Translating the Psychopharmacology of Antipsychotics to Individualized Treatment for Severe Mental Illness: A Roadmap

Peter J. Weiden, M.D.
University of Illinois at Chicago

Sheldon H. Preskorn, M.D.
Clinical Research Institute and University of Kansas School of Medicine-Wichita

Peter A. Fahnestock, M.D.
Washington University School of Medicine

Daniel Carpenter, Ph.D.
Comprehensive NeuroScience, Inc.

Ruth Ross, M.A.
Ross Editorial

John P. Docherty, M.D.
Comprehensive NeuroScience, Inc.

Editing and Design. David Ross, M.A., M.C.E., Ross Editorial

Acknowledgments. The authors thank all of the experts who completed the survey and acknowledge Paola Vega, of Expert Knowledge Systems, for managing the data collection.

Reprints. Reprints may be obtained by sending requests with a shipping/handling fee of $19.95 per copy to: Comprehensive NeuroScience, Inc., 21 Bloomingdale Road, White Plains, NY 10605. For pricing on bulk orders of 50 copies or more, please call Expert Knowledge Systems at (914) 997-4005. For more information on the Expert Consensus Guidelines or to order copies by credit card, visit www.psychguides.com.

Disclaimer. Any set of published recommendations can provide only general suggestions for clinical practice and practitioners must use their own clinical judgment in treating and addressing the needs of each individual patient, taking into account that patient's unique clinical situation. There is no representation of the appropriateness or validity of the Roadmap recommendations for any given patient. The developers of the Roadmap recommendations disclaim all liability and cannot be held responsible for any problems that may arise from their use.

PUBLISHED BY PHYSICIANS POSTGRADUATE PRESS, INC.

THE JOURNAL OF
CLINICAL PSYCHIATRY
VOLUME 68 2007 SUPPLEMENT 7

Translating the Psychopharmacology of Antipsychotics to Individualized Treatment for Severe Mental Illness: A Roadmap

Steering Committee and Editorial Board for the Roadmap

The Expert Consensus Panel for the Roadmap

Participants in the Roadmap Survey were identified from several sources: recent research publications and funded grants on the psychopharmacology of antipsychotics, work on guidelines on serious and persistent mental illness, and/or participation in previous Expert Consensus Surveys on psychotic disorders or bipolar disorder. Twenty-seven (84%) of the 32 experts to whom we sent the survey completed it. The recommendations in the Roadmap reflect the aggregate opinions of the experts and do not necessarily reflect the opinion of each individual on each question.

Anissa Abi-Dargham, M.D.
Columbia University College of Physicians and Surgeons

George S. Alexopoulos, M.D.
Weill Cornell Institute of Geriatric Psychiatry

Ross J. Baldessarini, M.D.
Harvard Medical School

Robert W. Buchanan, M.D.
Maryland Psychiatric Research Center

Peter F. Buckley, M.D.
Medical College of Georgia

Matthew J. Byerly, M.D.
University of Texas Southwestern Medical Center at Dallas

William T. Carpenter, M.D.
University of Maryland School of Medicine

Robert R. Conley, M.D.
University of Maryland School of Medicine

Christoph U. Correll, M.D.
Albert Einstein College of Medicine

David G. Daniel, M.D.
United BioSource Corporation

Peter A. Fahnestock, M.D.
Washington University School of Medicine

Donald C. Goff, M.D.
Massachusetts General Hospital

Dilip V. Jeste, M.D.
University of California, San Diego

Shitij Kapur, M.D.
University of Toronto

Paul E. Keck, Jr., M.D.
University of Cincinnati College of Medicine

David C. Mamo, M.D., M.Sc., F.R.C.P.
University of Toronto

Stephen R. Marder, M.D.
Semel Institute for Neuroscience at UCLA

Joseph P. McEvoy, M.D.
Duke University Medical Center

Alexander L. Miller, M.D.
The University of Texas Health Science Center at San Antonio

Henry A. Nasrallah, M.D.
University of Cincinnati College of Medicine

John W. Newcomer, M.D.
Washington University School of Medicine

Sheldon H. Preskorn, M.D.
Clinical Research Institute and University of Kansas School of Medicine-Wichita

Delbert Robinson, M.D.
The Zucker Hillside Hospital

Gary S. Sachs, M.D.
Massachusetts General Hospital

Michael J. Sernyak, M.D.
Yale University

Rajiv Tandon, M.D.
University of Florida

Peter J. Weiden, M.D.
University of Illinois at Chicago

I. Introduction

ABSTRACT

Objectives. **The goal of the Roadmap is to provide guidance on how to use currently available antipsychotics to achieve best outcomes for patients with serious mental illness. The Roadmap orientation is that clinicians often make treatment decisions based on their underlying model of the illness. The Roadmap therefore begins with a review of two theoretical models often used by clinicians who treat patients with severe mental illness (Section II). The "maintenance model" emphasizes achieving clinical stability; once the patient is stable, this model gives priority to relapse prevention and maintenance of stability. The "recovery model" also aims for achieving stability, but it places more emphasis on achieving further gains in physical and emotional health once stability is achieved. While a simplification, these models are based on different assumptions about the course and outcome of schizophrenia and the potential risks and benefits of different pharmacologic treatment options. These treatment models serve as the framework for the Roadmap recommendations, which are based on the clinical and psychopharmacologic research literature as well as expert consensus on questions not definitively answered in that literature.**

Methods. **On the basis of results of an initial survey and a roundtable meeting, a panel of 10 experts developed a list of psychopharmacologic topics not adequately addressed by the evidence-based literature, but which clinicians who use antipsychotic medications need to understand. These questions were posed in a survey to a larger panel of 32 experts, 27 (84%) of whom responded. Results of this survey and data from the literature were then used to develop recommendations for applying psychopharmacologic principles to individualize treatment for patients with severe mental illness.**

Results. **Recommendations are presented to help clinicians make informed decisions about choice of medication, dosing, and switching strategies, based on the pharmacodynamic and pharmacokinetic properties of different antipsychotics (Section III); diagnosis, prominent symptoms, and treatment history (Section IV); the patient's age, gender, and psychosocial characteristics (Section V); and the patient's medical conditions whether related to antipsychotic treatment or not (Section VI). The final section illustrates how to apply the principles presented in the first six sections in real-world clinical situations.**

