead to dysregulation in neurotransmission, and neuroprotective mechanisms and result in chronic and progressive deterioration in emotional, cognitive, and psychosocial functions of patients.

8.8.1.1 Mechanism of Action

Experimental and clinical observations suggest that PREG, DHEA and their sulfates (PREGS, DHEAS) [together abbreviated as PREG(S) and DHEA(S)] display multiple effects on the central nervous system (CNS) such as modulation of neurotransmitter receptors [203–205], anti-stress effects [206], neuroprotective properties [207], cognitive-enhancing effects [208, 209], androgenic, estrogenic activities, and neuropsychopharmacological effects [210, 211]. In particular, they regulate the growth of neurons, enhance myelinization and synaptogenesis in the CNS, affect

synaptic functioning, and thus may be effective as brain protectors [212, 213]. In elderly populations they are reduced to 20–30% of the peak levels of young adulthood [214, 215]. Studies in experimental animals revealed important roles of neuroactive steroids in the control of central nervous system functions in physiological and pathological conditions, suggesting that they may represent good candidates for the development of neuroprotective strategies for neurodegenerative and psychiatric disorders [216]. Specifically, neurosteroids have various functions associated with neuroprotection, response to stress, mood regulation and cognitive performance. In addition, neurosteroid levels are altered in stress-related neuropsychiatric disorders, see review, e.g., [36].

8.8.1.2 Clinical Studies

Several randomized, double-blind, placebo-controlled clinical trials were conducted with PREG [217, 218] and DHEA [219–224] for the treatment of schizophrenia and schizoaffective patients. Comparative critical analyses of these clinical trials were published [36, 225]. Overall, the results of these clinical trials with two neurosteroids are based on 117 patients who received DHEA and 34 patients treated with PREG. The clinically significant benefits of both DHEA and PREG augmentation remain unclear. Limitations of the studies reviewed include small sample sizes. It is crucial to replicate these trials with larger samples of schizophrenia or schizoaffective patients, and for a longer duration of treatment.

In summary, experimental and clinical observations support the speculation that neurobiological alterations in PREG(S)/DHEA(S) neurosteroids are related to the pathophysiology of schizophrenia and other neuropsychiatric disorders. Based on the accumulated evidence, it is also possible to conclude that PREG(S)/DHEA(S) might play a relevant role in the expressions of stress response, anxiety, and cognitive deficit in schizophrenia. Finally, these insights underscore the need for development of novel treatment strategies such as neuroprotective strategies using neurosteroids and other compounds, to help overcome the limitations of current antipsychotic drugs and to improve the cognitive deficits and negative symptoms, as well as functioning and quality of life outcomes of people affected by schizophrenia. Pilot clinical trials indicate that PREG and DHEA augmentation may improve some clinical symptoms and neurocognitive response in schizophrenia. Clinical trials for the evaluation of these neurosteroids pose a few challenges, and further investigation of neurosteroid treatment in schizophrenia and related disorders is warranted.

8.8.2 Estrogen, Raloxifene and Testosterone

There is a wealth of historical and circumstantial evidence to suggest that female patients with schizophrenia may suffer from a deficit in estrogenic function [226]. Epidemiological and life-cycle data point to significant differences in the incidence

and course of schizophrenia between men and women, suggesting a protective role of estrogen. In-vitro and in-vivo preclinical research has confirmed estradiol's interactions with central neurotransmitter systems implicated in the pathogenesis of schizophrenia [227, 228].

8.8.2.1 Mechanism of Action of Estrogen

Estrogen is known to have diverse *neuroprotective properties*; in particular, estrogenic compounds can protect brain cells against injury from excitotoxicity, oxidative stress, inflammation and apoptosis [229–231]. They can also enhance neurogenesis, angiogenesis, synaptic density, plasticity and connectivity, axonal sprouting and remyelination and expression of neurotrophic factors [232, 233]. Furthermore, estradiol has been found to significantly interact with the dopaminergic, serotonergic and glutamatergic systems, giving it properties similar to those of FGAs [234, 235].

8.8.2.2 Clinical Studies

Estrogen has recently been used as an adjunct to standard antipsychotic medication in quite a few studies of female schizophrenia patients [236, 237]. Cochrane review and meta-analysis summarized four studies with a total of 108 women and concluded that adjunctive estrogen with or without progesterone does not appear to offer convincing advantages over placebo [238]. In men, consideration of estrogen therapy has been impacted by concerns of feminising side effects, however, clinical trials of the use of estrogen in treating prostate cancer, bone density loss and even aggression and psychosis in dementia or traumatic brain injury, show this to be a safe and effective therapy. A 14-day randomised placebo-controlled trial involving 53 men with schizophrenia was conducted to evaluate the efficacy of 2 mg oral estradiol valerate as an adjunct to FGAs [239]. Results demonstrated a more rapid reduction in general psychopathology that occurred in the context of greater increases in serum estrogen levels and reductions in FSH and testosterone levels in participants that received estradiol. Approximately 28% of the estradiol participants did not achieve an increase (at least a 50% from baseline) in serum estrogen suggesting that further research is needed to refine the type, dose and administration route for estrogen therapy in men.

Raloxifene

Another therapeutic strategy may be related to add-on raloxifene hydrochloride. It is a selective estrogen receptor modulator that acts as an estrogen antagonist in breast tissue and may have agonistic actions in the brain, potentially offering mental health benefits with few estrogenic side effects [240]. Kulkarni et al. [241] examined

the effect of a therapeutic dose of adjunctive raloxifene (120 mg/day, n = 13) versus oral placebo (n = 13) in postmenopausal women with schizophrenia. Analysis of variance found significant interaction effects for total and general PANSS scores. The demonstrated benefit of adjunctive treatment with 120 mg/day raloxifene hydrochloride offers support for the potential role of this selective estrogen receptor modulator in treating postmenopausal women with schizophrenia.

Usall et al. [242] conducted a 12-week, double-blind, randomized, placebo-controlled study with 33 postmenopausal women with schizophrenia who exhibited prominent negative symptoms. The addition of raloxifene (60 mg/day) to regular antipsychotic treatment significantly reduced negative ($p = 0.044$), positive ($p = 0.031$), and general psychopathological ($p = 0.045$) symptoms during the 12-week trial as compared to the add on placebo group. If more extensive and longer-term studies confirm and expand upon these positive results, the use of raloxifene could be recommended in postmenopausal patients with schizophrenia.

Testosterone

To explore the therapeutic effect of *testosterone augmentation* of antipsychotic medication on symptoms in male patients with schizophrenia, Ko, Lew, Jung et al. [243] performed a placebo-controlled, double-blind trial with 30 schizophrenic men, using either 5 g of 1% testosterone gel or a placebo added to a fixed dosage of antipsychotic medication over a period of 4 weeks following a 2-week washout period. Results indicated a significant improvement of negative symptoms in both the last observation carried forward and the completer analyses and a nonsignificant trend for the improvement of depressive symptoms in completers. There were no significant changes in serum hormone levels except total and free testosterone. The findings of this study suggest that testosterone augmentation may be a potential therapeutic strategy in patients with schizophrenia.

8.9 Retinoid-Based Strategy

Retinoids are a family of molecules that are derived from vitamin A. Several studies reported that retinoids are involved in neurodevelopment [244] and regulation of genes thought to be important in the pathogenesis of schizophrenia [245]. It has been suggested that retinoid dysregulation might be involved in the pathogenesis of schizophrenia. It is hypothesized that the availability in the brain of retinoid acid, the final product of the retinoid metabolic cascade, influences the onset of the disease [246, 247]. Defects in retinoid acid signaling have been implicated in several neurological diseases, including schizophrenia, movement disorders, and motor neuron disease [246, 248]. Because the retinoid acid level is controlled by genes involved in retinoid acid synthesizing, metabolizing and transporting, Chunling Wan et al. [249] investigated the polymorphisms of seven genes involved in these functions to reveal the possible role of retinoid acid in schizophrenia.

8.9.1 Mechanism of Action

There are two types of retinoid nuclear hormone receptors: retinoic acid receptors (RARs) and retinoid X receptors (RXRs). Both belong to the corticosteroid receptor superfamily and co-exist in most cells. The alpha, beta, and gamma subtypes of the RARs and RXRs have distinct and conserved amino and carboxy terminal domains. Each receptor subtype has a specific pattern of expression during embryonal development and a different distribution in adult tissues. This differential expression of receptor subtypes is thought to regulate the expression of distinct sets of genes. Heterodimers of the RARs and RXRs bind and regulate a specific DNA sequence known as the retinoic acid response element, which is located in the promoter region of genes such as the *RAR-b2* gene, reviewed in [250].

Retinoids modulate neurotransmission. The expression of D_2 receptors been shown to be regulated by retinoid acid [251], and single and compound null mutations for the RARB, RXRB 8 and RXRG in mice result in reduced expression of D_1 and D_2 receptors and impaired dopamine signaling [252]. Retinoid analogs have therefore been proposed as candidates for the treatment of schizophrenia [253, 254].

8.9.2 Clinical Study

Bexarotene (Targretin) belongs to the group of synthetic medicines derived from vitamin A (retinoid). Its chemical name is 4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl) ethenyl] benzoic acid [255]. To date this medication has been exclusively used as treatment of neoplastic or dermatological diseases. Adverse events potentially related to bexarotene include lipid abnormalities, hypothyroidism, headache, asthenia, rash, leucopenia, anemia, nausea, and increased risk of infection, peripheral edema, abdominal pain, dry skin, dizziness, hyperesthesia, hypoesthesia, and neuropathy. Based on the retinoid hypothesis in schizophrenia, our group conducted a 6-week open label trial in two mental health centers [256]. It was assumed that the combined effect of antipsychotic agents and bexarotene would have a beneficial effect in treatment of psychopathological symptoms in chronic schizophrenia patients. Since high daily doses of bexarotene can produce numerous adverse effects, the first trial was aimed to examine safety and preliminary efficacy of a low daily dose (75 mg/day) of bexarotene in an open label pilot study. Twenty-five patients with chronic schizophrenia received a low dose of bexarotene (75 mg/day) augmentation. Significant improvement from baseline to endpoint was observed on the total PANSS score, general psychopathology, and on the positive and the dysphoric mood factor scores. Low doses of bexarotene were well tolerated. Bexarotene was found to be a safe medication as measured by all laboratory parameters with the exception of increased total cholesterol serum levels. This short-term pilot study supports bexarotene as a potential valuable adjunct in the management of schizophrenia. A double-blind controlled study is currently underway to replicate these preliminary results.

8.10 Nonsteroidal Anti-inflammatory Drugs (NSAID)

This strategy is based on the hypothesis that immune-mediated glutamatergic-dopaminergic dysregulation may lead to the clinical symptoms of schizophrenia, and, consequently, to the use of anti-inflammatory drugs (cyclo-oxygenase-2 inhibitors, acetylsalicylic acid) [257, 258].

8.10.1 Mechanism of Action

A literature search identified more than 100 articles pertaining to suspected immunologic influences on schizophrenia published over the past 15 years [259]. Evidence suggests that a (prenatal) infection is involved in the pathogenesis of schizophrenia. Due to an early sensitization process of the immune system or to a (chronic) infection, which is not cleared through the immune response, an immune imbalance between the type-1 and the type-2 immune responses takes place in schizophrenia [257]. For instance, the differential activation of the enzyme indoleamine 2,3-dioxygenase and of the tryptophan/kynurenine metabolic pathway, resulting in the increased production of kynurenic acid in schizophrenia, and a possible increase in quinolinic acid in depression, also may play a key role in these diseases. Such differences are associated with an imbalance in glutamatergic neurotransmission that may contribute to increased levels of NMDA agonism in depression and NMDA antagonism in schizophrenia. In addition, immunological imbalance results in the increased production of prostaglandin E_2 in schizophrenia and depression, as well as increased cyclooxygenase-2 (COX-2) expression in schizophrenia [260].

8.10.2 Clinical Studies

8.10.2.1 Cox-2 Inhibitors

The selective cyclooxygenase-2 inhibitor (celecoxib) is a non-steroidal anti-inflammatory drug that selectively targets the COX-2 enzyme. A study of 50 patients undergoing acute exacerbation of their symptoms reported a significant improvement in their PANSS total score using 400 mg/d for 5 weeks; a reanalysis showed that it had the most effect in patients with an illness of less than 2 years' duration [261]. A follow-up study of 40 patients using 400 mg/d for 8 weeks reported no overall effect; however, a reanalysis showed that patients with recent-onset illness showed the most improvement [262]. One study of 35 patients with chronic schizophrenia, average duration of illness 20 years and using 400 mg/d for 8 weeks, reported negative results [263], but another trial of 60 patients with chronic schizophrenia, average duration of illness 8 years and "in an active phase of illness," also

using 400 mg/d for 8 weeks, reported a significant improvement in positive and total symptoms on PANSS [264]. Most recently, a study of 49 individuals with first-episode schizophrenia, using 400 mg/day for 6 weeks, reported significant improvement in negative and total symptoms on PANSS [265].

8.10.2.2 Acetylsalicylic Acid

Laan et al. [266] reported findings from a randomized (aspirin 1,000 mg/d or placebo), double-blind, placebo-controlled study with 70 antipsychotic-treated inpatients and outpatients with a DSM-IV-diagnosed schizophrenia spectrum disorder from ten psychiatric hospitals. Patients were randomized to adjuvant treatment with aspirin 1,000 mg/d or placebo. The authors report a mean modest reduction of the PANSS total score. Effect size was approximately 0.5. Aspirin did not significantly affect cognitive function. No substantial side effects were recorded.

Sommer et al. [37] summarized five double-blind, randomized, placebo-controlled trials, with a total of 264 patients. Four studies applied celecoxib, and one used acetylsalicylic acid. Authors found a mean effect size of 0.43 ($p=0.02$) in favor of NSAIDs on total symptom severity. For positive and negative symptom severity, the mean standardized difference was about 0.3 ($p<0.05$). These results suggest that NSAID augmentation could be a potentially useful strategy to reduce symptom severity in schizophrenia. Since these initial studies were conducted on small samples, the obtained results should be interpreted with caution.

8.11 Acetilcholinesterase Inhibitors

Alterations in the central cholinergic system of patients with schizophrenia such as reduced numbers of muscarinic and nicotinic receptors in the cortex and hippocampus may contribute to the cognitive impairment associated with schizophrenia [267]. Furthermore, several lines of evidence suggest that cholinergic deficits may contribute to the pathophysiology of schizophrenia, depression, and dementia [268, 269]. Therefore, pharmacological treatments that enhance central cholinergic function may be useful as cognitive enhancers in schizophrenia.

8.11.1 Mechanism of Action

To understand the underlying mechanism for the clinical effectiveness of, for example, galantamine, neuropharmacological studies have been performed in animal models of several psychiatric disorders. These studies suggest that the nicotinic receptor-modulating properties as well as muscarinic receptor activation contribute to the galantamine's antipsychotic effect and contribution to the improvement of

cognitive dysfunction [270]. Donepezil is an acetylcholinesterase inhibitor that appears to enhance cognitive functioning in patients with dementia [268].

8.11.2 Clinical Studies

8.11.2.1 Donepezil

In a randomized placebo-controlled add-on trial, schizophrenia patients were randomly assigned to donepezil titrated up to 10 mg/day or placebo for 12 weeks (donepezil, n = 121; placebo, n = 124). Donepezil did not improve performance on any cognitive test compared to placebo and was associated with worsening of negative symptoms [271].

8.11.2.2 Galantamine

Add-on galantamine to the FGAs of patients with schizophrenia did not produce a change in the cognitive function or state of psychopathology [272]. Lindenmayer and Khan [273] performed a 52-week double-blind, randomized study of treatment with long-acting injectable risperidone (25 mg or 50 mg every 2 weeks). Adjunctive galantamine (up to 24 mg/day) or placebo treatment was administered from month 6–12. Galantamine showed no ameliorative effects on cognitive measures in this 6 month trial.

8.11.2.3 Meta-analysis

Ribeiz et al. [274] conducted a literature search (up to December 2008) for randomized, double-blind, placebo-controlled trials with donepezil, rivastigmine or galantamine in patients with SZ/SA disorder. The meta-analysis of 13 double-blind studies (four with rivastigmine, six with donepezil and three with galantamine) suggests that specific cognitive deficits (memory, and the motor speed and attention part of executive function) of patients with SZ/SA disorder respond to rivastigmine, donepezil and galantamine as adjunctive therapy.

Recently, Singh, Kour, and Jayaram [269] evaluated the clinical effects, safety and cost effectiveness of acetylcholinesterase inhibitors by analyzine all clinical randomized trials comparing acetylcholinesterase inhibitors with antipsychotics or placebo either alone, or in combination, for schizophrenia and schizophrenia-like psychoses. The acetylcholinesterase inhibitor plus antipsychotic showed benefit over antipsychotic and placebo in the following outcomes: PANSS negative and general psychopathology, improvement in depressive symptoms, cognitive domains—attention, visual memory, verbal memory and language and executive functioning. Confirmatory studies are needed to determine the clinical utility of this treatment strategy.

8.12 Purinergic-Related Drugs

A purinergic hypothesis of schizophrenia postulates that increased adenosinergic transmission reduces the affinity of dopamine agonists for dopamine receptors [275]. This model also addresses the systemic aspects of schizophrenia, based on peripheral roles of purines, such as modulation of the immune system.

8.12.1 Mechanism of Action

Allopurinol, a xanthine oxidase inhibitor, may increase circulating pools of adenosine and may have antipsychotic and anxiolytic effects [276].

8.12.2 Clinical Studies

8.12.2.1 Allopurinol

Clinical trials show that adjuvant allopurinol may benefit treatment refractory schizophernia patients. Allopurinol is well tolerated by most patients [276]. In another trial, 59 schizophrenia outpatients (51 patients completed the trial) were randomly assigned to receive adjunctive allopurinol 300 mg bid or identical placebo for 8 weeks after a 2-week placebo run-in [277]. A total of 4 of 31 in the allopurinol group and 0 of 28 in the placebo group had at least a 20% reduction in total PANSS score at the final study visit ($p = 0.049$). Among the completers ($n = 51$), individuals in the allopurinol group rated themselves as more improved than those in the placebo group ($p = 0.025$). Allopurinol was well tolerated. Allopurinol may be an effective adjunctive medication for some patients with persistent schizophrenia.

Weiser et al. [278] performed a multicenter, 8-week randomized clinical trial of allopurinol vs. placebo added to anti-psychotic medications in 248 patients with SZ/SA disorder. Both groups showed improvement in the PANSS (effect size = 1.13) and in clinical and cognitive measures. No between group differences were observed in any outcome measures. These findings do not support allopurinol as a treatment for schizophrenia.

8.13 Psychostimulants

8.13.1 Mechanism of Action

Psychostimulants increase the release of dopamine and norepinephrine and are a well-established treatment for attentional disorders.