Conclusions. **The experts reached a high level of consensus on many key questions about treatment strategies. The Roadmap recommendations provide guidance for clinicians on how to fine-tune their psychopharmacologic strategies with antipsychotics to achieve the best outcomes for each individual patient.**

(J Clin Psychiatry 2007;68[suppl 7]:1–48)

THE ROADMAP CONCEPT

Treatment of severe mental illness has improved significantly over the past decade with advances in pharmacology and psychosocial interventions. Introduction of the second generation (atypical) antipsychotics (SGAs) has increased options for clinicians and patients. Since the reintroduction of clozapine, six other SGAs have been approved by the U.S. Food and Drug Administration (FDA). These agents are associated with significantly fewer neurologic side effects so that patients receiving antipsychotics no longer have to live as if they had Parkinson's disease. While metabolic and weight problems are associated with some of the SGAs, the reduced burden of neurologic side effects is an important step forward. However, despite advances in antipsychotic treatment, many needs are unmet and many questions remain. The SGAs are still unlikely to eradicate all symptoms for patients with schizophrenia, and even patients with bipolar disorder are unlikely to remain stable and symptom-free on a long-term basis. The President's New Freedom Commission on Mental Health[1] stressed the importance of incorporating the latest scientific information into mainstream health care as rapidly as possible. The goal of the Roadmap is to help clinicians apply the latest information on antipsychotic psychopharmacology in day-to-day clinical situations they face.

Recent data show that having a major mental illness (e.g., schizophrenia, bipolar disorder) lowers life expectancy by 25–30 years, largely due to increased cardiovascular disease.[2] A complex set of risk factors contributes to this, including cigarette smoking, lack of physical activity, and limited access to medical care. A growing concern with some of the SGAs is the potential to contribute to or worsen these risks,[3] and an important focus of the Roadmap is strategies for minimizing these problems.

The goal of successful antipsychotic treatment is to reduce burden of illness while minimizing distressing or dangerous side effects, which can lead to substantial improvement in quality and length of patients' lives.[2] Yet a recent study by the American Psychiatric Institute for Research and Education's Practice Research Network[4] found that adult patients with schizophrenia treated by psychiatrists have complex clinical problems; of the sample, 41% had a comorbid Axis I disorder, 75% were unemployed, 35% had medication side effects, and 37% had adherence problems. The researchers questioned whether antipsychotics are being used optimally for patients with complex clinical problems treated in routine psychiatric practice.

Challenges in Clinical Decision-Making

Psychiatrists face challenges in selecting the most appropriate pharmacologic treatment for individual patients and titrating to an optimal dose. Problems can also arise in switching from one antipsychotic to another, depending on the agents involved, speed of the switch, use of or failure to use adjunctive agents, and emergent side effects. For example, a patient rapidly

switched from a medication with high to one with low anticholinergic activity may have withdrawal symptoms (i.e., cholinergic rebound). Such symptoms can be confused with lack of efficacy or poor tolerability and lead to premature discontinuation of the new medication, so that the patient is deprived of a full therapeutic trial of the new medication.

Goal of the Roadmap

The goal of the Roadmap is to provide a practical guide to help clinicians achieve best outcomes for individual patients. The recommendations are based on research findings and expert opinion on use of antipsychotics to treat psychosis. We included expert opinion to supplement, not replace, evidence-based findings. For example, we did not ask the experts whether clozapine is more effective for positive symptoms because the answer is available in the evidence-based literature. Instead, we wanted to know what the experts would do in the difficult situation when clozapine is indicated but the patient has diabetes mellitus—i.e., to get a sense of what they would do when there are competing priorities and goals and evidence-based information is lacking.

Limitations in Clinical Trial Data

Clinical trial data have a limited ability to provide this type of guidance. First, clinical trials tell us about average response but give little guidance for individual patients.[5] For example, doses are usually reported as means, standard deviations, and ranges with no details about which types of patients responded to which doses, or how titration schedules, side effects, and switching affected different types of patients. Second, the need to protect internal validity in trial design leads to restrictions on patient enrollment trials so that trial subjects are frequently not representative of patients seen in day-to-day practice, many of whom would not have met entrance criteria for clinical trials of drugs they are actually taking.[5–9] For example, patients who are highly agitated or have comorbid medical conditions are routinely excluded from antipsychotic trials. A recent study[10] found that approximately 40% of patients with schizophrenia and 55% with bipolar disorder treated in clinical practice would have been ineligible for a trial of a new agent targeting their diagnosis.

The Roadmap Strategy

Given limitations on the external validity and generalizability of clinical trial data, clinicians often rely on experience to guide patient care. The Roadmap project used several strategies to address this problem. We consulted clinical pharmacologists with expertise on antipsychotics about questions not adequately addressed by research. We also developed materials on the pharmacologic profiles of antipsychotics to help clinicians apply findings from clinical trials to day-to-day clinical situations and individualize the use of each medication for specific patients.

Organization of the Roadmap

The Roadmap begins with a discussion of how to work with patients to identify appropriate treatment objectives at different phases of the illness and then how to align pharmacologic decisions with those treatment objectives (Section II). Sections III–VI present information to help clinicians make decisions about medications, dosing, and switching strategies based on:

- Pharmacodynamic and pharmacokinetic properties of the different antipsychotics (Section III)
- Diagnosis, prominent symptoms, and treatment history of the patient (Section IV)
- Age, gender, and psychosocial characteristics of the patient (Section V)
- Medical conditions of the patient, whether related or unrelated to previous antipsychotic treatment (Section VI)

Section VII presents examples of how to apply these principles and balance competing priorities in real-life clinical conditions.

METHODOLOGY

1. Steering Committee

A small group of experts on treatment of psychosis served as the Steering Committee for this project. The group, chaired by Peter J. Weiden, M.D., included John P. Docherty, M.D., Peter A. Fahnestock, M.D., and Sheldon H. Preskorn, M.D. The Steering Committee provided guidance on program content based on clinical experience and knowledge of the research literature. They developed a list of psychopharmacologic topics that clinicians treating psychosis need to understand and developed a survey on questions not adequately addressed by available research.

2. Initial Expert Survey

A panel that included seven additional opinion leaders in the field with expertise in a range of clinical areas and settings was recruited to serve as Editorial Board for the Roadmap, with Peter J. Weiden, M.D., continuing as chair. The Board completed the initial survey developed by the Steering Committee.

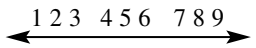
3. Roundtable Meeting

The Editorial Board met in April 2006 to decide on the structure of the program, review results of the initial survey, and discuss how to revise the survey for completion by a larger panel.

4. The Roadmap Expert Consensus Survey

The survey, revised based on the Board's recommendations, was distributed to 32 experts on the use of antipsychotics for psychosis (including the Editorial Board), 27 of whom (84%) completed it. Respondents understood the survey would not be used to create treatment guidelines but rather to supplement evidence-based recommendations in a monograph on use of antipsychotics. All respondents were aware that Bristol-Myers Squibb was providing funding for the project. Of the 27 respondents, 26 were male and 1 was female. Mean age was 49 years, with mean of 21 years in practice and/or research. Two thirds reported spending at least 25% of their time in clinical work seeing patients. The majority worked in an academic clinical or research setting, while a quarter worked in the public sector, and 10% in private practice. Over 90% had been principal investigator on NIH/NIMH studies and over 80% on industry-sponsored

Figure 1-1. The rating scale



9 = Extremely appropriate: this is your treatment of choice

7–8 = Usually appropriate: a first-line treatment you would often use

4–6 = Equivocal: a second-line treatment you would sometimes use (e.g., patient/family preference or if first-line treatment is ineffective, unavailable, or unsuitable)

2–3 = Usually inappropriate: a treatment you would rarely use

1 = Extremely inappropriate: a treatment you would never use

studies. Respondents had received grants, speaking fees, and study funding from a variety of sources, with at least 40% reporting support from Bristol-Meyers Squibb (67%), Eli Lilly (56%), Janssen (56%), AstraZeneca (48%), and Pfizer (44%).

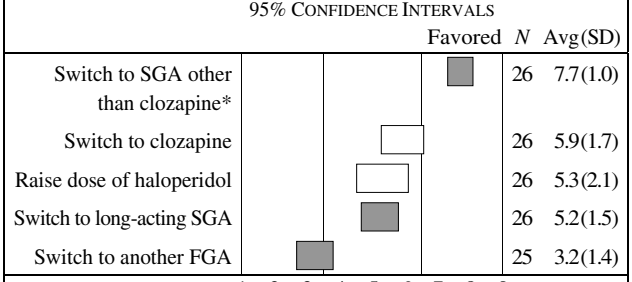
The Survey contained 37 questions concerning treatment models and objectives, pharmacodynamic and pharmacokinetic principles for optimizing antipsychotic treatment, and strategies for using antipsychotics for patients with varying presentations. Thirty-three questions asked respondents to rate 976 options using a 9-point scale slightly modified from a format developed by the RAND Corporation for ascertaining expert consensus.[11] The other questions asked respondents to write-in answers (e.g., doses, duration) or check boxes. We asked the experts to draw on their knowledge of the research (we did not provide a literature review) and their best clinical judgment in making their ratings, but not to consider financial cost. For most questions, the experts were asked to apply the scale using the anchors shown in Figure 1-1, although for some questions the scale was modified, for example, to indicate level of agreement, ranging from 9 = strongly agree to 1 = strongly disagree.

5. Data Analyses

In analyzing responses rated on the 9-point scale, we defined consensus as a distribution unlikely to occur by chance by performing a chi-square test ($p < 0.05$) of the score distribution across ratings. We also calculated the mean and 95% confidence interval (CI) for each option. Options receiving a rating of 9 from at least 50% of the experts were considered especially strong recommendations. For write-in options involving numeric responses, means and standard deviations were calculated. When respondents were asked to check boxes indicating an answer, percentages of respondents were calculated.

Graphic presentation of the survey results: Question 14 shows an example of the survey results, with CIs shown as horizontal bars and number of respondents who rated each option

Question 14. **Positive symptoms.** Assume you are treating a patient who is stable and not at imminent risk of relapse like Ms. A, but who, unlike Ms A, has ***persistent positive symptoms*** (voices, paranoid delusions) that she finds very distressing. Please rate the appropriateness of the following strategies to produce an improvement in persistent positive symptoms in a stable patient not at imminent risk of relapse.



SGA = second generation antipsychotic
FGA = first generation antipsychotic
**One of the currently available SGAs: aripiprazole, olanzapine, risperidone, quetiapine, ziprasidone*

and mean ratings and standard deviations listed on the right. Note some respondents did not rate some options, so the N does not always equal 27. An unshaded CI box indicates no consensus (i.e., based on chi-square test, responses on the item randomly distributed across the ratings). In this question about a stable patient with persistent positive symptoms taking haloperidol, the experts gave the highest rating to switching to an SGA other than clozapine, with some support for switching to clozapine, raising the haloperidol dose, or switching to a long-acting SGA, although with no consensus on the first two options. There was consensus on lack of support for switching to a different conventional antipsychotic.

Statistical differences among treatments: While we did not perform tests of significance for most items, significance can generally be estimated based on whether the CIs overlap. When they overlap, this roughly indicates no significant difference between options by t-test. The wider the gap between CIs, the smaller the p value would be (i.e., the more significant the difference).

6. Development of Roadmap Recommendations

Clinical trial data, information on the pharmacologic profile of the different antipsychotics, and results of the expert survey were used to develop clinically useful recommendations on how to use antipsychotic medications to achieve the best outcomes for patients. In basing recommendations on the expert survey results, we were aware that the way in which questions are worded can affect responses.[12,13] We therefore tried to take this possible bias into account in formulating our recommendations. Because of space limitations, only a small number of the actual graphic results from the survey could be included in this supplement. Instead, the experts' recommendations are often summarized in more concise tabular format or discussed in the text.

II. Aligning Pharmacologic Decisions With Treatment Objectives

Until recently, schizophrenia was considered to always be a "deteriorating" illness. Clinicians believed symptoms would worsen over time, leading to progressive loss of function. In this view, recovery was not possible, improvement would be very rare, and remaining stable was the only realistic outcome for most patients. Once stability was achieved, the most important goal was to retain it. The problem with attempting to achieve recovery beyond stability is that it can risk stability. Because improvement was believed to be unrealistic anyway, the question was frequently asked, "Why take the risk?"