8.13.2 Clinical Studies

8.13.2.1 D-amphetamine

In schizophrenia patients treated with haloperidol, D-amphetamine was found to enhance prefrontal cortical activation during performance of the Wisconsin Word Sort Test and to improve processing speed, whereas performance on memory and attentional tasks did not improve significantly [279]. Barch and Carter [280] found that, compared to placebo, D-amphetamine improved reaction times on spatial memory and Stroop tests, working memory accuracy, and language production when added to first generation antipsychotics. Healthy subjects displayed a similar pattern of cognitive improvement, though there was no change in working memory accuracy. Pietrzak and colleagues [281] reported improvement in executive function, attention, and speed of processing with D-amphetamine compared to placebo in chronic schizophrenia patients.

8.13.2.2 Modafinil

Modafinil is a Food and Drug Administration—approved medication with wake-promoting properties. Pre-clinical studies of modafinil suggest a complex profile of neurochemical and behavioral effects, distinct from those of amphetamines. In addition, modafinil shows initial promise for a variety of off-label indications in psychiatry, including treatment-resistant depression, attention-deficit/hyperactivity disorder, substance-dependence, and schizophrenia [282–284].

Compared to placebo, modafinil achieves positive but mainly variable results on different clinical and cognitive measures. Several studies have shown promising preliminary results in clinical domains when modafinil was added to antipsychotic treatment regimens [285, 286]. However, other clinical trials did not reveal any effect of modafinil on negative symptoms [287, 288] or wakefulness/fatigue or cognition compared to placebo [288, 289]. In a 4-week study, adjunctive armodafinil was not associated with an improvement in cognitive measures, and the negative symptoms of schizophrenia [290].

There were no significant differences in neurocognitive measures between adjunctive armodafinil (150 mg/d) and placebo in this 6-week study in 60 patients with schizophrenia or schizoaffective disorder. However, armodafinil was associated with significant improvement in the Scale for the SANS anhedonia-asociality ($F_{1,41}=4.1$, $p=0.05$), but not other negative symptom domains [291]. Scoriels et al. [292] aimed to establish modafinil's role in the adjunctive treatment of cognitive impairments. Forty patients with first episode psychosis participated in a randomized, double-blind, placebo-controlled crossover design study to assess the effects of a single dose of 200 mg modafinil on measures of executive functioning, memory, learning, impulsivity and attention. *Modafinil improved verbal working memory, spatial working memory errors and strategy use*. It also reduced discrimination

errors in a task testing impulsivity. Modafinil showed no effect on impulsivity measures, sustained attention, attentional set-shifting, learning or fluency. Thus, modafinil selectively enhances working memory in first episode psychosis patients. Modafinil significantly improved the recognition of sad facial expressions in first episode psychosis, while there was no effect of modafinil on subjective mood ratings, on tasks measuring emotional sensitivity to reward or punishment, or on interference of emotional valence on cognitive function [293]. Thus, evidence for the use of modafinil or armodafinil as add-on therapy to antipsychotic drugs in schizophrenia is inconclusive owing to small sample sizes and methodological differences of the various trials (cognitive testing). Adverse events include insomnia, headache, nausea, nervousness and hypertension. Further research is required to address the potential benefits and risks of chronic administration of modafinil to patients with schizophrenia.

8.14 Beta Blockers

8.14.1 Mechanism of Action

Propranolol is a non-selective beta-adrenergic receptor blocking agent. It has no other autonomic nervous system activity. Propranolol is a competitive antagonist which specifically competes with beta-adrenergic receptor stimulating agents for available beta-receptor sites. The most serious adverse effects that may be encountered with propranolol are congestive heart failure and bronchospasm.

8.14.2 Clinical Studies

8.14.2.1 Propranolol

High dose propranolol up to 1,200 mg/day has been shown to augment antipsychotic efficacy in treatment refractory schizophrenia. Reported beneficial effects include an ability to treat akathisia, increase antipsychotic serum levels, and decrease anxiety symptoms [38]. The latest Cochrane review and meta-analysis included only five studies with 117 patients and did not support the efficacy of antipsychotic augmentation with beta-blockers [294].

8.14.2.2 Pindolol

Treatment of aggression in schizophrenic patients is a major challenge. Caspi et al. [295] examined the efficacy of augmentation of antipsychotic treatment with

pindolol in the amelioration of aggression. Thirty male inpatients meeting DSM-IV criteria for schizophrenia, aged 20–65 years involved in four or more aggressive incidents in the two previous months, were enrolled in a double-blind crossover study. Aggression was evaluated per incident, with the Overt Aggression Scale. Patients received either pindolol or placebo augmentation 5 mg × three times a day until crossover, and then switched. revealed a significantly decline in the number According to Overt Aggression Scale scores, pindolol, with its dual beta and 5-HT_{1A} blocking effect ameliorated both number of aggressive incidents (0.59 versus 1.46, $p < 0.02$; 1.96 versus 3.23, $p < 0.05$, respectively).and severity of incidents towards objects and other persons (0.89 versus 3.58, $p < 0.0001$; 2.89 versus 6.85, $p < 0.004$, respectively). Influence on severity may be associated with a 5-HT_{1A} antagonistic effect.

8.15 Dietary Supplements

There is considerable scientific disagreement about the possible effects of dietary supplements on mental health and SZ/SA disorder.

8.15.1 Omega-3 Fatty Acids

Decreased n-3 fatty acid levels have been reported in patients with depression, schizophrenia, and Alzheimer's disease. Recently, eicosapentaenoic acid (EPA) was used to treat several psychiatric and neurodegenerative diseases due to its anti-inflammatory and neuroprotective effects [296, 297]. Published results are conflicting, and the antipsychotic efficacy of such augmentation strategies is not well established. A Cochrane review and meta-analysis included six short-term trials with 353 participants. The results were contradictory, leading the study authors to conclude that this treatment still needs further investigation [298]. A recent meta-analysis included double-blind, randomized, placebo-controlled studies using purified or EPA-enriched oils in schizophrenia: the database included 167 schizophrenic subjects under the placebo arm matched with 168 schizophrenic subjects in the EPA arm. The meta-analysis did not show a consistent significant beneficial effect for EPA augmentation on psychotic symptoms in schizophrenia [39].

8.15.2 L-Theanine

L-theanine is a unique amino acid present almost exclusively in the tea plant. It possesses neuroprotective, mood-enhancing, and relaxation properties.

8.15.2.1 Mechanism of Action

L-theanine is a water-soluble amino acid. L-theanine has been shown to have a direct influence on brain activity, such as reducing stress [299, 300]. At high doses (higher than usual doses found in a cup of black tea about 20 mg), it has the ability to relax the mind without causing drowsiness. Thirty-five participants were given either 50 mg of L-theanine or placebo. Electroencephalogram tests were done at baseline and then at specified times afterwards (45, 60, 75, 90, and 105 min). Researchers found that there was a greater increase in alpha activity in those who took L-theanine compared to placebo, demonstrating that the amino acid had an effect on the participants' general state of mental alertness and arousal.

8.15.2.2 Clinical Study

Ritsner et al. [301] conducted a first study designed to evaluate the efficacy and tolerability of L-theanine augmentation of antipsychotic treatment of 60 patients (40 patients completed the study protocol) with chronic SZ/SA disorder during an 8-week, double-blind, randomized, placebo-controlled study. 400 mg/day of L-theanine was added to ongoing antipsychotic treatment. Compared with placebo, L-theanine augmentation was associated with reduction of anxiety ($p = 0.015$) and positive ($p = 0.009$) and general psychopathology ($p < 0.001$) scores (measured by the PANSS 3-dimensional model). According to the 5-dimension model of psychopathology, L-theanine produced significant reductions on PANSS positive ($p = 0.004$) and activation factor ($p = 0.006$) scores compared to placebo. The effect sizes (Cohen *d*) for these differences ranged from modest to moderate (0.09–0.39). L-theanine was found to be a safe and well-tolerated medication. Regression models among L-theanine-treated patients indicate that circulating levels of brain-derived neurotrophic factor (BDNF) and cortisol-to-DHEAS*100 molar ratios were significantly associated with the beneficial clinical effects of L-theanine augmentation [302]. Variability of serum BDNF levels accounted for 26.2% of the total variance in reduction of dysphoric mood and 38.2% in anxiety scores. In addition, the changes in cortisol-to-DHEAS*100 molar ratio accounted for 30–34% of the variance in activation factor and dysphoric mood scores and for 15.9% in anxiety scores. Regression models among placebo-treated patients did not reach significant levels ($p > 0.05$). Thus, L-theanine augmentation of antipsychotic therapy can ameliorate positive, activation, and anxiety symptoms in SZ/SA disorder patients. Furthermore, results indicate that circulating BDNF and cortisol-to-DHEAS*100 molar ratio may be involved in the beneficial clinical effects of L-theanine as augmentation of antipsychotic therapy in schizophrenia and schizoaffective disorder patients. Long-term studies of L-theanine are needed to substantiate the clinically significant benefits of L-theanine augmentation.

8.15.3 S-Adenosyl-L-methionine

S-adenosyl L-methionine (SAMe) is the natural, universal methyl group donor, participating in transmethylation reactions, known and commonly used as a dietary supplement since 1952 [303]. It plays an important role in the synthesis of neuromediators and melatonin and mechanisms of epigenetic regulation. Since SAM-e is involved in several metabolic processes, its administration may have a role in the amelioration of several disorders.

8.15.3.1 Mechanism of Action

SAM-e is able to cross the blood-brain barrier. SAM-e's predominant function is as a primary methyl group donor for a wide range of compounds including catecholamines, membrane phospholipids, fatty acids, nucleic acids, porphyrins, choline carnitine and creatinine. Following release of its methyl group, SAM-e is converted to S-adenosyl-homocysteine which, in turn, acts as a competitive inhibitor of SAM-e-mediated methylation reactions. An important function of SAM-e involves methylation of certain phospholipids, particularly phosphatidylethanolamine, and proteins which aid in the maintenance/control of the fluidity and microviscosity of cell membranes. Intact SAM-e metabolism is also considered vital for myelin maintenance [304].

8.15.3.2 Clinical Study

The efficacy of SAM-e in managing schizophrenia symptomatology in patients with a low activity catechol-*O*-methyltransferase polymorphism was investigated in a pilot study [305]. Eighteen patients with chronic schizophrenia were randomly assigned to receive either SAM-e (800 mg) or placebo for 8 weeks in a double-blind fashion. Results indicated some reduction in aggressive behavior and improved quality of life following SAM-e administration. Female patients showed improvement of depressive symptoms. Clinical improvement did not correlate with serum SAM-e levels. Two patients that received SAM-e exhibited some exacerbation of irritability. This preliminary pilot short-term study cautiously supports SAM-e as an adjunct in management of aggressive behavior and quality of life impairment in schizophrenia.

8.16 Conclusions and Future Directions

Development of new antipsychotic drugs over the last decade has not produced dramatic improvement in the treatment of schizophrenia. To find better alternatives to the existing antipsychotics, novel receptors are being targeted to develop third-generation antipsychotic agents [306–308]. Other less classic pathways are also under study and have led to some agents that are in very early stages of development

Table 8.1 Possible improvement in schizophrenia dimensions after add-on adjunctive agents or supplements [22, 29–39]. *DHEA* dehydroepiandrosterone

Augmentative agents	Positive symptoms	Negative symptoms	General symptoms	Depressive symptoms	Cognitive deficit	Aggression, excitement	Functioning & Quality of life
Mood stabilizers	Lamotrigine Topiramate	Valproate	Valproate			Carbamazepine	
Antidepressants		Fluvoxamine Fluoxetine Mirtazapine Citalopram		Fluvoxamine Mirtazapine	Mirtazapine	Fluoxetine Citalopram	Citalopram
Anti-Anxiety agents	Alprazolam	Alprazolam					
Neuroendocrine agents	Estradiol	Pregnenolone DHEA			Pregnenolone DHEA		
	Sarcosine D-serine	Glycine Sarcosine D-serine	Sarcosine	Glycine D-serine	Glycine Sarcosine D-serine		Glycine
Anti-inflammatory strategy	Aspirin		Celecoxib				
Cholinesterase inhibitors					Rivastigmine Donepezil Galantamine		
Miscellaneous agents or supplements	Allopurinol Propranolol Omega-3 fats L-Theanine Bexarotene	Allopurinol Omega-3 fats	Allopurinol Omega-3 fats	Omega-3 fats L-Theanine	Amphetamine Modafinil Omega-3 fats	Propranolol Pindolol	Modafinil

Possible improvement in schizophrenia dimensions after add-on adjunctive agents or supplements [22, 42, 64, 97, 98, 133,171, 172, 213, 264, 292, 298]

such as those acting on sigma receptors, cholecystokinin antagonists, neurotensin agonists, neurokinin receptor antagonists, GABAergic enhancers, and cannabinoid receptor modulators [309].

Despite the availability of different classes of drugs for the treatment of SZ/SA disorder, there remains a high prevalence of drug resistance, partial response, subsyndromal symptomatology, and relapse. When treating patients who did not adequately respond to their first antipsychotic therapy, there are three additional options: (1) switch to a different antipsychotic; (2) combine two antipsychotics; or (3) augment the current drug treatment with a non- antipsychotic agent. In present clinical practice non-dopaminergic drugs are usually prescribed in order to gain an enhanced therapeutic effect when the response to antipsychotic monotherapy has been disappointing.

There is a range of potential augmenting agents in SZ/SA disorder, each with varying available evidence regarding efficacy and tolerability. The rationale behind the augmentation strategy is to simultaneously target different brain functions in the hope of providing symptom relief. It is increasingly evident that various non-dopaminergic receptors have an important role in the clinical profile of schizophrenia—with noradrenergic, glutamatergic and serotonergic receptors involved in the pathogenesis of positive and negative symptoms. These agents include multiple antidepressants, lithium, antiepileptic agents, hormone, stimulants, and others. Table 8.1 summarizes some evidence regarding improvement in the specific

dimension of schizophrenia after add-on adjunctive agents or supplements while no adjunctive agent has been clearly demonstrated to be markedly efficacious. Although there is an increasing volume of augmentation trials, some of the available studies reveal conflicting results, and recommendations are based upon theoretical assumptions rather than upon evidence-based knowledge. Augmentation is generally considered the best option when a first drug provides partial relief but does not completely alleviate symptoms [38, 310]. Disadvantages of this strategy include cost of additional treatment and (if drug augmentation is used) increased likelihood of side effects, drug interactions, and the general lack of evidence for effectiveness.

Acknowledgements I wish to express gratitude to Ms. Rena Kurs, B.A. (Shaar-Menashe Mental Health Center, Hadera, Israel) for editorial assistance.

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Chapter 9
Antidepressants in Schizophrenia: A Place for Them?

Viacheslav Terevnikov and Grigori Joffe

Abstract Antipsychotic monotherapy is often insufficient to achieve optimal outcome in schizophrenia. One of the numerous adjunctive psychopharmacological strategies proposed to overcome this drawback is a combination of an antipsychotic with an antidepressant. Existing evidence on the efficacy of such combination is ambiguous and varies by syndrome domains and antidepressant classes and—within a class—by individual compounds. The most dependable data favor—as a group—receptor-blocking antidepressants. Of these, mirtazapine demonstrates probably the most consistent beneficial effects, in particular for negative symptoms and cognitive deficits. While current guidelines warn about possible antidepressant-provoked psychotic exacerbation, no data today support these reservations, at least in chronic schizophrenia and when a contemporaneous antipsychotic therapy continues. Moreover, one randomized controlled trial (RCT) revealed an additive antipsychotic effect of an adjunctive antidepressant (mirtazapine) and, according to a recently published large cohort study concomitant antidepressants can reduce suicide rates and overall mortality of patients with schizophrenia. It appears hence that caution regarding the add-on antidepressant use recommended by current guidelines can be soon softened. Due to scarcity of data, conservative use of antidepressants may, however, be still justifiable in acute schizophrenia. If an antipsychotic-antidepressant combination is to be prescribed, a thorough knowledge of pharmacodynamic and pharmacokinetic (especially, regarding several CYP450 liver enzymes) interactions is essential to avoid adverse effects and complications.

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M.S. Ritsner (ed.), *Polypharmacy in Psychiatry Practice, Volume I: Multiple Medication Use Strategies*, DOI 10.1007/978-94-007-5805-6_9,

A convincing amount of evidence is emerging on some previously unknown mechanisms of action beyond the classical neurotransmitter/monoamine receptor theory—findings that may boost research and development in the nearest future. For instance, the novel body of data on the proneuroplastic effect of antidepressants may help us to understand how an add-on antidepressant can improve neurocognition in chronic schizophrenia, and how antidepressant monotherapy can prevent psychosis in high-risk groups. More large RCTs with various combinations are needed to reveal the most feasible antidepressant therapy strategies for schizophrenia.

Abbreviations

AIMS	Abnormal Involuntary Movement Scale
APA	American Psychiatric Association
BDI	Beck Depression Inventory
EPS	Extrapyramidal Symptoms
FGA	First-Generation Antipsychotic
HDRS	Hamilton Depression Rating Scale
MDD	Major Depressive Disorder
NICE	National Institute for Health and Clinical Excellence
PANSS	Positive and Negative Syndrome Scale
RCT	Randomized Controlled Trial
SAS	Simpson-Angus Scale
SGA	Second Generation Antipsychotic
SNRI	Selective Noradrenaline Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic Antidepressant

9.1 Background and Rationale

Schizophrenia is one of the most debilitating and difficult-to-treat psychiatric disorders, with a worldwide prevalence of about 0.7% [1]. The mainstay of acute and maintenance treatment of schizophrenia nowadays is antipsychotic medication [2]. Despite adequate treatment with antipsychotics, the optimal outcome can, however, be achieved in only 10–20% of patients, with 15–20% showing partial or complete treatment resistance [3]. In cases of insufficient response to at least two adequate trials of a First Generation Antipsychotic (FGA) or Second Generation Antipsychotic (SGA), the gold standard is clozapine monotherapy. Though efficacious in treatment-resistant schizophrenia, clozapine medication fails to invariably yield the optimal outcome [4]. Moreover, treatment with clozapine is associated with a number of adverse effects, some of them serious and potentially fatal. Thus, there still exists a call for alternative strategies.

During recent decades, a numerous adjunctive psychopharmacological treatments are emerging to improve clinical and functional outcomes in schizophrenia, including lithium, anticonvulsants, sex hormones, COX-inhibitors, glutamatergic drugs, acetylcholine esterase inhibitors, and antidepressants [5].

Antidepressants as adjuncts in schizophrenia are under extensive study and are—despite contradictory evidence regarding their efficacy—in wide clinical use [5, 6]. The existing guidelines do not yet unconditionally recommend antidepressants for treatment of negative, positive, or cognitive symptoms—neither in the acute nor in the stable phase of the disease. For example, the *Practice Guideline for the Treatment of Patients with Schizophrenia* developed by the American Psychiatric Association suggests that antidepressants "can be considered for treatment of comorbid major depression," with caution, due to a possible risk that sometimes an antidepressant may exacerbate psychosis [7]. Similarly, the NICE guideline on the treatment of schizophrenia by the British Royal College of Psychiatrists suggests limiting the augmentation of antipsychotics with antidepressants only to treatment of "comorbid or secondary psychiatric problems, such as depression and anxiety" [8].