Recently, a new treatment paradigm has been introduced in mainstream psychiatry. Its basic premise is that continued functional improvement is common, even expected, among patients with serious psychotic disorders and that treatment should endeavor to facilitate ongoing recovery.[14–18] While the advantages of this shift in focus seem self-evident, this approach sometimes requires one to assume greater risk, especially risk of relapse. This approach is also more labor-intensive and, if it leads to unrealistic expectations of cure, may, in the long run, be self-defeating.

Why is this issue important in a monograph on the psychopharmacology of newer antipsychotics? Our current understanding of psychotic illnesses and the medications used to treat them is in great flux. The promise of the newer medications is sometimes offset by disappointing research findings. There is no universally accepted standard for what constitutes a "good" or "bad" outcome and, consequently, no universal standard for how to establish pharmacologic treatment goals for schizophrenia and other related psychotic disorders. Therefore, before any recommendations about best use of antipsychotics can be made, it is necessary to consider the goals of medication for the individual patient receiving treatment. The following sections describe how to frame clinical decisions concerning antipsychotics in the context of treatment models and goals.

TREATMENT MODELS

Clinicians generally make treatment decisions for persistent psychotic illness based on their underlying model of the illness, prognosis, and available treatments, even if they are not explicitly aware of these models. By operationalizing two such models, we hope to help clinicians understand the rationale underlying treatment decisions they make in day-to-day practice.

- ***Maintenance model:*** The goal is achieving and maintaining psychiatric stability, often reflecting a disease model that assumes the natural course of schizophrenia is to get worse. If a patient maintains response to treatment without getting worse, it is considered a good outcome. In this model, stability should not generally be jeopardized in an attempt to improve symptoms or reduce side effects.
- ***Recovery model:*** This model reflects a belief that it is possible for the symptoms of schizophrenia to improve over time once stability is achieved. In a recovery model, achieving stability and avoiding relapse, while important and necessary first steps, are not endpoints but rather the beginning of the treatment plan. Defined this way, a pharmacologic approach to a recovery model means there is an active pursuit of continued improvement over and above the current level of symptoms or side effects.[19]

TREATMENT OBJECTIVES

In the Roadmap, we hope to translate both of these models into treatment objectives that clinicians can use to structure therapeutic decisions based on the patient's and clinician's larger goals (i.e., where they are trying to go).

Psychopharmacologic Objective 1 (Maintenance Model): Maintain gains to date and protect from worsening of the illness

- Achieve psychiatric stability
- Prevent relapse
- Prevent worsening of symptoms, especially those that might threaten health or safety of the patient or others
- Protect from adverse effects of treatment intervention.

Psychopharmacologic Objective 2 (Recovery Model): Continued efforts to achieve healthier mental and physical functioning as indicated by:

- Reduced overall burden of side effects
- Level of functioning beyond what has been achieved on the current regimen
- Reduction in functional impairment
- Ultimately, a level of functioning associated with lack of psychiatric disease.

INTEGRATING OBJECTIVES

Patients often have many problems so that treatment needs to target multiple objectives. Sometimes one objective cannot be achieved until another goal has been reached. Or different objectives, especially related to a maintenance versus recovery model, may seem contradictory (e.g., desire for continued improvement versus concern about risk of relapse). Making a medication change for one objective (e.g., reducing dose due to a side effect) may threaten another objective (e.g., maintaining stability). Achieving the treatment objectives listed above depends on many factors, including disease severity, psychological strengths (e.g, motivation, perseverance), range and effectiveness of currently available treatments, social factors (e.g., family/social support), and systems factors (e.g., access to medication, the clinician's technical knowledge and skill). Despite these uncertainties, we hope that awareness of fundamental objectives will give clinicians a sounder philosophical basis for individual medication decisions.

III. Psychopharmacology of Antipsychotics

The goal of the Roadmap is to help clinicians better understand pharmacologic principles in order to tailor treatment choices to individual patient characteristics. This section begins with an overview of drug classification and antipsychotic development and then discusses pharmacodynamics and pharmacokinetics of available antipsychotics and implications of these properties for clinical decisions. While the focus is on pharmacology, clinicians should keep in mind the importance of integrating appropriate psychosocial interventions in treatment to achieve best outcomes.

OVERVIEW: HOW CAN DRUGS BE CLASSIFIED?

Drugs can be classified in four ways:

- ***Chemistry:*** according to basic chemical structure; this is how drugs are designed or discovered.
- ***Pharmacodynamics:*** according to what they do in the body (e.g., receptors they affect).
- ***Pharmacokinetics:*** according to what the body does to them (e.g., half-life, metabolism, clearance).
- ***Therapeutic indications:*** according to diseases they are indicated to treat; this is how drugs are approved for marketing by the U.S. FDA.

Pharmacodynamics and pharmacokinetics ultimately determine the effect for good or ill a drug will produce in an individual and hence are the focus of this section. (A discussion of the pharmacologic chemistry of antipsychotics is beyond the scope of this monograph, while therapeutic indications are discussed in later sections.) In the Roadmap survey, we asked about the clinical relevance of pharmacodynamic differences among antipsychotics. The panel indicated overwhelmingly that clinical trial data are the most important information to consider in making medication choices. However, a majority felt that, when clinical trials show roughly *equal* efficacy, pharmacodynamic profiles can play a useful role in selecting the most appropriate medication. A majority also believed it was important to consider pharmacodynamic properties of *both* antipsychotics when switching from one to another to avoid withdrawal or additive effects. When switching antipsychotics for lack of efficacy, 65% endorsed choosing an antipsychotic with a different pharmacodynamic profile.

Currently, most clinicians select medications based on therapeutic class, even though that classification provides little or no biologically useful information. Therapeutic class does not describe precisely what a drug does in the body, since there may be more than one mechanistic way to achieve a global effect (e.g., relief of psychosis). It is thus important to consider a drug's pharmacodynamics and pharmacokinetics, which have biologically meaningful corollaries, in making treatment decisions. The distinction between therapeutic indication and clinical effects is clear when one considers that quite a few psychoactive medications have indications for multiple disorders, reflecting limited knowledge of the biology underlying the illnesses we treat. For example, atypical antipsychotics, first used to treat schizophrenia, now also have labeled indications for bipolar disorder, and a number of drugs first marketed as antidepressants are now approved for anxiety disorders. In psychiatry, only a few classes of medications—selective serotonin and serotonin-norepinephrine reuptake inhibitors—have effects as targeted as, for example, β-blockers or angiotensin-converting enzyme (ACE) inhibitors. And even with those classes, relationship between mechanism of action and clinical effect is more tenuous than, for example, between ACE inhibitors and reduction in blood pressure.

HISTORY OF ANTIPSYCHOTIC DEVELOPMENT

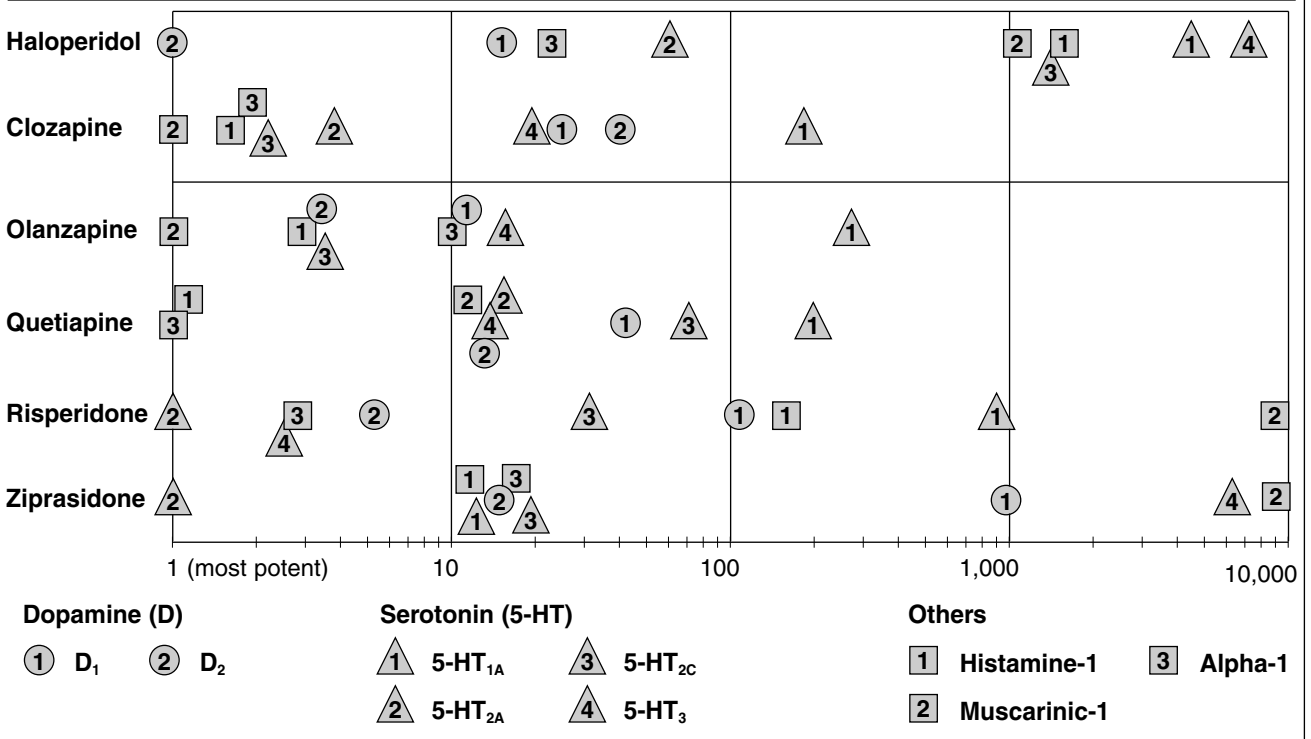
The first drugs in every major psychiatric class were identified by clinical observation (e.g., someone noticed a beneficial effect in a specific syndrome). The beneficial "psychic" effects of chlorpromazine, the first antipsychotic, were discovered by French surgeons at the end of World War II looking for pre-anesthetic agents. The first antipsychotics, including thioridazine and mesoridazine, introduced in the 1940s–50s, are referred to as *low-potency* agents. They have multiple mechanisms of action and affect histamine-1 (H_1), muscarinic-1 (M_1) acetylcholine, and alpha-1 (α_1) norepinephrine receptors more than dopamine-2 (D_2) receptors. The *high-potency,* "conventional" antipsychotics (e.g., haloperidol, fluphenazine, perphenazine), introduced in the 1960s, were rationally developed (i.e., based on a plan in contrast to a chance discovery) to have a specific selective mechanism of action—D_2 receptor blockade—and were the treatment of choice for patients with psychosis for nearly 20 years (1970s–80s).

In the late 1980s, a new class of antipsychotics was introduced in the United States, beginning with clozapine, followed by risperidone, olanzapine, quetiapine, ziprasidone, and paliperidone. These agents were initially called "atypical" because they did not behave like high-potency agents in a number of ways. *Atypicality* in antipsychotics, as originally defined by Meltzer et al.,[20] referred to drugs that had antipsychotic efficacy but a low risk of acute extrapyramidal side effects (EPS), tardive dyskinesia, and serum prolactin elevation. This clinical profile has generally been attributed to greater binding for serotonin 5-HT_{2A} than D_2 receptors. Another "atypical" criterion specified by Meltzer was superior efficacy for schizophrenia compared with the older antipsychotics. To date, only clozapine has convincing evidence supporting this claim.[21–23]

The initiation or discontinuation of drugs such as clozapine with multiple mechanisms of action results in changes in effects on multiple sites of action and hence many different pharmaco-

Much of this section was developed by Sheldon H. Preskorn, M.D. The authors gratefully acknowledge the participants in a teleconference in which this material was reviewed, whose helpful comments helped shape the discussion: Joseph P. McEvoy, M.D., Peter F. Buckley, M.D., John P. Docherty, M.D., Naveed Iqbal, M.D., and Christoph U. Correll, M.D.