Nevertheless, recent research data show that in actual practice clinicians tend widely to use antidepressants to overcome, in addition to co-occurring depression, posttraumatic stress disorder, anxiety, or schizoaffective disorder [6], also negative symptoms and cognitive deficits. In the Clinical Trials of Intervention Effectiveness (CATIE) study, approximately a third of the participants were receiving an antidepressant at the study baseline [9].

9.1.1 Rationale for Antidepressant Medication in Schizophrenia

In earlier studies, use of antidepressants for (other than comorbid depression) symptoms of schizophrenia relied on the clinical overlap between some symptoms of the disease and unipolar depression. An assumption of antidepressants' stimulative effects prompted, for instance, antidepressant treatment of anhedonia and avolition [10].

In regard to biological understanding of both major depressive disorder and schizophrenia, the 1990s became the Serotonin Decade; manipulation of the serotonin system became the focus of interest. In particular, the adjunctive SSRIs were supposed to affect the primary negative symptoms and cognitive deficits by re-setting the dysfunctional serotonergic system [11, 12].

The mechanism of action of the SSRIs and the vast majority of other antidepressants is based on inhibition of transporters of serotonin or other monoamines, and thereby hindered re-uptake and enhanced availability of monoamines for neurotransmission. There exists, however, a small group of antidepressants that act via inhibition of monoamine receptors rather than of transporters. These antidepressants—trazodone, nefazodone, mianserin, and mirtazapine—share the ability to inhibit several receptors, including postsynaptic 5-HT_2 receptors. The rationale for combination of these antidepressants with antipsychotics stemmed from the theory of "atypicality"

especially popular in the late 1990s to early 2000s. According to this theory, antipsychotics inhibiting $5HT_2$ receptors more than inhibiting D_2 receptors ("atypical", or SGAs) were more effective in treating positive, negative, and cognitive symptoms, while causing fewer extrapyramidal side effects than did their conventional counterparts—D_2 blockers with negligible $5HT_2$ inhibition [13, 14]. One proposal was that combination of an inhibitor of the $5HT_2$ receptor with a "pure" D_2 blocker would result in a clinical effect resembling that of an atypical antipsychotic, with additional benefits in terms of both efficacy and tolerability [15, 16].

Preliminary evidence supporting this theory grew out of an earlier study in haloperidol-treated schizophrenia patients receiving add-on ritanserine, a pure $5HT_2$ blocker devoid of antidepressive properties; ritanserin alleviated negative symptoms [17]. After that, interest in research concerning combinations of receptor-blocking antidepressants with FGAs has gradually grown. Several studies performed during the 1990s and 2000s have provided additional evidence in support of this theory (see Sections 9.2.1–9.2.5).

Though theoretically a combination of receptor-blocking antidepressants with SGAs (which are $5HT_2$ inhibitors, too) might make little sense, this approach became popular in the 2000s due to current clinical realities—SGAs became a first-line antipsychotic medication, while the use of FGAs was rapidly fading [18]. These findings fueled the existing interest in research into the pathogenesis of schizophrenia and the role therein of serotonin receptors [14].

Some of these receptor-blocking antidepressants demonstrate—beyond their inhibition of the $5HT_2$ receptors—effects on other types of receptors, e.g. mirtazapine and mianserin that inhibit $5HT_3$ serotonin receptors, presynaptic alpha-2 noradrenaline receptors, and postsynaptic histamine receptors, and they also indirectly stimulate $5HT_{1A}$ serotonin receptors. A possible role for these receptors in the pathogenesis of some psychiatric disorders, including schizophrenia, has been the subject of intense research.

There exists a body of preclinical evidence that 5-HT_{1A} receptors, together with cholinergic and glutamatergic systems, modulate learning consolidation. For instance, 5-HT_{1A} receptor antagonists may alleviate a cognitive deficit caused by an N-Methyl-D-Aspartate glutamatergic receptor antagonist [19]. In clinical studies, treatment with the adjunctive partial 5-HT_{1A} agonists tandospirone [20] and buspirone [21] improved schizophrenia patients' cognitive performance.

Moreover, 5-HT_3 receptor antagonists demonstrated, in preclinical studies, procognitive effects [22]. In a clinical study as well, Zhang and co-authors [23] found that the 5-HT_3 blocking agent ondansetron, when added to on-going haloperidol, improved negative symptoms, general psychopathology, and cognitive functions.

Alpha-2 noradrenoreceptor blockade also seems a potentially useful mechanism to improve schizophrenia treatment. In a preclinical study by Wadenberg and co-authors [24], the alpha-2 antagonist idazoxan enhanced the efficacy of both typical (haloperidol) and atypical (olanzapine) antipsychotics and reversed haloperidol-induced catalepsy. This was replicated in another preclinical study, by Marcus and co-authors [25], when idazoxan enhanced the therapeutic effect of risperidone and

facilitated cortical dopaminergic and glutamatergic neurotransmission. Earlier, in an RCT by Litman and co-authors [26], idazoxan combined with fluphenazine produced clinical improvement comparable to that of clozapine.

The pathophysiology of schizophrenia appears to include neurodegeneration and altered neurogenesis [27]. Some antipsychotics may demonstrate neuroprotective and neurotrophic/neuroplastic properties [28, 29] that result in improved outcome, including enhanced neurocognition [30]. Antidepressants may also reactivate neuroplasticity [31] and thus—though, in themselves devoid of antipsychotic activity—contribute to the improved treatment outcomes in different phases of schizophrenia. This might be an underlying mechanism of encouraging results in a recent open study by Cornblatt and collaborators [32]. In that study, antidepressants prevented conversion to psychosis in subjects with prodromal schizophrenia symptoms more effectively than did SGAs.

What Is the Empirical Evidence?

9.2 Efficacy Studies: Data from RCTs[1]

In the literature, we were able to locate 31 RCTs designed to study the efficacy of antidepressants in schizophrenia treatment. None of these studies explored antidepressants as monotherapy, and all of them employed the add-on design, i.e. subjects received antidepressants added to their stable antipsychotic treatment. The vast majority of the studies were of small size, with subject populations ranging from 14 to 47 and with only two studies exceeding this number—90 patients in an add-on citalopram study by Salokangas and co-authors [33] and 53 patients in a add-on fluvoxamine study by Silver and co-authors [34]. The duration of the studies ranged from 1 to 24 weeks; most of them lasted from 6 to 8 weeks.

9.2.1 Efficacy of Antidepressants in Treatment of Negative Symptoms

Negative symptoms constitute a major clinical domain of schizophrenia. According to recent estimates, 15–20% of the patients demonstrate primary negative symptoms (alogia, avolition, blunted affect, anhedonia) [35]. These symptoms contribute to social isolation, poor level of functioning, and low quality of life. Compared to positive symptoms, negative symptoms tend to be less responsive to standard medical treatment, especially with FGAs. Introduction of SGAs in 1990s was accompanied by much enthusiasm based on a number of earlier reports indicating their better

[1] Open label trials are not the focus of this review; only a few will be mentioned and discussed.

efficacy against negative symptoms. More recent research data show, however, that they demonstrate at best modest benefits [36].

Antidepressants have undergone wide study as potential adjunctive agents for treatment of negative symptoms.

Earlier studies with TCAs yielded mainly positive results [10, 37, 38], but they had substantial methodological limitations, especially in regard to the outcome measures, which called their conclusions into question.

Later, the 1990s and early 2000s saw many studies of selective serotonin reuptake inhibitors. Quantitatively, the numbers with positive and negative results were approximately the same, but when analyzed separately, the efficacy of individual SSRIs appeared to differ. Namely, both studies with fluvoxamine were positive [34, 39], as was also the only study with paroxetine [40]. The studies with fluoxetine yielded, however, controversial results, with two earlier studies being positive [41, 42] and four later studies, negative [43–46]. All trials with adjunctive sertraline or citalopram in the treatment of negative symptoms in schizophrenia failed to demonstrate their superiority over placebo [33, 47–49], as did both trials with the selective noradrenaline reuptake inhibitor reboxetine [50, 51].

The vast majority of studies with receptor-blocking antidepressants as add-on treatment in chronic schizophrenia were positive. Of this type of drugs, mirtazapine appears to have demonstrated the most consistent findings. Four [16, 52–54] of five RCTs demonstrated the superiority of mirtazapine added to conventional or novel antipsychotics over add-on placebo, with effect size ranging from 0.28 to 1.92 (CI 95%) [55]; only one trial [56] failed to show any advantages of mirtazapine over placebo. Two RCTs with add-on trazodone [57, 58] were also positive, with the effect size ranging from 0.34 to 0.92 (CI 95%). The data for mianserin seem more controversial with one positive study [58] and two negative ones [59, 60]. It should be mentioned, however, that the latter study was small (n = 18). The size effect for mianserin ranged from 0.03 to 0.53 (CI 95%) [55]. No RCTs with nefazodone have yet appeared.

To summarize, results of the RCTs suggest that add-on antidepressant treatment may become a useful option in treatment of negative symptoms of schizophrenia. The receptor-blocking antidepressants may perhaps inspire more confidence than do antidepressants from other groups, since their effect on negative symptoms seems to be rather consistent.

9.2.2 Positive Symptoms

While not focused specifically upon psychotic symptoms, many of the adjunctive antidepressant reports also provided data on the positive symptoms of schizophrenia.

No RCTs with the transporter inhibitors nor the receptor inhibitors showed any additive antipsychotic effect of antidepressants with the exception of our own [53]. In that study, mirtazapine added to stable doses of FGAs in patients with chronic, highly symptomatic schizophrenia out-performed placebo in all outcome measures, including

the PANSS positive subscale. This result was replicated in an extension phase of that same study, in which positive symptoms improved after a switch of the placebo group to add-on mirtazapine [61]. The latter findings should be accepted with caution, however, since this extension phase had an open-label design, as did the earlier small pilot nefazodone study of Joffe et al. [62] in which positive symptoms also improved. Poyurovski and his group [63] also concluded that with mirtazapine, psychosis improved, but their claim seemed to be based on the change in total PANSS scores, whereas improvement on the PANSS-positive subscale scores was unspecified.

Though evidence as to the efficacy of adjunctive antidepressants for the positive symptoms of schizophrenia remains scarce, it should be emphasized that antidepressant treatment does not appear to cause any additional risk of the worsening of psychosis, provided that patients' parallel antipsychotic medication continues. Interestingly, in the study by Poyurovski and co-authors [45], patients experiencing their acute first-episode schizophrenia who received fluoxetine 20 mg/day added to a stable dose of 10 mg olanzapine demonstrated less improvement in positive and disorganized symptoms than did those who received add-on placebo. However, the patients in the fluoxetine group also demonstrated a certain degree of improvement of their positive symptoms.

Thus, although evidence is still insufficient to allow recommendation of any of the existing antidepressants to enhance the antipsychotic effects of the FGAs and SGAs, the use of add-on antidepressants seems to be safe at least in chronic schizophrenia (see also 2.3). As mentioned, the APA Guidelines suggest special caution in using antidepressants in patients with schizophrenia—a recommendation that may no longer be justified in light of the current evidence.

9.2.3 Efficacy of Antidepressants in Treatment of Depression in Schizophrenia

Depressive symptoms are common in schizophrenia (in particular, in its acute phase [64]), with an estimated overall prevalence of 50% [65]. Comorbid depression significantly elevates the risk for suicide and negatively influences patients' quality of life and level of functioning [66, 67]. Moreover, at chronic stages of schizophrenia, depression is associated with a higher risk for relapse [68].

Evidence regarding the possible role of various psychopharmacological agents in treating depression in schizophrenia is still far from convincing. FGAs may even worsen depressive symptoms [69], but some SGAs demonstrate antidepressive properties both in mood disorders and in schizophrenia [70–73]. Nevertheless, a considerable proportion of SGA-treated patients with schizophrenia suffer from depressive symptoms, as well.

The efficacy of a combination of an antipsychotic with an antidepressant for depressive symptoms has been a subject to extensive exploration. Noticeably, most of the existing body of evidence relies on patients with chronic schizophrenia and on trials not designed specifically for depression.

In regard to the TCAs, the only available RCT, the one by Siris et al. [74], revealed the superior efficacy of imipramine over placebo in the treatment of depressive symptoms in chronic schizophrenia.

For the SSRIs, of four RCTs carried out with add-on fluoxetine, only one [41] reported positive results (improvement in HDRS scores in favor of fluoxetine), whereas the later studies by Buchanan et al. [43], Arango et al. [44] and Bustillo et al. [46] failed to replicate this finding. In an RCT with another SSRI, sertraline added to different FGAs or to risperidone, HDRS- and BDI-measured depressive symptoms improved with clinical significance [48], while a study by Jockers-Scherubl et al. [40] of chronic patients treated with FGAs or SGAs revealed no superiority of paroxetine over placebo. Adjunctive citalopram led to an improvement in subsyndromal (≤8 on the HDRS) depressive symptoms as compared to adjunctive placebo in another RCT [75]. Two RCTs with a selective noradrenaline reuptake inhibitor reboxetine produced contradictory results. First, Schutz and Berk [50] found no additional antidepressant efficacy from reboxetine added to stable treatment with haloperidol. In a later RCT by Poyurovski et al. [51], reboxetine significantly improved depressive symptoms in olanzapine-treated patients with chronic schizophrenia.

Of receptor-blocking antidepressants, mianserin does not seem to be efficacious in the treatment of depressive symptoms in schizophrenia. In two published RCTs [59, 60], it failed to outperform placebo in FGA-treated subjects with chronic schizophrenia. Mirtazapine failed to improve depressive symptoms when added to haloperidol [16], clozapine [52], or various SGAs [56]. However, in a recent study by Terevnikov et al. [76], mirtazapine added to stable, relatively low doses of some FGAs in patients with chronic schizophrenia demonstrated a clear-cut superiority over placebo in the treatment of depressive symptoms (a decrease of 52% on the Calgary Depression Scale). This effect was independent of the desired effects of mirtazapine on other clinical domains.

Thus, an increasing body of evidence suggests that antidepressants may be beneficial for depressed patients with chronic schizophrenia. This evidence (although with some degree of controversy) comprises sertraline, fluoxetine, reboxetine, and mirtazapine. It should be noted that due to the small sample sizes of the majority of the studies, these results cannot be considered definite. Moreover, these studies were primarily designed to study the efficacy of antidepressants for negative or cognitive, but not for depressive symptoms of schizophrenia—another factor that limits the interpretation.

Another important question to be resolved is whether antidepressants should be used (or precluded) in the acute or chronic stage of schizophrenia. All the studies reviewed in this section involved populations with duration of illness exceeding 10 years, meaning that in chronic schizophrenia there is no reason to avoid adjunctive antidepressants.

The role of antidepressants in the acute phase of disease is less clear. An early precaution of antidepressants' ability to trigger psychotic exacerbation [77] was not based on evidence, nor has such evidence emerged later on. In the abovementioned trial by Poyurovsky and co-authors [45] fluoxetine added to olanzapine did not

prevent, though it delayed improvement of psychotic symptoms. Mirtazapine seems to improve psychotic symptoms when added to FGAs [53, 61]. To summarize, though the evidence is too sparse to be convincing, adjunctive antidepressants may be safer in the acute phase of schizophrenia than previously proposed. Nevertheless, not enough data exist on their benefits either, making a conservative attitude toward such co-administration still valid.

9.2.4 Efficacy of Antidepressants in Treatment of EPS

The theoretical assumption that add-on antidepressants may be effective against antipsychotic-induced EPS relies on the theory of dopamine deficiency in the basal ganglia. This theory states that pharmacological agents increasing available dopamine in this area may alleviate EPS symptoms. One possible mechanism may be their $5HT_2$ receptor antagonism—a property shared by SGAs and several receptor-blocking antidepressants.

Several studies tested this theory in the late 1990s and 2000s. Hayashi et al. [58] revealed a positive effect of trazodone on FGA-induced tardive dyskinesia. In contrast, both mianserin studies [58, 60] failed to demonstrate its superiority over placebo in treatment of EPS. Wynchank and Berk [78] found nefazodone to improve haloperidol-induced EPS measured by the SAS, but not to affect symptoms of akatisia or tardive dyskinesia. Results of several trials with mirtazapine were conflicting. Two studies found no improvement in haloperidol-induced [16] or risperidone-induced [54] EPS, while in another study [53], SAS-measured EPS improved in the mirtazapine-, but not in the placebo group (the difference in between-group comparisons was, however, not statistically significant).

There exists no theoretical basis for the possible efficacy of the transporter inhibitors in treatment of antipsychotic-induced EPS. Moreover, SSRIs may even cause EPS in patients with Major Depressive Disorder (MDD). Nevertheless, the influence of SSRIs and SNRIs on EPS was a secondary variable in a number of studies (see 2.1, 2.2 and 2.3.). Perhaps not surprisingly, all these studies yielded negative results.

Thus, some evidence suggests the plausible efficacy of the receptor-blocking antidepressants (except mianserin) in treatment of antipsychotic-induced EPS, but this evidence is rather limited and applies only to FGA-induced EPS.

9.2.5 Efficacy of Antidepressants in Treatment of Cognitive Symptoms of Schizophrenia

Cognitive impairment is one of the core components of schizophrenia [79]. Continuously growing evidence indicates that cognitive dysfunction is an even more important determinant of outcome in schizophrenia than are positive or negative

symptoms [80]. What still remains unclear is whether remediation of cognitive deficits in patients with schizophrenia may be achievable, and whether interventions targeting specifically cognitive symptoms may be beneficial [81]; if these are true, this would make the search for new, efficacious cognitive enhancement strategies meaningful. These strategies may include both psychosocial and pharmacological interventions [82]. The several groups of compounds identified to have a plausible cognitive-enhancing effect include alpha-7 nicotinic receptor agonists, M_1-muscarinic receptor agonists, dopaminergic agents, sympatomimetics, acetylcholinesterase inhibitors, glutamatergic agents, $5HT_{1A}$ receptor agonists, $5HT_{2A}$ receptor antagonists, and $\alpha 2$ adrenergic receptor antagonists [83].

The latter two mechanisms of action are shared by some receptor-blocking antidepressants. Of these, mianserin and mirtazapine served as potential cognitive enhancers in several trials. First, Poyurovski and co-authors [60] found that low-dose mianserin added to several FGAs in patients with chronic schizophrenia improved memory and learning, but not executive function as measured by the Wisconsin Card Sorting Test. In a 6-week RCT by Stenberg and co-authors [84], mirtazapine (n = 19 vs. placebo, n = 18) added to stable doses of various FGAs in patients with chronic schizophrenia significantly improved visuospatial functions as well as general mental speed and attentional control. Of note, a prolonged exposure to mirtazapine for an additional 6 weeks under open-label conditions led to further improvement in several neurocognitive parameters, as did a shift from placebo to open label mirtazapine in the control group [85]. In 2011, Cho and collaborators [86] published another RCT in which mirtazapine combined with risperidone improved not only negative symptoms, but also vocabulary and immediate memory in 21 patients with schizophrenia. And DelleChaie [87] found mirtazapine to improve some cognitive functions in clozapine-treated patients, but this study also relied on an open-label design and thus should not be overvalued.