Figure 3-1. In vitro relative receptor binding affinity profiles for newer antipsychotics: Profile for each drug is expressed relative to its most potent binding *© Preskorn 2007*



For the sake of simplicity, the figure includes only those receptors that are most clinically relevant.

logic effects. Some common effects associated with blockade of different receptors are shown in Table 3-1. The pharmacologic mechanism(s) that results in clozapine's unique efficacy remains a mystery, despite efforts to dissect clozapine's pharmacology in order to develop drugs with the same superior antipsychotic efficacy. As chlorpromazine served as structural blueprint for synthesis of clozapine in 1959, clozapine served as blueprint for more recent atypical agents. Because they affect multiple receptors, the newer antipsychotics are more closely related to the low-potency than high-potency conventional agents, but the newer agents were designed to avoid some problems caused by the low-potency agents, especially effects mediated by M_1, H_1, and α_1 blockade. Nevertheless, some of the newer antipsychotics can still affect and produce adverse effects mediated by blockade of one or more of these receptors.

Aripiprazole, the first drug in a pharmacologically distinct class of partial dopamine agonists, was recently introduced. Other agents in this class (e.g., bifeprunox) are expected to follow.

The relative receptor binding profiles of some commonly used antipsychotics are shown in Table 3-2. Whereas D_2 receptor blockade is universal among all marketed antipsychotics, there was no consensus among the experts on how serotonin receptor blockade relates to efficacy. Figure 3-1 shows relative binding affnities of haloperidol, clozapine, and the four atypical antipsychotics developed based on clozapine's structure and mechanistic model. (Note aripiprazole is not shown in the table since it was developed though a very different discovery process.)

Table 3-1. Effects caused by receptor blockade

Receptors	*Effects*
H_1	Sedation, weight gain, postural dizziness
α_1-adrenergic	Hypotension
M_1	Deficits in memory and cognition, dry mouth, constipation, tachycardia, blurred vision, urinary retention
D_2	EPS, prolactin elevation, antipsychotic
5-HT_{2A}	Anti-EPS (?)
5-HT_{2C}	Satiety blockade

Source: Gardner et al. 2005[24]

WHAT DETERMINES MEDICATION RESPONSE?

The equation in Figure 3-2 lays out the three major variables that determine the effect a drug produces in a specific patient (whether or not it is what the clinician wants to happen):

1. The drug has to have an affinity for and an intrinsic effect on a *site of action* (the "target" of the drug).
2. A sufficient amount of drug has to get to the target to affect it to a physiologically relevant degree (*drug concentration*).

Table 3-2. Binding affinity of selected antipsychotics for specific neuroreceptors © *Preskorn 2003*[25,26]

	D_1	D_2	D_3	D_4	5-HT_{1A}	5-HT_{2A}	5-HT_{2C}	α_1	H_1	M_1
Aripiprazole	265*	0.34*	0.80*	44*	1.7*	3.4*	15	57	61*	>10,000
Clozapine	85	126	473	35	875	16	16	7	6	1.9
Haloperidol	210	0.7	2	3	1,100	45	>10,000	6	440	>1,500
Olanzapine	31	11	49	27	>10,000	4	23	19	7	1.9
Quetiapine	455	160	340	1,600	2,800	295	1,500	7	11	120
Risperidone	430	4	10	9	210	0.5	25	0.7	20	>10,000
Ziprasidone	525	5	7	32	3	0.4	1	11	50	>1,000

*Data represented as K_i (nM); *Data with cloned human receptors*
Abbreviations: D = dopamine, 5-HT = serotonin, α_1 = alpha-1 norepinephrine, H_1 = histamine 1, M_1 = muscarinic acetylcholine-1
Sources: Richelson 1994[27]*; Abilify package insert*[28]*; Arnt and Skarsfeldt 1998*[29]*; Bymaster et al. 1996*[30]*; Seeger et al. 1995*[31]

Figure 3-2. Three variables that determine response to any drug © *Preskorn 1999*[32]

Clinical response = Affinity for the site of action (pharmacodynamics) X Drug concentration at site of action (pharmacokinetics) (ADME)
- absorption
- distribution
- metabolism
- elimination

X Underlying biology of patient (GADE)
- genetics
- age
- disease
- environment

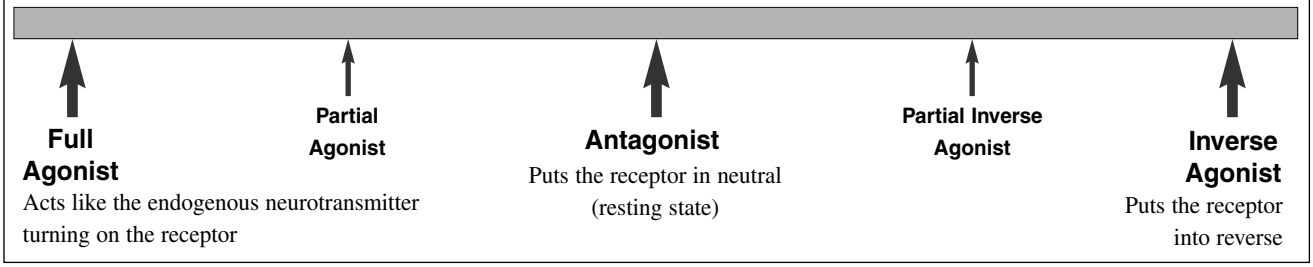
3. *Biological variance* in patients can shift the drug's usual dose-response curve, making patients more or less sensitive to desired or undesired effects of the drug. Factors causing biological variance are summarized by the mnemonic GADE:
   Genetic differences
   Age differences
   Disease (e.g., liver failure) can affect drug concentration. Other processes (e.g., increased susceptibility to EPS effects of D_2 blockers in subclinical Parkinson's disease) can affect pharmacodynamic responsiveness.
   Internal **E**nvironment includes things people consume (e.g., dietary substances, herbals, other drugs). A drug-drug interaction occurs when ingestion of one drug changes a person's biology and thus response to another drug.

Sites of action of virtually all drugs (with rare exceptions such as lithium) are regulatory proteins, divided into three classes:
- Receptors that are targets of specific neurotransmitters (principal target of most antipsychotics)
- Uptake pumps that conserve specific neurotransmitters (principal target of most antidepressants)
- Enzymes involved in synthesis or degradation of specific neurotransmitters (target of agents such as cholinesterase inhibitors for Alzheimer's disease and monoamine oxidase inhibitors for major depression).