Other classes of antidepressants have received negligible attention from researchers as potential cognitive enhancers in schizophrenia. Friedman and co-authors [49] found no statistically significant differences between effects of an adjunctive SSRI citalopram and placebo on any cognitive measures, indicating probably that increased availability of serotonin in the brain is by itself insufficient for treating cognitive impairment in schizophrenia.

Based on the theory that the noradrenergic system mediates cognitive dysfunction in schizophrenia patients, Poyurovsky and co-authors [88] investigated the efficacy of a Noradrenaline Reuptake Inhibitor reboxetine added to olanzapine on cognitive symptoms—also with disappointing results.

9.3 Effectiveness Studies

Only a handful of effectiveness studies (e.g., “real world” studies, in contrast to efficacy studies using an artificial “purified” scientific design, i.e., the RCT) concern adjuvant antidepressants in schizophrenia. A large study recently performed by

Tiihonen and co-authors [89] investigated relationships between polypharmacy and mortality rates in a complete nationwide cohort of 2,588 Finnish patients hospitalized for the first time with a diagnosis of schizophrenia between January 2000 and December 2007. They found that adjunctive antidepressant treatment was associated with diminished mortality from all causes (HR 0.57; 95% CI 0.28–1.16) including that from suicide (HR 0.15; 95% CI 0.03–0.77).

In a recent prospective study, Längle and co-authors [90] investigated the effects of psychotropic polypharmacy, including antidepressants, benzodiazepines, and mood stabilizers, on clinical outcomes and quality of life in 374 patients with schizophrenia and schizoaffective disorder treated with SGAs. Patients were assessed with the PANSS, the Global Assessment of Functioning, the Lancashire Quality of Life Profile, SAS, and AIMS during 24 months' follow-up. In that study, combinations of SGAs with antidepressants were associated with PANSS-measured clinical outcomes similar to those from antipsychotic monotherapy alone. Patients treated with an SGA-antidepressant combination demonstrated, however, a significantly larger improvement in EPS than with all other treatments, including monotherapy with SGAs. Notably, in that study population the mean baseline PANSS scores were low, ranging from 49.8 to 57.7, making it thus unclear whether these results can be extrapolated to more severely ill patients.

Glick and co-authors [91] investigated the clinical effect of tapering of an antidepressant treatment in a group of 22 stabilized patients with schizophrenia during their 3–12 months of follow-up. The outcome measure was the Clinical Global Impression-Improvement Scale (CGI-I). Tapering of an antidepressant led to worsening of a patient's mental condition in only one case, while in 18 cases no change was evident, and in three cases the patients' condition improved. This led the authors to conclude that tapering the adjunctive antidepressant treatment does not change outcome and that clinicians should attempt to withdraw from their adjunctive medications those stabilized chronic patients already on adequate antipsychotic therapy.

To conclude, it appears that in real-life clinical settings no reason exists for concern about the general safety of antidepressants among schizophrenic patients. Moreover, in this patient group, antidepressants seem to reduce mortality and prevent suicide; hence, the threshold for their use should be lowered.

9.4 Safety and Tolerability of Antidepressants in Schizophrenia

9.4.1 Adverse Effects

The main classes of antidepressants are characterized by typical adverse effects which affect their tolerability and, in some cases, limit their use in clinical practice. Exacerbation of psychosis as a complication of antidepressant treatment in schizophrenia has been discussed above (see 2.3) and seems not to be an issue of

concern, at least in antipsychotic-treated patients with chronic schizophrenia. Detailed description and analysis of the general adverse effect profile for each group of antidepressants is beyond the scope of this chapter and will be mentioned only in brief. The most common adverse effects of any antidepressants in general differ by class and compound and include (although are not limited by) anticholinergic and cardiotoxic effects and sometimes sedation for TCAs; gastrointestinal and sexual adverse effects for SSRIs; nausea, dizziness, headache, insomnia, and perspiration for SNRIs and reboxetine; sedation and weight gain for most receptor-blocking antidepressants; possible hepatotoxicity for nefazodone and agomelatine; and tyramine crisis for monoamineoxidase inhibitors [92, 93]. The "second generation" antidepressants such as SSRIs, SNRIs, receptor-blocking antidepressants, and some other newer agents, are in general safer and better tolerated than are the older drugs, i.e. TCAs and monoaminooxidase-inhibitors [94, 95]. The safety and tolerability of antidepressants in schizophrenia have not inspired a separate area of pharmacological research. However, data from the efficacy studies suggest that antidepressant-induced adverse effects in patients with schizophrenia do not differ from those in patients with MDD. Nevertheless, polytherapeutic combinations of antidepressants and antipsychotics may lead to increased risk for adverse effects due to drug interactions.

9.4.2 Drug Interactions

Drug interactions can be classified as either pharmacokinetic (when a drug interferes with absorption, distribution, metabolism, or excretion of other drugs) or pharmacodynamic (when they target the same organs or neurotransmitter pathways) [96].

9.4.2.1 Pharmacokinetic Interactions

Pharmacokinetic drug interactions between antidepressants and antipsychotics are associated mainly with the CYP 450 oxidases—a family of liver enzymes that play a key role in the biotransformation of both classes of drugs [97]. Some psychotropics may inhibit certain enzymes, often causing an unpredictable, drastic, or even toxic increase in blood concentrations of medications metabolized by these same enzymes (substrates) [98]. Conversely, some other drugs (inductors) noticeably whip up the activity of a CYP enzyme which can "eat away" correspondent substrates. Finally, two or more substrates of the same CYP enzyme prescribed concomitantly compete for this enzyme with a resultant moderate increase in their concentrations.

Three of the CYP 450 enzymes are responsible for the main metabolic pathways of antipsychotics and antidepressants (and thus of their potential pharmacokinetic interactions): CYP1A2, CYP2D6, and CYP3A4.

The role of these enzymes must be kept in mind when combining antidepressants and antipsychotics, especially if any of them (most often, an antidepressant but in some cases, an antipsychotic [99]) is an inhibitor of a CYP enzyme.

Since current knowledge relies mostly on in vitro studies [98], and reports on clinically significant interactions are scarce, some authors [100] conclude that the risks of antipsychotic-antidepressant pharmacokinetic interactions are theoretically rather than clinically relevant. Conversely, some others [101] suggest that such interactions, especially those with SSRIs, must become a matter of serious concern; they postulate that, for instance, fluoxetine and fluvoxamine should be used in combinations "cautiously," if at all.

For safety's sake, the authors of this chapter recommend a modestly conservative approach, meaning caution when using combinations with well-established major interactions such as fluvoxamine-clozapine, fluoxetine-perphenazine, or paroxetine-risperidone. Nevertheless, at best clinically significant interactions may even be used by skilled clinicians on purpose. For instance, Lu and co-authors [102] co-administered fluvoxamine and clozapine, and this enabled a decrease in dosage of the latter, with consequent monetary savings. Likewise, Albers and co-workers [103] achieved a reduction in olanzapine dosage by co-administration of a nontherapeutic dose of fluvoxamine.

9.4.2.2 Pharmacodynamic Interactions

Risk for clinically relevant and potentially dangerous pharmacodynamic interactions with antipsychotics is substantially higher for the TCAs and monoamineoxidase inhibitors than for the "second-generation" antidepressants. The most common mechanism of the interaction is augmentation of the same neurotransmitter pathway [104]. Another possible mechanism is competition at receptor sites and a direct effect on an organ/system's physiological functioning. Mechanisms of some interactions remain at least in part unclear.

The most common pharmacodynamic interactions between antipsychotics and antidepressants are:

1. Anticholinergic effects:

Both TCAs (especially amitriptyline, doxepine and imipramine) and numerous antipsychotics (especially clozapine, chlorpromazine, flupentixol, fluphenazine, and zuclopentixol) are blockers of muscarine receptors. Co-administration of these drugs may lead to worsening of anticholinergic adverse effects such as constipation, dry mouth, blurred vision, and cognitive impairment.

2. Sedation:

Although sedation in antidepressants and antipsychotics may be mediated via differing neurotransmitter mechanisms (H_1-receptor blockade in TCAs and some receptor-blocking antidepressants, melatonin receptor blockade in agomelatine, dopamine receptor blockade in antipsychotics), co-administration of two drugs with pronounced sedative effects may lead to excessive sedation. The agents providing the most pronounced sedation among antipsychotics are chlorpromazine, clozapine,

levomepromazine, olanzapine, promazine, and zotepin, and among antidepressants are amitriptyline, doxepine, trimipramine, mianserin, mirtazapine, trazodone, and agomelatine [105].

3. Weight-gain and untoward metabolic effects (dyslipidemia, impaired glucose tolerance):
   Among antipsychotics, clozapine, olanzapine, and chlorpromazine are associated with an increased risk for weight-gain [106]. Clozapine and olanzapine also share a propensity to induce a number of other untoward metabolic side-effects [107]. These features may be exaggerated in concomitant use of TCAs, mianserin, trazodone (weight-gain), and mirtazapine—notorious metabolic offenders among antidepressants.
4. Extrapyramidal symptoms:
   In animal studies, combination of haloperidol with fluoxetine, paroxetine, or clomipramine can lead to worsening of haloperidol-induced extrapyramidal adverse effects, whereas combination with mirtazapine has led to alleviation of EPS [108]. Several case reports suggest a plausible role for TCAs and SSRIs in augmentation of antipsychotic-induced EPS [109]. What remains unclear is whether the mechanism of this interaction is pharmacodynamic or pharmacokinetic. It should be kept in mind that TCAs and SSRIs may in themselves produce akatisia and some other EPS in antipsychotic-naive patients [110].
5. Cardiac effects:
   The TCAs have established arrythmogenic effects, whose principal mechanism is cardiac sodium channel blockade [111]. Some antipsychotics, too, are arrhythmogenic, especially at high doses [112]. A prolongation of the QT-interval often observed on the ECG of patients using TCAs may lead to Torsades de Pointes—a dangerous and potentially fatal condition. The TCAs should thus be combined with caution with haloperidol, thioridazine, olanzapine, ziprazidone, or sertindole [113]—antipsychotics that also tend to lengthen the QT interval.
   TCAs cause tachycardia, most likely due to their anticholinergic properties [104]. Reboxetine may also cause increased heart rate, presumably because of its noradrenergic mechanism [114]. Combinations of TCAs and reboxetine with antipsychotics sharing the same adverse effect (regardless of its mechanism), for example, clozapine and low-potency FGAs, may potentiate tachycardia, although clinical evidence regarding this interaction is lacking.
6. Vascular effects:
   Hypotension due to alpha-1 receptor blockage is a common adverse effect of both TCAs and numerous antipsychotics—chlorpromazine, levomepromazine, thioridazine, trifluoperazine, clozapine, risperidone, zotepine, and sertindol [115].
7. Proconvulsive effect:
   TCAs, especially maprotiline and clomipramine [116] and bupropion [117], can lower the seizure threshold, as do chlorpromazine, clozapine, and zotepine [118]. The seizure risk is dose-dependent [116].

Despite the current recommendations to use only monotherapy with antipsychotics in the treatment of schizophrenia [7], in clinical practice, polytherapy and polypharmacy are common. Many patients receive one or more other drugs in addition to their

antipsychotic-antidepressant combination [5]. Hence, the whole spectrum of concomitant medications must be taken into account in choosing an adjunctive antidepressant. This requires prudent decisions based on the existing broad but still insufficient knowledge of the pharmacodynamics and pharmacokinetics of a wide range of psychotropics. If a combination of drugs with a potential for pharmacodynamic interactions is necessary, careful monitoring is to be strongly recommended, and discontinuation or a shift to another antidepressant should be an option in case of significant adverse effects or insufficient clinical response.

9.5 Summary and Further Directions

Despite the proven effectiveness of antipsychotics in treatment of schizophrenia, there exist a substantial number of patients with only a sub-optimal clinical outcome. This is especially true for negative symptoms and cognitive deficits, but often also positive symptoms. Insufficiently treated depressive symptoms contribute to poor outcome and increased suicide rates.

To date, evidence in favor of antidepressant augmentation of both FGAs and SGAs for negative symptoms is fairly convincing, being probably the most consistent for receptor-blocking antidepressants, especially mianserin and mirtazapine. For SSRIs as a group the data are equivocal.

Antidepressants seemingly fail to improve positive symptoms of schizophrenia (with the possible exception of mirtazapine), but in contrast to widely accepted opinion, nor do they appear to worsen psychosis—at least in chronic schizophrenia and when combined with antipsychotic medication. Moreover, they may reduce rates of suicide and overall mortality in patients with schizophrenia. The current level of caution in the use of add-on antidepressants in schizophrenia therefore needs reappraisal.

With some degree of uncertainty, several antidepressants such as sertraline, fluoxetine, reboxetine, and mirtazapine can be recommended for the treatment of depressive symptoms in schizophrenia. This recommendation, however, applies mostly to patients in the chronic stage of the disease, whereas for depressive symptoms in acute episodes, antipsychotic therapy may suffice. The same uncertainty exists regarding antidepressants as agents alleviating antipsychotic-induced EPS. The receptor-blocking antidepressants are seemingly worth trying in patients treated with the FGAs. Conversely, the SSRIs may even provoke EPS and should be avoided in patients predisposed to neurological adverse effects of antipsychotics.

Some antidepressants, especially mirtazapine (and possibly mianserin), may be of interest as potential neurocognitive enhancers, but more evidence is required. When co-administering an antidepressant and an antipsychotic, a clinician should consider possible drug pharmacokinetic (especially for some SSRIs with a propensity to inhibit CYP 450 enzymes) and pharmacodynamic (especially for TCAs) interactions. Preference should usually go to the most pharmacokinetically and pharmacodynamically neutral agents.

In general, evidence regarding the efficacy and effectiveness of add-on therapy with antidepressants supports their use in schizophrenia, but further well-designed,

randomized, controlled trials are necessary, ones of larger size in differing subpopulations of patients with schizophrenia; more naturalistic effectiveness trials are needed, too. Possible areas of interest are, for example, the comparative efficacy of various antidepressants in treatment of negative and depressive symptoms of schizophrenia, as well as head-to-head comparison of an add-on antidepressant with plausible additive antipsychotic potential (such as mirtazapine), combined with FGAs or SGAs vs. clozapine in treatment-resistant schizophrenia. Add-on antidepressants, especially the receptor-blocking ones, may be promising neurocognitive enhancers, but large, methodologically sound research in this field is vital. A capability of antidepressant monotherapy to preclude or postpone onset of schizophrenia in high-risk groups is another promising field of research.

Aknowledgements The authors thank Jan-Henry Stenberg, PM, for providing the most up-to-date information on the cognitive impairment in schizophrenia and its treatment.

The authors are also indebted to Kari Raaska, MD, PhD, for comprehensive consultations in the field of pharmacokinetics.

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Chapter 10
Stress Sensitization and Anticonvulsant Medication in Psychiatric Patients

Petr Bob

Abstract Recent reported findings indicate that stress experiences are related to psychological and neurobiological processes that may have lasting consequences and significantly influence brain functions. Cognitive and emotional dysregulation related to traumatic stress is likely linked to deficits in inhibitory functions and increased limbic excitability that may lead to temporo-limbic seizure-like activity. These findings strongly suggest that stress-activated limbic kindling may be involved in the pathogenesis of depression, posttraumatic stress disorder (PTSD), schizophrenia and other psychiatric disorders which may explain efficacy of antiepileptic drugs in their treatment.

Keywords Anticonvulsants • Depression • Epileptiform activity • Schizophrenia • Seizure-like symptoms • Sensitization • Stress • Trauma • Posttraumatic stress disorder

Abbreviations

ACC	Anterior Cingulate Cortex
BDNF	Brain Derived Neurotrophic Factor
EEG	Electroencephalograph
GABA	Gamma-Aminobutyric Acid
LSCL-33	Limbic System Checklist
PTSD	Posttraumatic Stress Disorder

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M.S. Ritsner (ed.), *Polypharmacy in Psychiatry Practice, Volume I: Multiple Medication Use Strategies*, DOI 10.1007/978-94-007-5805-6_10,

10.1 Introduction

Recent increasing evidence indicates that traumatic stress experiences caused by unescapable adverse physical, emotional or social events represent significant conditions in pathophysiology of various psychiatric disorders [1–4]. As current data show mainly early stress and child abuse may determine developmental abnormalities in the amygdala, hippocampus, cerebellum, anterior cingulate cortex (ACC), corpus callosum and other brain structures [1, 4–6]. Recent data also indicate that most serious disturbances caused by traumatic events such as childhood abuse or neglect in the first years of life often have long-term impact on emotional, behavioral, cognitive, social and physiological functions [1]. In addition stress may inhibit brain-derived neurotrophic factor (BDNF) expression and there is evidence that decreased BDNF expression may significantly influence reparative processes and neurogenesis of hippocampal neurons with resulting hippocampal atrophy and similarly in other brain structures which may influence neurodegenerative process [1, 5–7]. One of the typical consequences of these various psychological responses is an increased sensitivity to other upcoming stress stimuli, subjectively experienced as increased vulnerability to stressors. This hypersensitivity is also linked to heightened vulnerability on physiological level which determines progressively increasing responses with serious consequences on mental, physiological, morphological and genetic levels of disintegration related to self-regulatory responses with respect to external perceptual stimuli and internally generated neural activity.

10.2 Traumatic Stress, Sensitization and Epileptiform Activity

Recent research findings provide evidence that repeated stressful events may determine an increase in responsiveness to a stress stimuli resulting from repeated stressors and sensitization with significantly increased vulnerability to stressors that have more lasting consequences with kindling-like progression [8–10]. The kindling-model of stress-related sensitization [8] seems to be in agreement with suggestive evidence that stress may influence occurrence of EEG abnormalities that have been reported in traumatized patients mainly in the frontotemporal region, which consisted of spikes, sharp waves, or paroxysmal slowing, predominantly in the left hemisphere [1, 4, 11–13].

Stress-related sensitization has also been proposed to cause changes in GABA postsynaptic receptors that may lead to overstimulation of neurons mainly in the limbic system, resulting in limbic system irritability manifesting as markedly increased prevalence of symptoms suggestive of a subclinical form of temporal lobe epilepsy [1, 4, 8]. Recent data strongly suggest that early stress may determine limbic irritability and temporal-limbic seizure-like activity and close link between limbic irritability and cerebellar vermis has been reported [1, 4, 14]. Teicher et al. [1, 4, 11] also found that adult outpatients with a self-reported history of physical or sexual abuse had increased levels of symptoms reflecting limbic irritability measured by

questionnaire LSCL-33 (Limbic System Checklist) that were dramatically elevated in patients with a history of combined abuse, both physical and sexual.

The results are consistent with findings that cerebellar vermis controls limbic activation and inhibition and also influences the onset and spread of seizures [1, 4, 15–17]. These findings suggest that cognitive and emotional dysregulation related to traumatic stress likely is linked to deficits in inhibitory functions that may also lead to temporo-limbic seizure-like activity. This epileptic-like process may emerge in the form of symptoms similar to ictal temporal lobe epilepsy such as somatic, sensory, behavioral and memory symptoms that may occur also in nonepileptic conditions that may be clinically measured by LSCL-33 [1, 4] or using Structured clinical interview for complex partial seizure-like symptoms [18–20] (Table 10.1). These symptoms likely reflect abnormal neural excitability and disturbances in brain inhibitory systems that in certain neural mechanisms are similar to epilepsy.

10.3 Sensitization and Epileptiform Changes in Depression

Recent evidence indicates that sensitization process with kindling-like progression frequently leads to maladaptive responses and negative influences on brain structures that manifest as an increased probability of relapses, recurrences, residual symptomatology and other forms of psychopathology which may result to deficits in inhibitory functions and limbic system irritability [1, 4, 19, 21, 22]. These findings are in agreement with evidence of positive clinical response to anticonvulsant treatment in many depressive and other psychiatric patients although the EEG frequently may be without abnormalities [1, 4, 11, 18, 19, 23–25].

This increased vulnerability related to sensitization and kindling may cause that the brain becomes more sensitized and many patients with depression are unresponsive to antidepressant treatment and may respond well to antiepileptic drugs as an effective adjunctive treatment [1, 8, 23, 25–27]. In this context, recent findings strongly suggest that usefulness of anticonvulsant drugs is not limited only for treatment of bipolar disorder and that mood-stabilizing drugs as lithium and valproate but also other anticonvulsants (such as carbamazepine and lamotrigine) and also several antipsychotics in addition to their therapeutic effects for the treatment of acute manic episodes may be useful as prophylaxis against future episodes and as adjunctive antidepressant medications. Even mechanisms of action of majority of mood-stabilizing drugs is to a great extent unknown, these drugs may also have ameliorating influence on changes in cellular plasticity underlying pathophysiology of mood disorders and likely have neuroprotective effects and may regulate BDNF and other neuthrophic factors expressed in the cortex, hippocampus and other brain areas that play an important role in emotional and cognitive functions [7, 25–27].

Taken together these findings suggest that sensitization and its typical effects may be linked to brain changes that could be effectively regulated by anticonvulsant drugs and other mood stabilizers. For example, Silberman et al. [18] assessed the occurrence of transient sensory, cognitive and affective changes resembling

Table 10.1 Items of structured clinical interview for complex partial seizure-like symptoms (also called Iowa Interview for Partial Seizure-like Symptoms) by Roberts et al. [19]

1. Do you sometimes smell things which other people can't smell, such as feces, urine, rot, body odor, or smoke? Be sure in responding to this that the smells you report have no apparent cause (e.g., smelling kitty litter when you don't own a cat).
2. Do you sometimes have a bad taste in your mouth, such as a metallic taste, which comes and goes for no reason?
3. Do you sometimes sense movement in peripheral vision, but when you turn to look you cannot see anything?
4. Do you sometimes see things in your peripheral vision, such as stars, bugs, snakes, worms or threads?
5. Do you sometimes see mice or cockroaches run across the floor, but when you turn to look, you do not see them?
6. Do you sometimes feel as though bugs are crawling on you or that something is brushing up against your skin, such as a cobweb?
7. Do you sometimes go numb in a part of your body for no apparent reason?
8. Do you sometimes get a ringing, buzzing, rushing or tapping noise in your ears which comes and goes for no reason?
9. Do you sometimes answer the telephone only to find that it had not actually been ringing?
10. Do you sometimes get severe headaches that are so bad you become nauseated or want to throw up?
11. Do you sometimes get a pain in your head which you would not classify as 'headache'?
12. Do you sometimes have marked urinary urgency, but fail to produce any urine when going to the bathroom?
13. Do you sometimes have trouble with the pronunciation of words with the effect that you appear a bit intoxicated even though you are not?
14. Is it a common problem of yours that you will suddenly have trouble thinking of words you should know and were able to say moments before?
15. Do you sometimes find that you have uttered a sentence which doesn't make any sense and involves words other than those you wished to say?
16. Do you sometimes become quite suddenly and intensely confused and perplexed and then have the feeling pass in a few minutes?
17. Do you sometimes have an overwhelming feeling that things are weird, strange, or wrong, sort of like entering the twilight zone?
18. Do you sometimes feel that familiar places or persons are somehow not familiar or the way they should be?
19. Do you sometimes get the feeling that you have experienced something or been someplace before even though you know you have not?
20. Do you have clear cut gaps in your memory during which you cannot remember anything that happened over a period of 5 min or more?
21. Do you sometimes find that you have missed major sections of TV shows you have been watching, like someone has spliced a section out of a movie?
22. Have you ever found yourself driving without remembering how you got there or where you are going?
23. Do people often tell you about things you have done or said for which you have no memory at all?
24. Do you have staring spells where you become sort of hypnotized by a bright or shiny object?
25. Do people often tell you that there are times when you are staring and have a blank look on your face?

(continued)

Table 10.1 (continued)

26. Do you feel that your memory or concentration is getting substantially worse every year? (no = 0; yes = 5)
27. Do you sometimes lose consciousness or just black out?
28. Are you regularly so depressed that you think seriously about suicide? (no = 0; yes = 5)
29. Do you sometimes become abruptly more depressed than you were a few minutes or seconds earlier with no apparent cause?
30. Are you often inclined to panic or become very anxious for no reason?
31. Do you sometimes become extremely and intensely angry for no reason?
32. Do people tell you that you have become very angry and you do not remember?
33. Do people tell you that you sometimes have an intensely angry expression on your face while asleep?
34. Do you sometimes feel an irresistible urge to sleep during the day and then sleep so soundly that no one can arouse you?
35. Do you sometimes wake up to realize that you have been sweating so much that the bed sheets are soaked?

The items are rated by the patient for frequency of occurrence on the Likert scale (0, 1, 2, 3, 4, 5): 0 Never or not in the past year; 1 Two a three times in the past year; 2 At least once a month; 3 At least once a week; 4 Several times a week; 5 At least once a day. Score is a sum of all items (70 or higher is a criterion for epilepsy spectrum disorder—Roberts et al. [19])

those described by temporal lobe epileptic patients in 44 patients with affective illness, 37 with complex partial seizures, and 30 controls. Their results indicate that the symptoms occurred frequently in association with episodes of affective illness and epilepsy, but were rare in controls. They also reported that greater numbers of symptoms were associated with better response to lithium and tricyclic antidepressants. The authors conclude that transient sensory, cognitive, and affective phenomena may be more common in affective illness and other psychiatric conditions than is generally recognized [18].

Similarly also Varney et al. [25] in the study of 13 depressed patients, with documented histories of failure to respond to tricyclic antidepressant medications and reported multiple partial seizure like symptoms, found that 11 of the 13 patients showed moderate or substantial improvement in affective status in response to carbamazepine. In addition, the mean number of reported partial seizure-like symptoms decreased significantly with treatment. The authors conclude that these preliminary observations suggest that there is likely to be a subgroup of treatment-resistant, carbamazepine-responsive depressive patients, who can be identified by evaluating for the presence of the seizure-like symptoms [25].

In agreement with these findings clinical study Bob et al. [28] in 113 patients with unipolar depression also indicates that in depressive patients seizure-like symptoms display significant correlation with depression and specifically influence contents of consciousness and subjective experience. Several data also suggest that complex partial seizure-like symptoms may be specifically linked to epileptiform phenomena in the autonomic nervous system and reflect changes in brain dynamics related to information transfer between hemispheres that might be linked to spreading epileptiform activity from one hemisphere to the other [29].

10.4 Stress, Sensitization and PTSD

Recent evidence indicates that various environmental factors such as perinatal damage, hypoglycemia, childhood stressful experiences, and other influences interacting with genetic basis may significantly affect persisting sensitivity to stress and other stimuli in later times and influence vulnerability to PTSD [1, 4, 10, 24, 30]. This state of increased sensitivity related to sensitization and kindling-like progression with consequent alterations in cognitive biases may present important and critical conditions in pathogenesis of PTSD and other stress related psychopathological symptoms [1, 4, 10, 11, 24, 30, 31]. Recent findings suggest that the kindling related focal after-discharges within the amygdala and other brain structures may cause local changes in synchronization and seizure-like activity which could be important in pathogenesis of PTSD [10, 31]. These findings potentially may explain treatment resistance to usual psychotropic medication in several PTSD patients and clinical importance of appropriate anticonvulsant medication even in patients who do not display seizures or epileptiform changes on scalp EEG [23, 26, 32].

Several recent data suggest that this epileptic-like process may emerge in the form of symptoms similar to several symptoms of temporal lobe epilepsy (the so-called complex partial seizure-like symptoms) such as somatic, sensory, behavioral and memory symptoms that may occur also in nonepileptic conditions [18, 19, 25] and may play a role in PTSD. Clinical importance of these symptoms in PTSD patients suggests study by Roca and Freeman [33], who reported relevance of psychosensory complex partial seizure-like symptoms for the study of chronic PTSD and found that their presence is associated with significantly more severe PTSD symptoms, dissociative symptoms, aggression, and overall psychopathology.

These reported findings are in agreement with clinical evidence that many patients with PTSD are unresponsive or display only moderate responses with frequent side effects to first-line serotonin reuptake inhibitor treatment and several studies suggest that antiepileptic drugs may be an effective treatment alternative or efficient adjunctive treatment for PTSD [23, 32]. Recent clinical evidence from case reports, double-blind controlled studies and placebo-controlled trials on the efficacy and tolerability of antiepileptic drugs in PTSD have shown that lamotrigine, topiramate, and tiagabine seem to be effective for PTSD treatment [23, 32]. Other antiepileptic drugs that seem to be promising in open-label trials in PTSD patients include carbamazepine, valproate, gabapentin, vigabatrin, phenytoin, and levetiracetam [32].

These findings also suggest that stress-activated limbic kindling may be involved in the pathogenesis of PTSD and may explain efficacy of antiepileptic drugs in the treatment of PTSD due to their antikindling effect. Future research needs to determine whether patients with PTSD who have heightened level of complex partial seizure-like symptoms are more likely to benefit from treatment interventions that use antiepileptic drugs.

10.5 Stress Sensitization and Epileptiform Changes in Schizophrenia

Recent evidence indicates that the state of increased sensitivity related to sensitization and phenomena similar to kindling may be related to an imbalance in interactions between dopaminergic and glutamatergic systems, altered dopamine neurotransmission and consequent alterations in cognitive biases that present critical conditions in pathogenesis of schizophrenia, and may cause local changes in synchronization and seizure-like activity which may be important in pathogenesis of schizophrenia [34–36].

These findings potentially may explain treatment resistance to usual antipsychotic medication in several schizophrenia patients and also clinical importance of an appropriate anticonvulsant medication, even in patients who do not display seizures or epileptiform abnormalities on scalp EEG [23, 26, 37]. Several findings also show that symptoms similar to temporal lobe epilepsy [1, 4, 19] may play a role also in schizophrenia and significant presence of these symptoms in treatment resistant patients might indicate good response to anticonvulsant drugs [38].

Within this context also dopaminergic hypothesis of schizophrenia provides results that show positive schizophrenic symptoms as consequences of hyperdopaminergic kindling in mesolimbic dopaminergic system [35, 36, 39]. The concept of kindling as a model for psychopathology in several schizophrenia patients is in agreement with recent findings that schizophrenia is often related to a loss of physiological balance between excitation and inhibition [35]. Typical for this disbalance is that the normal equilibrium between excitation and inhibition is permanently altered by repeated focal excitation or kindling, resulting in a permanent state of excessive focal excitability and spontaneous seizures [35, 40]. Several recent findings suggest that similar "kindling" or sensitization may originate in inhibitory systems in response to focal physiological pulsed discharges of limbic neurons and this excess of inhibitory factors may then manifest as a psychosis [35]. This excessive focal inhibition may be induced by increased release or increased receptor density of several inhibitory transmitters [41].

According to these findings discharges related to increased excitatory neural activity may also be modulated by a regionally-specific compensatory upregulation of GABA-A receptors in response to decreased GABAergic input in hippocampal pyramidal cells [42, 43]. In general, GABAergic neurons provide both inhibitory and disinhibitory modulation of cortical and hippocampal circuits, contribute to the generation of oscillatory rhythms and participate in discriminative information processing such as gating of sensory information, and attentional filtering within the corticolimbic system that are typically affected in schizophrenia [34, 44–47].

In agreement with this role of GABAergic neurons in cognitive functions several findings also suggest that disturbances in GABA system might be related to stressful conditions and alterations in the dopamine system [1, 4, 44, 48]. Furthermore influence on disturbances in GABA system may also exert increased flow of excitatory activity from the basolateral nucleus of the amygdale [44].

10.6 Conclusions and Future Directions

Taken together there is evidence that sensitization or "kindling-like" phenomena play an important role in pathogenesis of some mental disorders and have received a great deal of attention in efforts to conceptualize the pathophysiology of seemingly diverse psychiatric disorders such as, mood disorders, posttraumatic stress disorder, schizophrenia and likely also some other psychiatric disorders [10, 31, 49–51]. These findings also suggest that likely there is a link between disturbances in GABA system and stress influences that may determine the relationship between reported symptoms similar to symptoms of temporal epilepsy reflecting abnormal neural excitability that specifically influence pathogenesis of several mental disorders and their resistance on usual psychothropic medication that may be compensated using anticonvulsant medication. Nevertheless specific indication of anticonvulsant treatment needs further research that prospectively could provide research and clinical data indicating diagnostically useful neurobiological markers that would enable to identify subclinical epileptiform process and might provide criteria for specific medication.

Acknowledgements The study was supported by the grant GACR P407/12/1957, project MSM0021620849 provided by Czech Ministry of education and the project "CEITEC – Central European Institute of Technology" (CZ.1.05/1.1.00/02.0068) from European Regional Development Fund.

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Chapter 11
Multiple Medication Use in Somatic Symptom Disorders: From Augmentation to Diminution Strategies

Adrian P. Mundt

Abstract The diagnostic category of somatoform disorders (F45.X in the ICD-10) includes somatization disorder, undifferentiated somatoform disorder, somatoform autonomous disorder, somatoform pain disorder, hypochondriac disorder, and other somatoform disorders. The DSM-IV includes a similar category. The categories will undergo significant changes in the forthcoming editions of both classifications (ICD-11 and DSM-V).

Diagnosis and treatment of the disorders require interdisciplinary approaches of somatic, psychosomatic, psychotherapeutic and psychiatric departments. Extensive exclusion of somatic illness is needed to establish the diagnoses. Non-response to somatic medication can be one factor supporting the diagnoses. The disorders result in high utilization of the health care system and in high costs. Psychotherapy is the first line treatment but unacceptable to many of the patients. Medication is a second line treatment option, more acceptable to many of the patients. There are two distinct pharmacological strategies to influence the symptoms. One is the use of somatic medication targeting symptoms in the periphery. Second is the use of psychotropic drugs with central nervous action.

The chapter will outline the evidence base for psychotropic, in particular antidepressant, antiepileptic and antipsychotic medications for the treatment of somatic symptom disorders. Challenges arising with the use of psychotropic medication in somatic symptom disorders will be discussed:

- It is mostly initiated after non-response to somatic medication.

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M.S. Ritsner (ed.), *Polypharmacy in Psychiatry Practice, Volume I: Multiple Medication Use Strategies*, DOI 10.1007/978-94-007-5805-6_11,

- It is frequently started in addition to somatic medications resulting in multiple medication use across medical specialties.
- It may require an increase of dosage and augmentation upon non-response similarly to other disease entities outlined in the more general chapters of this book.
- Hypochondriac ideation may cause sensitivity to adverse drug reactions and frequent changes of treatment strategies.
- Adverse drug reactions are hard to distinguish from the symptoms of the disorders.

The evidence for efficacy of psychotropic medication is scarce in somatic symptom disorders. Pharmacological combination treatment is frequently initiated and rarely useful. After multiple frustrating diagnostic and/or therapeutic contacts with medical services, the patients often encounter doubts on the side of their therapists about the genuineness of their complaints. Holding on to multiple medications may alleviate this doubt. Strategies for systematic reduction of medication without disrespect to the feeling of genuineness of complaints seem a necessary yet difficult to achieve goal.

Keywords Somatic symptom disorders • Somatoform • Somatization • Multiple medication use

Abbreviations

APAP	Acetaminophen
CBT	Cognitive Behavioral Therapy
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ICD-10	The International Classification of Diseases, Tenth revision
ICD-11	The International Classification of Diseases, 11th revision
NaSSA	Noradrenergic and Specific Serotonergic Antidepressant
NSAID	Non-steroidal anti-inflammatory drug
OTC	Over-the-counter
SNRI	Serotonin and Noradrenalin Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor

11.1 Introduction

The diagnostic category of somatoform disorders in the ICD-10 (F45.X) includes somatization disorder, undifferentiated somatoform disorder, somatoform autonomous disorder, somatoform pain disorder, hypochondriac disorder, and other somatoform disorders. The DSM-IV includes a similar category (Table 11.1).

Table 11.1 Somatoform disorders in the ICD-10 and DSM-IV classifications

ICD-10 somatoform disorders		DSM-IV Somatoform disorders	
F45.0	Somatization disorder	300.81	Somatization disorder
F45.1	Undifferentiated somatoform disorder	300.7	Body dysmorphic disorder
F45.2	Hypochondriacal disorder	300.7	Hypochondriasis disorder
F45.3	Somatoform autonomic dysfunction	300.11	Conversion disorder
F45.4	Persistent somatoform pain disorder	307.8	Pain disorder with psychological features
F45.8	Other somatoform disorder	307.89	Pain disorder associated with psychological features and medical conditions
F45.9	Somatoform disorder, unspecified		

Table 11.2 Functional syndromes in medical specialties [2]

Medical specialty	Functional syndrome
Gastroenterology	Irritable bowel syndrome
Gynecology	Lower pelvic pain
Neurology	Tension headache
Orthopedics	Chronic lower back pain
Rheumatology	Fibromyalgia
Cardiology	Atypical chest pain
Infectious diseases	(post-viral) fatigue syndrome
Respiratory medicine	Hyperventilation syndrome
Immunology	Idiopathic environmental intolerance

The categories will undergo significant changes in the forthcoming editions of both classifications (ICD-11 and DSM-V) [1].

One of the major goals will be to make the category more acceptable to patients and service providers. Changing the name of the category into somatic symptom disorders is a first step to underline respect for the genuineness of the complaints. In addition to the psychiatric classifications, almost each medical specialty has a category for functional somatic symptoms (Table 11.2) [2].

Medical specialties are frequently struggling to define or acknowledge those syndromes as disease entities for the absence of clear physiological tests, e. g. as for the hyperventilation syndrome going as far as recommending to avoid the term and calling it an epiphenomenon [3]. This, however, does not solve the problem that the patients with a common disease spectrum occur and need to be managed in almost all medical specialties.