The equation in Figure 3-2 makes it clear that clinical trials are population pharmacokinetic studies in which the goal is determining the usual dose needed to achieve a concentration that will engage the right target to the right degree to achieve maximum efficacy with optimal tolerability and safety. Usual dose is determined by usual clearance in the usual patient in the trial and by the drug's binding affinity for the desired target. Factors in the third variable modify the first two to magnify/diminish effects in a specific patient relative to a "usual" patient in the registration trials. Trials usually exclude very young or old patients or those with complicating medical conditions to reduce variance in response.

The equation in Figure 3-2 can be used to go either from the observed response to mechanisms mediating that response or from mechanisms to the response they mediate. For example, a serendipitously observed response (a chance drug discovery) can provide a signal that leads to the discovery of pharmacodynamic mechanisms mediating that response, which in turn can result in a pharmacodynamic theory that forms the basis for rational discovery of newer, more precisely targeted drugs. Clinicians can use the same approach in treating a patient, moving from the patient's response to try to identify the drug's site(s) of action mediating that response and, based on that hypothesis, further refining their medication management. Modern drug development usually follows the equation in the other direction, from pharmacodynamic theory about what mediates the pathophysiology or pathoetiology of an illness (site of action) to produce compounds that are expected to yield the desired clinical response when tested in humans in drug registration trials.

Figure 3-3. Functionally different classes of drugs can be developed for receptors © *Preskorn 2007*[25]



PHARMACODYNAMICS OF ANTIPSYCHOTICS

How Drugs Affect Receptors

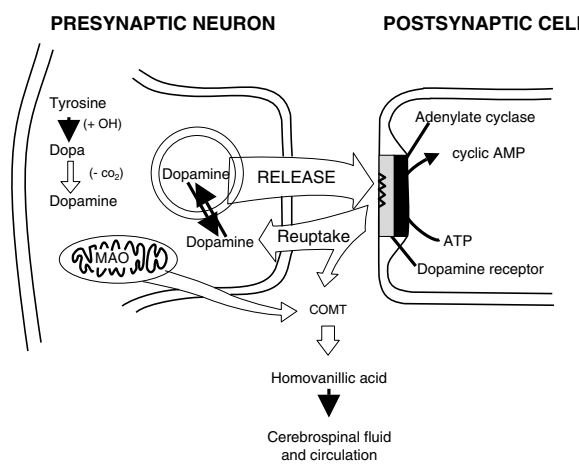
Three classes of drugs can theoretically be developed for any receptor (Figure 3-3). *Agonists* act like the endogenous neurotransmitter to fully activate the receptor; *antagonists* produce no activation and take the receptor "out of play." *Inverse agonists* shift the receptor in the reverse direction of its normal resting state. Although full inverse agonists have generally lacked clinical utility, they have helped elucidate basic pharmacology and increased our understanding of receptor physiology. Drugs can also be developed that fall between these reference points, such as partial agonists (producing partial activation of the receptor) or partial inverse agonists (partially moving the receptor in the opposite direction). Such agents can fall at different points on the spectrum and may be closer to a full agonist or inverse agonist or a full antagonist or anywhere between.

Figure 3-4 shows the presynaptic neuron terminating near the postsynaptic receptor and the vesicles that store the biogenic amine neurotransmitter (dopamine in this case) and protect it from the degradatory enzyme monoamine oxidase in the mitochondria in the cystol of the cell. When the cell fires, these vesicles migrate to and fuse with the neuronal cell wall, releasing stored neurotransmitter into the synaptic cleft so it can be "propelled" across the cleft to interact with its receptor (in this case, the D_2 receptor). The relevant point for this discussion is that, when the D_2 receptor is activated, conversion of ATP to cyclic AMP is inhibited. The gene for the human D_2 receptor has been identified, so that, using molecular biology techniques, researchers can measure degree of activation of this receptor under different conditions. The process involves transfecting the human gene for the D_2 receptor into a single cell organism that does not possess it so that the organism expresses that gene and its gene product (in this case the D_2 receptor and its associated machinery, the G protein, the second messenger system, and the cascade of events inside the postsynaptic cell that are activated when the receptor is engaged by an agonist). The single cell organism is thus humanized so that it can be used to assess the receptor's degree of activation under different conditions by measuring conversion of ATP to cyclic AMP.

What Does Partial Agonism Mean?

Until the introduction of the class of D_2 partial agonists, all available antipsychotics were D_2 antagonists, and clinicians therefore tended to equate affinity for D_2 receptors with degree of D_2 antagonism. Because clinicians are not as familiar with the concept of partial agonism at the D_2 receptor for antipsychotics, the following section presents data to help clarify how partial agonists affect the D_2 receptor. Burris et al. performed three experiments using humanized Chinese hamster ovarian D_2 cell lines, developed using the process described above.[33] In the first experiment, humanized Chinese ovarian hamster cells were incubated with dopamine. Since dopamine is a full agonist for this receptor, it exerts maximum effect on the conversion of ATP to cyclic AMP. As the concentration of dopamine in the test tubes containing the humanized Chinese ovarian hamster cells was increased, the receptor was increasingly activated to the point of maximum activation as measured by change in conversion of ATP to cyclic AMP (i.e., full agonist effect). The second experiment used haloperidol and found that, no matter how much the haloperidol concentration was increased, no change in conversion of ATP to cyclic AMP occurred, because haloperidol is a full antagonist (i.e., puts the receptor in resting state). Haloperidol may occupy the receptor completely but it does not activate the receptor to generate the cascade of events inside the postsynaptic cell (i.e., simply blocks the effect of the endogenous neurotransmitter on the receptor). The third experiment involved aripiprazole. Consistent with its partial agonism, aripiprazole did turn the D_2 receptor on but, in contrast to what occurred with dopamine, not

Figure 3-4. Synapse: Dopamine terminal



© *Preskorn 2007*

to the maximum extent possible. No matter how much the aripiprazole concentration was increased, the cyclic AMP signal did not exceed 30% of the maximal signal generated by saturating the receptor with its natural full agonist, dopamine. (Although there has been debate as to whether the Chinese hamster ovarian D_2 cell line is the best model for effects in human cells, that aripiprazole is a partial agonist is supported by the observation that doses of the drug [30 mg/day] that produce over 90% occupancy of D_2 receptors in the human brain do not have substantial risk for EPS in contrast to a full antagonist such as haloperidol.[34])

In other experiments, Burris et al.[33] incubated Chinese hamster ovarian D_2 cells with 100 nM of dopamine (somewhat above the physiologically relevant concentration in human synapses and possibly closer to synaptic concentration in patients with psychotic illnesses). They then added increasing concentrations of haloperidol and found, as expected, that haloperidol competes with dopamine so that, at higher concentrations, it completely blocks the action of dopamine on the D_2 receptor despite presence of the endogenous agonist. This experiment was intended to model what happens in the dopamine synapse in the human brain when a patient with schizophrenia is treated with haloperidol.