11.2 Diagnostic Procedures

Somatic symptom disorders require challenging diagnostic procedures. The diagnoses are based on a long lasting exclusion of somatic diseases after multiple consultations with general practitioners and specialists after discarding a list of

suspected somatic diseases. The disorders are characterized by one or multiple somatic symptoms, which cannot be better explained by a disease if present. The exclusion of differential somatic diagnoses may include a range of imaging, blood and tissue exams. It may even require exploratory invasive and surgical interventions in some cases. Increasing technological possibilities, financial incentives on the side of the clinicians and fear of an environment with increasing risk to be sued can prolong this process. The multiple diagnostic procedures are frequently perceived as strenuous, stressful and frustrating for both patients and clinicians. The escalation of diagnostic procedures may be determined by the readiness to consider a psychological explanation of the symptoms on the side of the patient and the clinician. Tentative somatic pharmacological treatment in cases of negative or ambiguous somatic examination targeted at the symptoms usually accompany this process and may be a treatment option for subjects rejecting psychological explanatory models. The clinicians' rational is to target false negative cases, to use a possible placebo effect and to acknowledge the genuineness of complaint. It may be clinically impossible to distinguish biological or psychological response to the treatment. Partial response may entail further pharmacological treatment lines or augmentation of the regimen. Non-response after several pharmacological treatment strategies and augmentation strategies generates further evidence for a somatic symptom disorder.

At any time of this process psychological evaluation and treatment may be initiated according to the acceptability to the patient to consider psychological explanations of the symptoms. The benefit of an early referral of the patient is the possible support during the sometimes protracted and frustrating diagnostic procedures. The risk of an early referral of the patient is a premature cessation of thorough somatic examination. Other risks for the patient include the early trial of several somatic and psychotropic medications and a long lasting polypharmacy that psychologically perpetuates the disease, the risk of secondary effects and drug interactions.

11.2.1 Diagnostic Shifts

A general agreement on diagnostic criteria for somatoform disorders is still lacking [4]. The criterion and the predictive validity are considered to be low [5]. Diagnostic shifts commonly take the following course: The symptoms first guide to somatic disease, then to a functional syndrome diagnosed within one of the somatic specialties (Table 11.2), then to diagnosis of somatoform disorder within the psychiatric classifications (ICD-10 or DSM-IV, Table 11.1), then the diagnostic process may turn to mood disorders, anxiety disorders or other disorders that require psychological explanatory models of the symptoms and that are preferred by psychiatrists because they entail clearer pharmacological treatment recommendations. Somatic syndromes can be the leading sign of a major depressive disorder. Somatoform disorders commonly co-occur with depression, anxiety and chronic pain [6]. In its most severe dimension, there may be a psychopathological spectrum

of continuity between severe cases of somatoform disorders and hypochondriacal delusions [7] or coenaesthopathic schizophrenia as a special form of coenaesthetic schizophrenia [8]. Differential diagnosis of somatoform disorders and coenaesthopathic schizophrenia can be challenging especially when cultural and language barriers are present [9]. A psychotic dimension of hypochondriasis and body dysmorphic disorders has been postulated rather than coding psychosis as a different co-morbid entity [10].

11.2.2 Treatment Strategies for Somatic Symptom Disorders

Most important in the treatment of somatic symptom disorders are non-specific elements of treatment, such as creating a safe therapeutic environment, motivational interviewing, tangible explanations, reassurance and regularly scheduled appointments. The first line specific treatment of somatic symptom disorders is cognitive behavioral therapy (CBT) [11, 12]. So-called mind-body therapies are multimodal psychotherapeutic approaches for the management of chronic pain. They include CBT, educational elements, biofeedback, coping skills training and relaxation. Non-pharmacological interventions with the active participation of the patient such as psychotherapy and exercise seem to be more effective than passive physical measures (e.g. massages, acupuncture), injections and operations [13]. They may be complemented by pharmacological therapies. For many patients psychotherapy is unacceptable or unavailable, whereas pharmacological treatment interventions may be more common [14]. Pharmaceutical treatment has lower costs than psychotherapy in most countries. In current clinical practice, therefore, pharmacological treatments are often the first specific treatment. There are two distinct pharmacological strategies to influence the symptoms: The use of medications targeting symptoms in the periphery and the use of psychotropic drugs with central nervous action.

If somatic symptom disorders are managed in surgical specialties, surgical interventions are common escalations of the pharmacological treatment [15].

11.3 General Considerations for the Use of Medications

Even though there is an overlap in the phenomenology of different functional syndromes [2], there have been only few pharmacological trials for somatoform disorders or somatization disorders due to methodological problems [16]. Most of the trials are directed towards specific functional syndromes.

The use of medications for somatoform disorders is subject to interpersonal aspects of the doctor and patient relationship and to patient preferences. The intensity and quality of the presentation of symptoms may directly influence the pharmacotherapy. A subgroup of patients actively seeks for somatic medications to feel a reward regarding the genuineness of medical symptoms after having heard over and

over again: “it’s nothing” [17]. Medication use can become part of the attention focus on somatic explanations of the disease, at the same time part of the avoiding strategy to consider psychological explanations. A subgroup of patients is very reluctant to take any medication at all due to hypochondriac ideation. Psychological aspects of the disease itself can lead to an irrational use of medications and polypharmacy. Seeking for medication as an acknowledgement of the complaints and irrational fear of medication due to hypochondriac ideation may be present at the same time favoring rapid changes of pharmacological strategies. The frequent shift of syndromes and frustration during long diagnostic procedures may lead to multiple consultations with different specialists. Patients tend to accumulate pharmacological treatments across different specialties. In each specialty, including psychiatry, augmentation strategies (polypharmacy) to overcome treatment resistance are common. At times rather young patients carry long lists of medications (more than five substances across different medical specialties are not exceptional [18]). Some patients enter in a vicious cycle of possible adverse drug effects that are indistinguishable from somatic symptoms linked to the disease, demanding more treatment and more medication. At this point diminution strategies for pharmacological therapies have to be initiated by the doctor who succeeds to establish a stable relationship with the patient. Diminution strategies must include critical revision of pharmacological treatments across other medical specialties. It requires psychotherapeutic skills on the side of the doctor. Reducing medication without hurting the patients’ feelings of genuineness of complaint requires working on informing and reassuring about the safety of this strategy. And it requires working on the possibility of acknowledging psychological factors influencing the symptoms. During the diminution process of the medication the same hypochondriac ideation including temporary increase of symptoms may occur that makes it difficult to start and to establish a continuous and rational pharmacological regimen. A slow weaning from the medication based on a stable doctor-patient relationship is indicated rather than an abrupt stop. In the case of polypharmacy, it is recommendable to wean from one medication after the other rather than stopping several at a time.

11.4 Medications Targeting the Periphery

Medications targeting the periphery include substances for the physiological function of peripheral organs. They include antibiotics, antispasmodics, anti-inflammatory drugs, muscle relaxants, antihistamines, α-blockers and phytotherapy. There are recommendations on how to treat functional syndromes within each medical specialty. Rather than to repeat the recommendations on how to treat those syndromes, the following section intends to give an idea what degree and type of non-psychotropic polypharmacy psychiatrists can expect when patients are referred. In addition to medications listed in the following section, most of the treatment recommendations for functional syndromes within medical specialties include psychotropic drugs, which are readily used to complement medications targeted at the periphery.

Antispasmodics are considered to be effective for the treatment of irritable bowl syndrome. The individual substance groups include cimetropium/dicyclomine, peppermint oil, pinaverium and trimebutine [19]. There is no evidence for the efficacy of bulking agents for the treatment of irritable bowl syndrome.

Lower pelvic pain syndromes are initially treated with long-term course of an antibiotic (e.g. quinolone or co-trimoxazole) [20] in combination with an anti-inflammatory drug [21]. The anti-inflammatory drugs that are used include non-steroidal anti-inflammatory drugs (NSAID), prednisone and cyclosporine [22, 23]. Adjunct pharmacological management may include glucosaminoglycans (pentosan polysulfate) [24], α-blockers (tamsulosin, alfuzosin) [25], antihistamines (hydroxizine and montelukast) [26], muscle relaxants (cyclobenzaprine, tizanidine and clonazepam) and phytotherapy (quercetin and cemilton) [23]. Most of these treatments are not approved by the U.S. Food and Drug Administration.

NSAID are routinely used as a first line treatment for different kinds of pain syndromes. Combinations of drugs acting on the periphery and on the central nervous system, which are discussed below, are commonly used for the management of chronic persistent pain. The commonly practiced polypharmacy for the treatment of pain is highly questionable. Even for the treatment of cancer related pain, where a smaller psychological aspect could be expected than in somatoform pain disorders, there is no clear evidence for the superiority of the combination of NSAID and opioids over either one of the treatments alone [27]. An internet based survey of 2,569 persons with fibromyalgia reported that the most commonly used medications were acetaminophen (APAP), ibuprofen, naproxen, cyclobenzaprine, amitriptyline, aspirin, celecoxib, rofecoxib,[1] codeine + APAP, tramadol, hydrocodone + APAP, zolpidem, sertraline, fluoxetine, paroxetine, bupropione, trazadone, gabapentin and alprazolam followed by oxycodone + APAP [14].

During the long lasting course of diagnostic exclusion procedures patients commonly seek relief in self-medication, which may be taken in addition to prescribed drugs. Many patients with somatic symptom disorders take over-the-counter (OTC) medication, such as hormones, phytotherapy, vitamins, minerals and other supplements [18]. The internet survey of patients with fibromyalgia showed that nutritional supplements were taken by 68%, OTC pain medication by 67%, prescription pain medication by 66%, prescription sleep medication by 52%, OTC sleep medication by 22% of the patients [14].

11.5 Medications with Central Nervous Action

For several functional syndromes (Table 11.2) that are usually treated in non-psychiatric medical specialties, psychotropic drugs are prescribed as a first line pharmacological management. There have been a number of trials with antidepressants for

[1] No longer available in the U.S.

the treatment of atypical chest pain with moderate results [28]. For fibromyalgia a combination of antidepressants, NSAID and antiepileptic medication with different mechanisms of action is considered to be rational [29], even though evidence beyond mono-medication trials is scarce. In chronic tension type headache, preventive treatment is commonly done with tricyclic antidepressants such as amitriptyline or nortriptyline, which seem to be superior to SSRI [30]. Clomipramine and the tetracyclic antidepressants such as mirtazapine, maprotiline and mianserin also seem to be effective over placebo [30]. Duloxetine given as concomitant medication to NSAID was equally effective for the treatment of chronic lower back pain as duloxetine alone. This indicates evidence for the safety of this combination but by no means that the combination is more effective than duloxetine given as monotherapy [31].

Antidepressants are widely used as a pharmacological option for the treatment of somatoform disorders diagnosed within the psychiatric classifications (Table 11.1) [32] even though evidence is still inconclusive. Tricyclic antidepressants and a number of selective serotonin reuptake inhibitors (SSRI) have shown promising effects. Fluoxetine and sertraline seemed to be similarly effective for the treatment of undifferentiated somatoform disorders in an open label trial [33]. Fluoxetine was superior to placebo in a randomized controlled treatment trial for body dysmorphic disorder [34]. Mirtazapine, a noradrenergic and specific serotonergic antidepressant (NaSSA) and venlafaxine, a dual serotonin and noradrenaline reuptake inhibitor SNRI, were both effective in an open label trial with marginal advantages for mirtazapine [35]. The SNRI duloxetine has an outstanding role for the treatment of chronic neuropathic pain and fibromyalgia [29, 36]. There is evidence for the effectiveness of St. John's wort extract (LI 160) for the reduction of somatic symptoms independently of the reduction of depressive symptoms in the treatment of somatoform disorders [37].

The antiepileptic drug pregabalin (300–600 mg/d) has been used in addition to antidepressants and shown promising results in a case series of patients with somatoform disorders [38]. The antiepileptic levetiracetam (250–3,000 mg/d) has been used as an add-on to antidepressants or as a single regimen after therapy resistance to antidepressants with a benefit to a majority of a series of cases with body dysmorphic disorder [39]. Both studies need follow-up with randomized controlled trials. Pregabalin and gabapentin, $\alpha_2\delta$ ligands at voltage-gated calcium channels, play a role for the treatment of chronic pain [40], especially of neuropathic type and fibromyalgia [41, 42]. In clinical practice, pregabalin is often combined with duloxetine for the treatment of fibromyalgia and other functional syndromes [43].

Low-dose antipsychotic medication for severe and therapy refractive cases is a common strategy in the clinical management of somatoform disorders [18] even though the evidence is scarce. There is evidence for the effectiveness of sulpiride and L-sulpiride in the reduction of somatic symptoms [44] and the treatment of somatoform disorders [45, 46], in particular for the management of functional dyspepsia [47] and somatoform gastrointestinal pain [48]. Sulpiride, a benzamide, is known for antidepressant effects in lower dosages (50–200 mg/d) and antipsychotic effects in higher dosages (600–1,600 mg/d). For its structural similarity to sulpiride, amisulpride has been used as an alternative to antidepressants [49]. Amisulpride

(25 mg/d) was superior to fluoxetine in a pilot study for the reduction of somatic symptoms in chronic fatigue syndrome [50]. The use of low-dose amisulpride (200 mg/d) as an adjunctive to escitalopram and lorazepam was evaluated to be useful in a case of severe motor conversion disorder [51]. There is evidence on the level of a case report for aripiprazole as augmentation to SSRI for the treatment of body dysmorphic disorder [52].

Especially for the management of chronic pain, augmentation and combination strategies are common and not always successful, if tested in rigorous trials [53]. In the management of pain, somatization can impact the adherence to opioid prescriptions and therefore impact the safety of its use. Whereas all levels of somatization can be associated with patterns of under-use, severe somatization may lead to overuse of opioid drugs [54].

11.6 Conclusions and Future Directions

Epidemiological research supports complex biopsychosocial approaches to somatic symptom disorders rather than a simplistic divide in "medically unexplained" symptoms and physical disease [55]. Diagnostic approaches will integrate psychological and behavioral symptoms rather than mere somatic symptom lists to move towards positive diagnostic criteria [56], e.g. selective attention, symptom catastrophizing, body checking, focusing on organic explanations, seeking for repeated testing and symptom expectation [57]. The psychological and behavioral symptoms may relegate the need to "exclude" a disease and require that the somatic symptoms may not be "better explained" by a disease if present [58]. All future directions will require closer collaborations between medical specialties, psychology and psychiatry in clinical practice. There must be an interdisciplinary discussion on pharmacological strategies based on individual cases rather than a parallel of strategies resulting in potentially harmful and costly polypharmacy [18]. In clinical practice, psychiatrists are mostly in a situation, which needs diminution of polypharmacy based on a stable doctor-patient relationship rather than augmentation strategies to overcome possible treatment resistance.

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Appendix 1. Annotated Bibliography on Polypharmacy

Rena Kurs

Abstract Treatment resistance in schizophrenia and other mental disorders often challenges guideline-recommended monotherapy. Antipsychotic polypharmacy is thus increasingly encountered in clinical practice, and surveys of prescribing in psychiatric services internationally have identified the relatively frequent and consistent use of combined psychotropic medications, usually for people with established psychotic disorders. To date there are no clear cut acknowledged evidenced based clinical practice guidelines for the use of psychotropic polypharmacy. The following annotated bibliography is a collection of representative publications on this controversial subject. The articles presented were chosen based on timeliness, and generalizability. They will be of interest to clinicians, multidisciplinary caregivers, and families of patients treated with psychotropic medications. There are links to the full text of open access publications, and to abstracts of articles available for purchase or to subscribers of the specific journals. For convenience sake, the publications have been divided into the following sections: General polypharmacy reviews and guidelines, Pediatric polypharmacy, and Disease specific polypharmacy. The last section includes links to various clinical practice guidelines for psychiatric disorders.

Publications appear in descending order of year of publication

Keywords Polypharmacy • Annotated bibliography • Clinical practice guidelines • Open access publications

R. Kurs, B.A. (✉)
Medical Library, Sha'ar Menashe Mental Health Center, Hadera, Israel
e-mail: rena@sm.health.gov.il

M.S. Ritsner (ed.), *Polypharmacy in Psychiatry Practice, Volume I: Multiple Medication Use Strategies*, DOI 10.1007/978-94-007-5805-6,

General Polypharmacy Reviews and Guidelines

Antipsychotic Polypharmacy: Update and Guidelines for Practice
Rajiv Tandon

An evaluation of the appropriateness of the many rationales for antipsychotic combinations with a brief outline of recommendations for the role of polypharmacy in antipsychotic therapy.

http://medicaidmentalhealth.org/files/Guidelines/Antipsychotic%20Polypharmacy%20Update%20and%20Guidelines%20for%20Practice2012011708263376.pdf (Full text).

Polypharmacy with antipsychotics, antidepressants, or benzodiazepines and mortality in schizophrenia.
Tiihonen J, Suokas JT, Suvisaari JM, Haukka J, Korhonen P. *Archives of General Psychiatry. 2012 May;69(5):476–83.*

The authors investigated whether the use of benzodiazepines, antidepressants, or multiple concomitant antipsychotics is associated with increased mortality among patients with schizophrenia

http://www.ncbi.nlm.nih.gov/pubmed/22566579 (Abstract)

Antipsychotic polypharmacy: review of mechanisms, mortality and management
Julie LanganPolash Shajahan *The Psychiatrist (2010) 34: 58–62*

In this review the authors consider the reasons behind antipsychotic polypharmacy and the patterns of its use. They consider the evidence of effectiveness of combined therapy *v*. monotherapy and the rationale behind the potentially beneficial combinations that are used. The potential dangers of antipsychotic polypharmacy are also discussed and the limited research regarding switching from polypharmacy to monotherapy is reviewed. Some provisional recommendations regarding antipsychotic polypharmacy are proposed. http://pb.rcpsych.org/content/34/2/58.full (Full text).

Polypharmacy or medication washout: an old tool revisited
Hoffman DA, Schiller M, Greenblatt JM Iosifescu D

The authors discuss the role of washout, and whether it can help physicians select appropriate polypharmacy more effectively and safely, if necessary.

Neuropsychiatric Disease and Treatment 2011:7 639–648

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3215520/pdf/ndt-7-639.pdf (Full text)

Psychiatric Polypharmacy: Identifying Risks and Seeking Solutions
The Joint Commission Perspectives on Patient Safety, November 2008, Volume 8, Issue 11

Copyright 2008 Joint Commission on Accreditation of Healthcare Organization

Discusses four types of polypharmacy: same-class polypharmacy, multiclass polypharmacy, adjunctive polypharmacy, augmentation.

http://ebookbrowse.com/polypharmacy-pdf-d98995356 (Full text)

Quality Concerns in Psychotropic Prescribing: Reducing Psychotropic Polypharmacy

Reference Guide

New York State Office of Mental Health

In 2007, the NYS Office of Mental Health convened a Scientific Advisory Committee of national experts in psychopharmacology. Six workgroups (schizophrenia, depression, bipolar disorder, older adults, youth, and women) identified approximately 80 quality concerns in psychotropic prescribing that are common, costly, and measurable. This clinical module provides information on the quality domain of polypharmacy, including an overview of the evidence base and definitions of each indicator.

http://www.omh.ny.gov/omhweb/psyckes_medicaid/quality_concerns/reference_guide/polypharmacy.pdf (Full text)

A Critical Review of Atypical Antipsychotic Utilization: Comparing Monotherapy with Polypharmacy and Augmentation

S.M. Stahl, M.M. Grady *Current Medicinal Chemistry, 2004;11:313–327*

This article reviews evidence for the increasingly common means of treating schizophrenia and psychosis, with particular emphasis on polypharmacy and augmentation.

http://www.nascos.org/library_files/Atypicals%20Review.pdf (Full text).

Polypharmacy in Psychiatry

S. Nassir Ghaemi *New York, NY: Dekker; 2002, 346 pages.*

This practical reference book examines the advantages and disadvantages of polypharmacy in psychiatry, and provides up-to-date clinical guidelines on the appropriate use of combinations of pharmacological therapy in major psychiatric disorders-including multidisciplinary approaches to treatment. The book consolidates available and current material on polypharmacy and psychiatry into one comprehensive volume. Polypharmacy in Psychiatry also discusses the use of alternative and herbal medications psychosocial aspects of polypharmacy the psychology of polypharmacy cultural components of polypharmacy historical background

http://books.google.co.il/books?id=TthcnM15c0sC&printsec=frontcover&hl=iw&source=gbs_ge_summary_r&cad=0#v=onepage&q&f=false (Excerpts from google books)

Decision Making in Psychopharmacology: Pocketbook

Siegfried Kasper, Joseph Zohar, Dan J. Stein

Martin Dunitz, Oct 10, 2002–112 pages

Rather than providing treatment guidelines this book highlights the different available avenues of treatment for mental disorders. Decision Making in Psychopharmacology is intended to stimulate discussion and clear thinking about the evaluative process.

http://books.google.co.il/books/about/Decision_Making_in_Psychopharmacology_Po.html?id=cvq5lNZCI_QC&redir_esc=y

NASMHPD Medical Directors' Technical Report on Psychiatric Polypharmacy

Approved by the NASMHPD Medical Directors Council October 9, 2001, for distribution to the NASMHPD Membership

This report is the seventh in a continuing series of reports initiated by the Medical Directors Council of the National Association of State Mental Health Program Directors (NASMHPD) (Alexandria, Virginia, USA).

The purpose of this report is to review information on the use of polypharmacy, to outline guidelines for the use of polypharmacy, and to make recommendations that decrease the inappropriate use of multiple psychiatric medications in patients with psychiatric illness.

http://www.nasmhpd.org/docs/publications/archiveDocs/2001/Polypharmacy.PDF (Full text).

Polypharmacy: When is it rational?

Sheldon H. Preskorn *Journal of Practical Psychiatry and Behavioral Health, July 1995, 92–98*

Though published in 1995, this is a landmark paper in which the author discusses when it makes sense to consider using more than one medication to treat a single condition. He gives a brief history of the use of polypharmacy in psychiatry and discusses how new discoveries in psychotropic drug development are making polypharmacy an increasingly important topic. The author then presents a list of ten criteria to guide the rational use of psychotropic polypharmacy and explains each in detail with examples drawn from clinical practice.

http://www.preskorn.com/columns/9507.html (Full text).

Pediatric Polypharmacy

The definition and prevalence of pediatric psychotropic polypharmacy

Chen H, Patel A, Sherer J, Aparasu R

Psychiatric Services. 2011 Dec;62(12):1450–5.

Using increasingly stringent criteria, this study evaluated the prevalence of psychotropic polypharmacy among children on the basis of duration of overlap between two or more psychotropic medications.

http://www.ncbi.nlm.nih.gov/pubmed/22193792 (Abstract)

Antipsychotic polypharmacy in the treatment of children and adolescents in the fee-for-service component of a large state Medicaid program.

Constantine RJ, Boaz T, Tandon R.

Clinical Therapeutics 2010;32(5):949–59.

The aims of this study were to quantify and describe antipsychotic polypharmacy use among patients aged 6–12 years (children) and 13–17 years (adolescents) and to identify the characteristics of polypharmacy recipients.

http://www.ncbi.nlm.nih.gov/pubmed/20685503

Predictors of polypharmacy and off-label prescribing of psychotropic medications: A national survey of child psychiatrists
Marcia Kearns

Thesis – Master of Arts 2011, University of Missouri

Anational survey of child psychiatrists to examine typical prescribing practices for children with anxiety, depression, and disruptive behavior disorders from a social judgment theory perspective. The author examined the extent to which polypharmacy and off-label prescribing occur in routine practice and the degree to which child characteristics, child psychiatrist characteristics, and medication availability may influence these prescribing practices.

https://mospace.umsystem.edu/xmlui/bitstream/handle/10355/11178/research.pdf.pdf?sequence=3 (Full text)

National trends in child and adolescent psychotropic polypharmacy in office-based practice, 1996–2007.
Comer JS, Olfson M, Mojtabai R.

Journal of the American Academy of Child & Adolescent Psychiatry. 2010;49(10):1001–10.

Analysis of the annual data from the 1996–2007 National Ambulatory Medical Care Surveys that examined patterns and trends in multi-class psychotropic treatment within a nationally representative sample of 3466 child and adolescent visits to office-based physicians in which a psychotropic medication was prescribed. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2952543/ (Abstract)

Pediatric Psychotropic Polypharmacy
Zonfrillo MR, Penn JV, Leonard HL. *Psychiatry (Edgmont (Pa.: Township) 2005 Aug;2(8):14-9.*

A literature review of relevant articles pertaining to polypharmacy using the Pub Med database from 1994 through April 2004 for pediatric populations under 18 years old.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3000211/ (Abstract)

Disease Specific Polypharmacy

Depression

Medication Augmentation after the Failure of SSRIs for Depression
Madhukar H. Trivedi, Maurizio Fava, Stephen R. Wisniewski, Michael E. Thase, Frederick Quitkin, Diane Warden, Louise Ritz, Andrew A. Nierenberg, Barry D. Lebowitz, Melanie M. Biggs, James F. Luther, Kathy Shores-Wilson,

A. John Rush, for the STAR*D Study Team *New England Journal of Medicine 2006;354:1243–52.*

This study might be considered a “real-world” trial of the augmentation of an SSRI—citalopram—with sustained-release bupropion or buspirone after a consistent, well-implemented trial of citalopram was performed. Remission rates in this trial were similar to thosefound in most previous uncontrolled trials of augmentation

of SSRIs, which have typically been conducted in research clinics and have involved symptomatic volunteers with nonchronic depression and few general medical and psychiatric coexisting illnesses. Remission rates in this trial should be generalizable to most outpatients with nonpsychotic major depressive disorder who are seen in both primary and psychiatric settings and who have not had adequate benefit with the use of an SSRI alone.

http://www.nejm.org/doi/pdf/10.1056/NEJMoa052964 (Full text).

Schizophrenia

Polypharmacy with antipsychotics, antidepressants, or benzodiazepines and mortality in schizophrenia.

Tiihonen J, Suokas JT, Suvisaari JM, Haukka J, Korhonen P.

Archives of General Psychiatry. 2012;69(5):476–83.

In a registry based linkage study, the authors investigated if the use of benzodiazepines, antidepressants, or multiple concomitant antipsychotics is associated with increased mortality among patients with schizophrenia.

They linked national databases of mortality and medication prescriptions among a complete nationwide cohort of 2588 patients hospitalized in Finland for the first time with a diagnosis of schizophrenia between January 1, 2000, and December 31, 2007. Hazard ratios (HRs) were computed for all-cause mortality during the use of antipsychotics, antidepressants, or benzodiazepines in outpatient care,

http://archpsyc.jamanetwork.com/article.aspx?articleid=1151489 (Abstract)

Treatment-resistant Schizophrenia: Evidence-based Strategies.

Englisch S., Zink M. *Mens Sana Monographs 2012;10:20–32.*

The authors report on findings of frequent use of polypharmacy in treatment-refractory cases, addressing psychotic positive, negative and cognitive symptoms, treatment-emergent side effects caused by antipsychotics and comorbid depressive or obsessive-compulsive symptoms.

http://www.msmonographs.org/article.asp?issn=0973-1229;year=2012;volume=10;issue=1;spage=20;epage=32;aulast=Englisch (Full text).

Effects of polypharmacy on outcome in patients with schizophrenia in routine psychiatric treatment.

Längle G, Steinert T, Weiser P, Schepp W, Jaeger S, Pfiffner C, Frasch K, Eschweiler GW, Messer T, Croissant D, Becker T, Kilian R.

Acta Psychiatrica Scandinavica. 2012;125(5):372–81.

The authors evaluated the effects of different types of psychotropic polypharmacy on clinical outcomes and quality of life (QOL) in patients with schizophrenia and schizoaffective disorder in routine care.

http://www.ncbi.nlm.nih.gov/pubmed/22321029 (Abstract)

Antipsychotic Polypharmacy in Schizophrenia: Benefits and Risks

Barnes, Thomas R.E.; Paton, Carol *CNS Drugs: 2011; 25(5) 383–399*

This review addresses the clinical trial data and other evidence for the following pharmacological approaches: the addition of a second antipsychotic to boost therapeutic response, the use of as-required antipsychotic medication (mainly to treat disturbed behaviour), gradual cross-titration while switching from one antipsychotic to another, and augmentation of clozapine with a second antipsychotic where the illness has failed to respond adequately to an optimized trial of clozapine. Also reviewed are examples of systematic, practice-based interventions designed to reduce the prevalence of antipsychotic polypharmacy, most of which have met with only modest success.

http://adisonline.com/cnsdrugs/Abstract/2011/25050/Antipsychotic_Polypharmacy_in_Schizophrenia_.3.aspx (Abstract)

Antipsychotic polypharmacy in the treatment of schizophrenia—a health technology assessment

Baandrup L, Lublin H, Nordentoft M, Peacock L, Srensen J, Andersen SE, Glenthj B

Copenhagen: National Board of Health, Danish Centre of Health Technology Assessment (DACEHTA), 2011.

Health Technology Assessment—funded projects 2011; 11(1)

Language: English summary of the full report in Danish

Version date: January 25 2011

This health technology assessment explored how antipsychotic polypharmacy may be reduced by intervention methods and organisational changes. The report is directed at decision-makers at the level of the management board of regions and mental health centres. This report only discusses antipsychotic polypharmacy in the context of schizophrenia spectrum disorders, because the principles of treatment regarding other psychiatric disorders, e.g. bipolar affective disorder, differ substantially.

http://www.sst.dk/publ/Publ2011/MTV/Polyfarmaci/polyfarmaciMTVsummary.pdf (Full text)

Combination and augmentation strategies in treatment-resistant schizophrenia

Susanne Englisch, Mathias Zink

Drug Discovery Today: Therapeutic Strategies Vol.8 (1–2) 2011, 17–23

This review discusses risks, benefits and levels of evidence of combination strategies involving multiple psychotropic substances, with a focus on their clinical relevance.

http://www.sciencedirect.com/science/article/pii/S1740677311000313 (Abstract)

Polypharmacy in schizophrenia

Zink M, Englisch S, Meyer-Lindenberg A.

Current Opinion in Psychiatry. 2010;23(2):103–11.

This review summarizes the current state of evidence of combined antipsychotic treatment strategies and the augmentation of antipsychotics with mood stabilizers,

antidepressants and experimental substances. http://www.ncbi.nlm.nih.gov/pubmed?term=Curr%20Opin%20Psychiatry%20AND%20Polypharmacy%20in%20schizophrenia.%20AND%20Zink%20M (Abstract)

Antipsychotic combinations vs monotherapy in schizophrenia: a meta-analysis of randomized controlled trials.
Correll CU, Rummel-Kluge C, Corves C, Kane JM, Leucht S.
Schizophrenia Bulletin 2009 Mar;35(2):443–57.

This paper reports on the evaluation of therapeutic and adverse effects of antipsychotic cotreatment vs monotherapy in schizophrenia, based on Cochrane Schizophrenia Group register and hand searches of relevant journals/conference proceedings. Study Selection included randomized controlled trials comparing antipsychotic monotherapy to cotreatment with a second antipsychotic. The authors concluded that in certain clinical situations, antipsychotic cotreatment may be superior to monotherapy. However, the database is subject to possible publication bias and was too heterogeneous to derive firm clinical recommendations, underscoring the need for future research.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2659301/pdf/sbn018.pdf (Full text)

Antipsychotic monotherapy and polypharmacy in the naturalistic treatment of schizophrenia with atypical antipsychotics
Douglas Faries, Haya Ascher-Svanum, Baojin Zhu, Christoph Correll, John Kane
BMC Psychiatry 2005, 5:26 doi:10.1186/1471-244X-5-26

This study assessed the annual rate and duration of antipsychotic monotherapy and its inverse, antipsychotic polypharmacy, among schizophrenia patients initiated on commonly used atypical antipsychotic medications. The authors concluded that despite guidelines recommending the use of polypharmacy only as a last resort, the use of antipsychotic polypharmacy for prolonged periods is very common during the treatment of schizophrenia patients in usual care settings. Reasons for and the impact of the predominant use of polypharmacy will require further study.

http://www.biomedcentral.com/1471-244X/5/26 (Full text).

Validation of Polypharmacy Process Measures in Inpatient Schizophrenia Care
Birgit Janssen, Stefan Weinmann, Mathias Berger, Wolfgang Qaebel *Schizophrenia Bulletin,* Vol. 30, No. 4, 2004 1023–1033

As part of a comprehensive quality management program, the authors prospectively evaluated two schizophrenia polypharmacy performance measures in a cohort of 1,075 consecutively recruited individuals with schizophrenia in seven psychiatric hospitals. The results show the strengths and limits of polypharmacy performance measures to compare clinical practice in inpatient schizophrenia care and to detect possible treatment problems.

http://schizophreniabulletin.oxfordjournals.org/content/30/4/1023.full.pdf (Full text)

Polypharmacy in patients with schizophrenia.
McCue RE, Waheed R, Urcuyo L. *Journal of Clinical Psychiatry. 2003 Sep;64(9):984–9.*

The objective of this report was to describe the changes in prescription practices with psychotropic medications for patients diagnosed with schizophrenia in 1995 and 2000. No patients were discharged on treatment with more than 1 antipsychotic in 1995, whereas in 2000, 15.9 % of patients were. Results of increased used of polypharmacy are discussed.

http://www.ncbi.nlm.nih.gov/pubmed/14628972 (Abstract)

General Practice Guidelines

Handbook of Schizophrenia Spectrum Disorders, Volume III

Therapeutic Approaches, Comorbidity, and Outcomes
Michael S. Ritsner (Editor), Springer, 2011, 462 p.

This collection of monographs by eminent investigators reviews recent research regarding the origins, onset, course, and outcome of schizophrenia spectrum disorders. The book provides an up-to-date overview of the rapid advances made in the clinical and basic science studies supporting our understanding of the relationship between cerebral processes and clinical, cognitive and other presentations of the schizophrenia spectrum disorders. In addition, this book aims to monitor important research developments, relevant to the treatment and rehabilitation of patients.

http://www.springer.com/biomed/neuroscience/book/978-94-007-0833-4

Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines

The Australian and New Zealand versions of RANZCP's Consumer and Carer Clinical Practice Guidelines are free of charge to download, using the links on the webpage. These booklets are a valuable resource to support consumers, their carers, families and friends in learning more about mental illness and the treatments that are available.

The RANZCP has developed Clinical Practice Guidelines (CPGs) to provide mental health practitioners, consumers, and carers with evidence-based information about particular mental illnesses and appropriate treatment options.Available guidelines: anorexia nervosa, bipolar disorder, deliberate self harm, depression, panic disorder and agoraphobia, schizophrena.

http://www.ranzcp.org/Publications/Clinical-Practice-Guidelines.aspx

National Institute for Health and Clinical Excellence (NICE)

Guidelines—National Institute for Health and Clinical Excellence—Links to guidelines in psychiatry

http://www.nice.org.uk/Search.do?searchText=psychiatry&newsearch=true&x=17&y=12&page=2#/search/?reload

Borderline personality disorder Borderline personality disorder: treatment and management

NICE clinical guideline 78 Developed by the National Collaborating Centre for Mental Health

Issue date: January 2009
http://www.nice.org.uk/nicemedia/live/12125/42900/42900.pdf

Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults

Management in primary, secondary and community care
Issue date: January 2011
http://www.nice.org.uk/nicemedia/live/13314/52599/52599.pdf

Schizophrenia

Core interventions in the treatment and management of schizophrenia in adults in primary and secondary care

NICE clinical guideline 82
Developed by the National Collaborating Centre for Mental Health, National Institute for Health and Clinical Excellence
http://www.nice.org.uk/nicemedia/live/11786/43608/43608.pdf

APA Practice Guidelines

http://www.psych.org/practice/clinical-practice-guidelines
American Psychiatric Association Clinical Practice Guidelines provide evidenced—based recommendations for the assessment and treatment of psychiatric disorders. The guidelines are published on PsychiatryOnline. Below are direct links to guidelines for some of the major psychiatric disorders.

Schizophrenia

Guideline Watch (September 2009): Practice guideline for the treatment of patients with schizophrenia

Dixon L, Perkins D, Calmes C.
The original guideline was published in February 2004. The November 2009 Guideline Watch associated with this guideline provides additional information that has become available since publication of the guideline, but it is not a formal update of the guideline.
http://psychiatryonline.org/data/Books/prac/Schizophrenia_Guideline%20Watch.pdf

Major Depressive Disorder

Practice guideline for the treatment of patients with major depressive disorder, Third Edition
Gelenberg AJ, Freeman MP, Markowitz JC, Rosenbaum JF, Thase ME, Trivedi MH, Van Rhoads, RX
American Psychiatric Association (APA). Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. Arlington (VA): American Psychiatric Association (APA); 2010 Oct. 152 p. (1170 references)
http://psychiatryonline.org/content.aspx?bookid=28&sectionid=1667485

Guideline Watch: Practice Guideline for the Treatment of Patients With Bipolar Disorder, 2nd Edition

Robert M. A. Hirschfeld

APA's *Practice Guideline for the Treatment of Patients With Bipolar Disorder,* 2nd Edition, was published in April 2002 (1). Since that time, a number of controlled treatment studies on aspects of bipolar disorder have been completed and published. This guideline watch briefly reviews the most important of the studies. The majority of the studies were industry supported.

http://psychiatryonline.org/data/Books/prac/Bipolar.watch.pdf

Practice guideline for theTreatment of Patients With Obsessive-Compulsive Disorder

Koran, LM, Hanna GL, Hollander E, Nestadt G, Simpson HB.

This practice guideline was approved in October 2006 and published in July 2007

http://psychiatryonline.org/data/Books/prac/OCDPracticeGuidelineFinal05-04-07.pdf

U.S. Department of Health & Human Services, Agency for Healthcare Research and Quality

National Guideline Clearinghouse—Guidelines for Mental Disorders

Includes 292 links to clinical practice guidelines from around the globe, for various mental disorders

http://guideline.gov/browse/by-topic-detail.aspx?id=1180&ct=1

Appendix 2. List of Psychotropic Medications

Rena Kurs

Abstract The following is a list of psychotropic medications arranged in alphabetical order, by generic names. The list is divided into the following subsections: Antipsychotic agents, Antidepressant Medications (also used for anxiety disorders), Mood Stabilizing and Anticonvulsant Medications, Anti-anxiety Medications, Sleep Agents

This list was compiled for the convenience of the reader. It is not intended or implied to be a substitute for professional medical or pharmacological advice. The information on psychotropic medications in this list is provided as an information resource only, and is not to be used or relied on for any diagnostic or treatment purposes. This information is not intended to be patient education, and should not be used as a substitute for professional diagnosis and treatment. Following the psychotropic drug list, there is an annotated list of internet links to sites with current psychotropic drug lists that include additional information such as dosage facts, recommended dosages/blood levels, half life, anticholinergic effects, sedation, orthostatic hypotension, sexual dysfunction, gastrointestinal effects, activation/insomnia, detailed side effects, medication management and black box warnings.

Keywords Psychotropic drugs • Generic drugs • Trade names • Brand names • Therapeutic class • Chemical ClassAbbreviations

Abbreviations

FGA	1st generation antipsychotic agent
MAOI	Monoamine oxidase inhibitor
MAOI-B	Monoamine oxidase -B inhibitor

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M.S. Ritsner (ed.), *Polypharmacy in Psychiatry Practice, Volume I: Multiple Medication Use Strategies*, DOI 10.1007/978-94-007-5805-6,

SGA	2nd generation antipsychotic agent
SNRI	Serotonin norepinephrine reuptake inhibitor
SPARI	Selective partial agonist and reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant

Antipsychotic agents

Generic name	Trade/Brand names	Therapeutic class	Chemical class
Aripiprazole	Abilify, Abilitat, Abilify Discmeltv	SGA	Benzisoxazole derivatives
Asenapine	Saphris	SGA	Dibenzo-oxepino pyrroles
Chlorpromazine	Largactil, Contomin, Thorazine, Propaphenin, Megaphen, Chlorderazin, Chloropromazine, Aminazine, Fenactil, Clozine	FGA	Phenothiazine
Clozapine	Clozaril, Leponex, FazaClo, Clopine	SGA	Dibenzodiazepine
Fluphenazine	Anatensol, Fludecasin, Dapotum D, Fludecate	FGA	Phenothiazine antipsychotics
Haloperidol	Aloperidol, Eukystol, Aloperidin, Aloperidolo, Brotopon, Galoperidol, Halopoidol, Serenace	FGA	Phenyl-piperidinyl-butyrophenone
Iloperidone	Zomaril, Fanapt, Fanapta, Fiapta	SGA	Piperidinyl-benzisoxazole derivatives
Loxapine	Cloxazepine, Dibenzoazepine, Oxilapine, Dibenzacepin, Loxapin, Loxapac	Tricyclic antipsychotic agents has been classed as FGA and SGA	Dibenzoxazepine
Lurasidone	Latuda	SGA	Benzisothiazol derivatives.
Molindone*	Moban, Molindone, Molindone Hydrochloride Tablets	Has been classed as both FGA and SGA	Dihydroindolone compound
Olanzapine	Zyprexa, Zyprexa Zydis, Olansek, Symbyax, Zalasta, Lanzac, Zyprexa Velotab	SGA	Thienobenzodi azepine class
Paliperidone	Invega, Paliperidone	SGA	Benzisoxazole derivatives
Perphenazine	Trilafon, Perfenazine, Etaperazine, Etaperazin, Ethaperazine, Fentazin, Perphenazin, Chlorpiprazine, Thilatazin	FGA	Piperazinyl phenothiazine

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Antipsychotic agents			
Generic name	Trade/Brand names	Therapeutic class	Chemical class
Pimozide (for Tourette's syndrome)	Orap, Opiran, Neoperidole, Halomonth, Pimozidum	FGA	Diphenylbutylpi peridine
Quetiapine	Seroquel, Quetiapine fumarate	SGA	Dibenzothiazepine derivatives
Risperidone	Risperdal, Risperidal, Rispolept, Risperin, Rispolin, Sequinan, Risperdal Consta, Risperidonum, Risperdal M-Tab	SGA	Benzisoxazole derivatives
Thioridazine	Mellaril, Melleril, Meleril, Mallorol, Malloryl, Mellerets, Mellerette, Melleretten, Thioridazin, Novoridazine, Thiori	FGA	Phenothiazine
Thiothixene	Tiotixene, cis-Thiothixene, Navane, (E)-Thiothixene, Thiothixine, Navan, trans-Thiothixene	FGA	Thioxanthene derivative
Trifluoperazine	Trifluperazine, Trifluoroperazine, Triperazine, Triflurin, Trifluoperazin, Trifluoperazina, Flurazine, Stelazine, Eskazine, Jatroneuroal, Modalina Trifluoromethylperazine	FGA	Phenothiazine
Ziprasidone	Geodon, Zeldox, Zipfasidone Hydrochloride	SGA	Benzisoxazole derivatives
Antidepressant medications (also used for anxiety disorders)			
Amitriptyline	Damilen, Elavil, Triptanol, Flavyl, Lantron, Seroten, Damitriptyline, Proheptadiene, Tryptanol, Tryptomer, Tryptizol, Laroxyl, Sarotex, Lentizol, Endep, Vanatrip	TCA	Dibenzocyclo heptadiene derivative
Amoxapine	Asendin, Demolox, Amoxepine, Moxadil, Desmethylloxapin, Amoxapina, Amoxapinum, Asendis, Defanyl, Amoksian, Demolox, Asendin	TCA	Dibenzoxazepine class
Bupropion	Bupropion hydrochloride, Wellbutrin, Zyban, Wellbutrin SR, Wellbutrin XL, Amfebutamone hydrochloride	Unicyclic antidepressant	Aminoketones
Citalopram	Nitalapram, Cipram, Celexa, Citalopramum, Cytalopram, Celapram, Ciprapine, Citabax	SSRI	Racemic bicyclic phthalane derivative

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Antipsychotic agents			
Generic name	Trade/Brand names	Therapeutic class	Chemical class
Clomipramine	Clomipramine hydrochloride, Anafranil, Clomipramine HCL, Anaphranil, Chlorimipramine hydrochloride	TCA	Dibenzazepine
Desipramine	Desipramine hydrochloride, Norpramin, Pertofran, Pertofrane, Norpolake, Nortimil, DMI hydrochloride, Pertofrin, Petylyl	TCA	Dibenzazepine
Desvenlafaxine	Pristiq extended release,	SNRI	
Doxepin	Doxepine, Zonalon, Quitaxon, Doxepinum	TCA	Dibenzoxepin
Duloxetine	Cymbalta, Yentreve, Xeristar Ariclaim, Duzela	SNRI	Naphthalenes
Escitalopram	Escitalopram, Cipralex, Seroplex, Nexito, anxiset-E, Lexapro, Lexamil, Lexam, Entact, Losita, Animaxen	SSRI	Furancarbonitrile
F`luoxetine	Prozac, Fluctin, Flunirin, Fluoxeren, Sarafem, Adofen, Lovan, Equilibrane, Rowexetina, Fontex, Fluval	SSRI	Phenylpropylamines
Fluvoxamine	Luvox, Faverin, Dumyrox, Dumirox, Favoxil, Floxyfral, Maveral	SSRI	2-aminoethyl oxime ethers of aralkylketones
Imipramine	Imidobenzyle, Antideprin, Melipramine, Berkomine, Dimipressin, Melipramin, Intalpram, Nelipramin, Dynaprin	TCA	Dibenzazepines and derivatives
Imipramine pamoate	Tofranil-PM	TCA	Dibenzazepines and derivatives
Isocarboxazid	Isocarbonazid, Isocarboxazide, Benazide, Enerzer, Marplan, Isocarbossazide, Isocarboxyzid, Maraplan, Marplon	MOAI	Hydrazine
maprotiline	Dibencycladine, Deprilept, Maprotilin, Maprotylina, Ludiomil	TCA	anthracenes
Mirtazapine	Remergil, Remeron, Zispin, Remergon, Rexer, Remeron SolTab, Mepirzepine, Promyrtil, Norset	TCA	Piperazino-azepine

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Antipsychotic agents			
Generic name	Trade/Brand names	Therapeutic class	Chemical class
Nefazodone*	Dutonin, Serzone	Synthetically derived phenylpipera-zine antidepressant	Phenols and derivatives
Nortriptyline	Sensaval, Avantyl, Noritren, Pamelor, Ateben, Desitriptilina, Nortryptiline, Nortrilen, Demethylamitriptyline, Aventyl, Lumbeck	TCA	Dibenzocyclo heptenes
Paroxetine	Paxil, Seroxat, Aropax, Paxil CR, Paroxetinum, Frosinor, Motivan, Paroxetina, Paxetil	SSRI	Phenylpiperidine
Paroxetine mesylate	Pexeva	SSRI	Mesylate salt of a phenylpiperidine compound
Phenelzine	Phenelzine sulfate, Estinerval, Nardelzine, Kalgan, Nardil, Alacine, Alazine, Alazin	MAOI	Hydrazine
Protriptyline	Amimetilina, Vivactil, Protryptyline, Triptil, Novopramine, Protriptilina, Protriptylinum, Rhotrimine	TCA	Dibenzocycloheptene
Selegiline	Eldepryl, Emsam, Jumex, L-Deprenalin, Carbex, Zelapar, Selegilinum, Selegilina, Selegyline, Anipryl,	MAOI-B	Levorotatory acetylenic derivative of phenethy lamine
Sertraline	Sertraline hydrochloride, Zoloft, Gladem, Serad, Lustral, Atruline, Tresleen, Tatig	SSRI	Tametralines
tranylcypromine	Parnate, Transamine, Jatrosom, Tranylcypromine	MAOI	phenethylamine and amphetamine class
Trazodone	Desyrel, Oleptro, Beneficat, Deprax, Desirel, Molipaxin, Thombran, Trazorel, Trialodine, Trittico, and Mesyrel	SARI	Triazolopyridine
Trimipramine	Surmontil, Rhotrimine, Stangil, Trimeprimine, Sapilent, Surmontil, Surmontyl, beta-Methylimipramine, Trimeproprimin, Stangyl,	TCA	Dibenzazepines and Derivatives

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Antipsychotic agents			
Generic name	Trade/Brand names	Therapeutic class	Chemical class
Venlafaxine	Elafax, Venlafaxina, Venlafaxinum, Effexor, Efectin, VenlafaxineXR	SNRI	Phenols and derivatives
Vilazodone	Vibryd	SPARI	Carboxamide derivative
Mood stabilizing and anticonvulsant medications			
Carbamazepine	Tegretol, Carbamazepen, Finlepsin, Carbazepine, Tegretal, Neurotol, Biston, Epitol	Anticonvulsant	Dibenzazepines and Derivatives
Divalproex sodium (valproic acid)	Depakote, Epival, Valproate semisodium, Depakote ER, Sodium divalproate, Divalproate, Delepsine, Sprinkle, Valcote, Zalkote	Anticonvulsant	
Gabapentin	Neurontin, Gabapentine, Aclonium, Fanatrix, Horizant, Gabarone, Gralise, Nupentin	Anticonvulsant.	GABA analogue
Lamotrigine	Lamictal, Lamotrigine	Anticonvulsant.	Phenyltriazine
Lithium carbonate	Eskalith, Lithobid, Dilithium carbonate, Lithonate, Liskonum, Lithane, Lithotabs, Micalith, Priadel, Limas	Mood-stabilizing agent	Inorganic ions and gases
Lithium citrate (generic only)	Lithium citrate, Trilithium citrate Demalit, Litarex, Eskalith	Mood-stabilizing agent	
Oxcarbazepine	Trileptal, Oxcarbamazepine, Timox, Epilexter	Anticonvulsant and mood stabilizer	Structural derivative of carbamazepine
Topiramate	Topamax, Epitomax, Topimax, Topomax, Topina, Tipiramate	Anticonvulsant.	Sulfamate-substituted monosaccharide
Anti-anxiety medications			
Alprazolam	Xanax, Trankimazin, Cassadan, Esparon, Tafil, Xanax XR, Alpronax, Intensol, Tranquinal	Antianxiety and sedative-hypnotic	Triazolobenz odiazepine compound
Buspirone	BuSpar, Ansial, Buspirona, Buspironum, Bespar, Ansiced, Anxiron, Buspisal	Anxiolytic agent	Azaspirodec anedione
Chlordiazepoxide	Librium, Chlozepid, Elenium, Helogaphen, Ifibrium, Kalmocaps, Librelease, Librinin	Anxiolytic agent	Benzodiazepine
Clonazepam	Klonopin, Rivotril, Clonex, Paxam, Kriadex, Antelepsin, Cloazepam, Iktorivil, Klonopin, Landsen	Anxiolytic, anticonvulsant, muscle-relaxant	Benzodiazepine

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Antipsychotic agents			
Generic name	Trade/Brand names	Therapeutic class	Chemical class
Clorazepate	Tranxene, Novo-Clopate	Anxiolytic, anticonvulsant, muscle-relaxant	Benzodiazepine
Diazepam	Valium, Ansiolisina, Assival, Diazemuls, Relanium, Stesolid, Apaurin, Faustan, Seduxen, Sibazon	Anticonvulsant, anxiolytic, sedative, muscle relaxant	Benzodiazepine
Lorazepam	Ativan, Temesta, Idalprem, Tavor, Bonatranquan, Delormetazepam, Almazine	Anti-anxiety agent hypnotic, anticonvulsant, sedative	Benzodiazepine
Oxazepam	Adumbran, Tazepam, Serax, Vaben, Ansioxacepam, Droxacepam, Anxiolit, Aplakil, Astress, Drimuel	Anti- anxiety, alcohol withdrawal, and insomnia	Benzodiazepine
ADHD medications			
Amphetamine	Mydrial, Adderall, dexedrine, Dextrostat, Desoxyn, Didrex, ProCentra. Fenopromin, Vivanxe, Benzedrine, Psychedrine	CNS stimulant	Phenethylamine
Atomoxetine	Strattera, Tomoxetine, Attentin	Non stimulant SNRI	Phenylpropylamines
Dexmethyl phenidate	Focalin	CNS stimulant	
Dextroamphe tamine	Dexedrine, Dextrostat, Dexamphetamine	CNS stimulant	Phenethylamines Amphetamines
Guanfacine	Intuniv, Estulic, Tenex, Guanfacinum, Guanfacina	Centrally acting antihyperten-sive agent	Phenethylamines
Lisdexamfetamine dimesylate	Vyvanse, Lisdexamfetamine mesilate	CNS stimulant	Phenethylamines amphetamines
Methamphe tamine	Desoxyn, Desyphed, Metamfetamine, Norodin, Stimulex	CNS stimulant	Phenethylamines amphetamines
Methylphenidate	Ritalin, Concerta, Daytrana, Metadate, Methylin, Riphenidate, Ritaline, Meridil,	CNS stimulant	Adrenergic agent, dopamine uptake inhibitors, adrenergic uptake inhibitors,
Sleep agents			
Eszopiclone	Estorra, Lunesta	Hypnotic	Lactams, cyclopyrrolones
Ramelteon	Roserem	Hypnotic	Benzofurans, indanes, phenylpropylam-ines

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Antipsychotic agents			
Generic name	Trade/Brand names	Therapeutic class	Chemical class
Zaleplon	Sonata, Zalaplon	Hypnotic	Acetanilides, pyrazolopyrimidines
Zolpidem	Ambien CR, Lorex, Stilnoct, Stilnox, Sanval	Hypnotic	Phynylporpenes, imidazopyridines

*Medications discontinued in some countries

Bibliography

1. Mental Health Medications. National Institute of mental Health
http://www.nimh.nih.gov/health/publications/mental-health-medications/complete-index.shtml#pub11
2. PubChem Compound
The PubChem Compound Database contains validated chemical depiction information provided to describe substances in PubChem Substance. Structures stored within PubChem Compounds are pre-clustered and cross-referenced by identity and similarity groups.
http://www.ncbi.nlm.nih.gov/pccompound
3. Daily Med: Current Medication Information
DailyMed provides high quality information about marketed drugs.
Drug labeling on this Web site is the most recent submitted to the Food and Drug Administration (FDA) and currently in use.
http://dailymed.nlm.nih.gov/dailymed/
4. DrugBank: Open Data Drug and Drug Target Database
http://www.drugbank.ca/
5. BehaveNet. BehaveNet is the Web's most comprehensive encyclopedic taxonomy of psychiatric drugs (including drugs of abuse), diagnoses (including diagnostic criteria), terminology and notable people with references to associated media and other resources
http://behavenet.com/

Links to Psychotropic Drug Lists

1. **Review of Psychotropic Drugs 2012**
Includes Medication categories, brand name, generic name, dosage facts, half life, anticholinergic effect, sedation, orthostatic hypotension, sexual dysfunction, GI effects, activation/insomnia, detailed side effects Authors' disclaimer: These Medication tables are NOT exhaustive for drug categories, dosage facts, side effects, adverse effects, indications or any special instructions (comments) and should only be used to guide learning. Use a pharmacologic text, drug guide such as the Physician's Desk Reference (PDR), or package insert for more complete medication information.

http://www.dhs.state.il.us/OneNetLibrary/27896/documents/By_Division/Division%20of%20DD/HumanRights/PsychotropicDrugsList.pdf

2. **Contemporary Psychotropic Medications listed alphabetically.**
   Metro Crisis Services
   In this table, both the generic or chemical names and the U.S. brand names are listed alphabetically. Brand names used in the United States, these medications may be sold outside the U.S. under different brand names. Includes links to Medline Plus for additional information for each drug.
   http://www.metrocrisisservices.org/7-learn-more/medications/medications-listed-alphabetically
3. **National Alliance on Mental Illness, NAMI, Policy Research Institute**
   Commonly Prescribed Psychotropic Medications
   Brand names are followed by the generic in parenthesis. A second chart below provides cross-referencing by generic name.
   *Although this medication has been approved by the FDA for the treatment of other disorders, it has not been approved for this particular use. Some evidence of this medication's efficacy for such use does exist however. This type of medication use is referred to as "off label."
   Remember, always consult your doctor or pharmacist with any specific medication questions http://www.nami.org/Template.cfm?Section=Policymakers_Toolkit&Template=/ContentManagement/HTMLDisplay.cfm&ContentID=18971
4. **University of Illinois at Chicago, Department of Children and Family Services (DCFS) Psychotropic Medication List**
   Includes Generic name, trade name, recommended doses/blood levels, medication management, black box warning, FDA indication for children
   http://www.psych.uic.edu/csp/DCFS_Psychotropic_Medication.pdf
5. **National Institute of Mental Health**
   This guide describes the types of medications used to treat mental disorders, side effects of medications, directions for taking medications, and includes any FDA warnings. http://www.nimh.nih.gov/health/publications/mental-health-medications/complete-index.shtml
6. **International Narcotics Control Board. Green List (24th edition, May 2010)**
   Annex to the annual statistical report on psychotropic substances (form P). List of Psychotropic Substances under International Control
   http://www.incb.org/pdf/e/list/Green_list_ENG_2010_53991.pdf
7. **Medication Safety team, Department of Health, Australia. Psychotropic Drug List**
   Current at January 2011.
   This is a list of pyschotropic medications available in Australia.
   This table has been developed in collaboration with the Medication Safety team, Department of Health. For ease of uses, the medications are listed alphabetically, whether by generic name, or by brand name.
   http://www.fallssa.com.au/documents/hp/Drug_list_in_SA_Health_Template_V2.pdf

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