In contrast, when aripiprazole was added to cells incubated with 100 nM dopamine, it reduced dopamine's effect on the D_2 receptor in a graduated fashion directly related to the concentration of aripiprazole up to a maximum of 30%. In other words, the net effect of giving a partial agonist is a function of the concentrations of both the partial agonist *and* the endogenous full agonist (in this case, dopamine).

The clinical message is that, unlike a full antagonist, a partial D_2 agonist cannot block D_2 receptor tone more than its intrinsic activity. In contrast, a full antagonist can completely block D_2 receptor tone, setting the stage for EPS, including neuroleptic malignant syndrome in extreme cases. Thus aripiprazole cannot block D_2 receptor tone more than 70% even when it occupies 100% of D_2 receptors because of its intrinsic 30% activity at these receptors. In the absence of the intrinsic agonist (conditions of dopamine deficiency), a partial D_2 agonist acts as an agonist and produces partial receptor activation (acts like a weak dopamine agonist). However, in the presence of fully activating concentrations of the intrinsic agonist (conditions of dopamine excess), the partial D_2 agonist acts like a dopamine antagonist and brings activation down to the intrinsic degree produced by the partial agonist.

What Does Selectivity Mean?

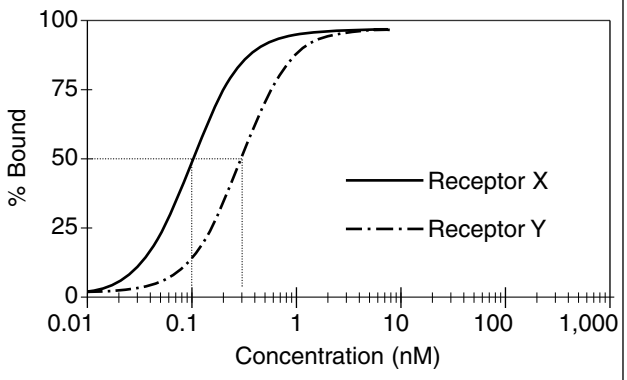
A drug can affect only one site of action at clinically relevant concentrations (i.e., be selective) or it can affect more than one site of action and have dual, triple, quadruple, or even more actions as a direct function of its relative binding affinity for more than one regulatory protein. An important means of conceptualizing whether a drug is likely to be selective is to consider its relative binding affinity for different regulatory proteins (referred to as "receptors" in this discussion, although the regulatory protein could be an enzyme or uptake pump rather than a classic neurotransmitter receptor). A drug's binding affinity (Kd) is a measure of the concentration of the drug needed to bind to a particular site of action.[35] Relative binding affinity (RBA) refers to a drug's affinity for a secondary site in relationship to its affinity for its most potent binding site (expressed by the equation RBA = Kd for secondary receptor/Kd for primary receptor).[25] The equation explains how much the concentration of the drug has to be increased above that needed to affect its most potent site of action to affect a secondary site of action.

Figures 3-5 to 3-8 illustrate the relative binding of three different types of drugs. The percent of drug bound to one of two different receptors (i.e., receptor occupancy) is shown on the vertical axis as a function of drug concentration on the horizontal axis. Theoretical drug A has a 3-fold greater affinity for receptor X than for receptor Y, but at any point that the drug engages receptor X to a meaningful degree, it also engages receptor Y to some physiologically relevant degree (Figure 3-5).[36] Thus, drug A is nonselective—it produces effects mediated by receptor Y, albeit to a lesser degree, at the same concentration that it produces effects mediated by receptor X. Most of the atypical antipsychotics are type A drugs, with X being the 5-HT_{2A} serotonin receptor and Y the D_2 receptor. These in vitro findings were confirmed Nyberg et al.[37] using positron emission tomography (PET) and radioligands to measure dopamine and serotonin receptor occupancy. In three healthy subjects, olanzapine 10 mg produced an average 84% occupancy of 5-HT_{2A} in the cortex and an average 61% occupancy of D_2 receptors in the basal ganglia at peak concentrations after the dose.

Figure 3-6 illustrates the occupancy produced by hypothetical drug B, which is 10 times more potent at binding to receptor X than Y. Ziprasidone (approximately 10 times more potent at binding to the 5-HT_{2A} than the D_2 receptor) is an example. The clinical implication of this profile is that low concentrations of ziprasidone will affect only the 5-HT_{2A} receptor, whereas higher concentrations (due to higher doses or reduced clearance) will affect both D_2 *and* 5-HT_{2A} receptors. Thus, ziprasidone is at the cusp of what would be termed a selective drug for the 5-HT_{2A} receptor. Figure 3-7 presents results of other PET studies,[38,39] which found that, at any concentration, ziprasidone blocks 5-HT_{2A} more than D_2 receptors and that the ziprasidone concentration needed to achieve at least 50% occupancy of D_2 receptors (usual minimum threshold for antipsychotic effect) is approximately 50 nM, which typically requires doses of 120–160 mg/day of ziprasidone. These are the doses of this drug that are usually necessary clinically to produce antipsychotic effects.[40, 41]

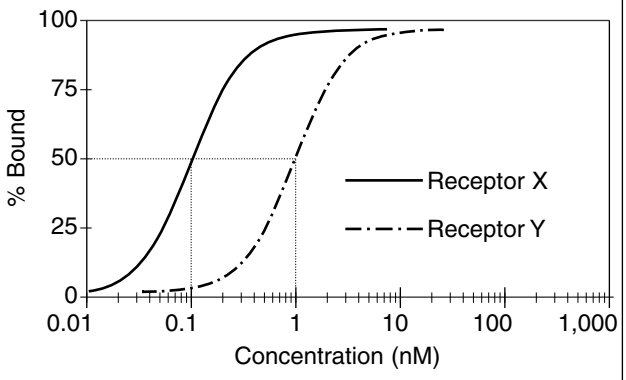
Figure 3-8 shows a drug with 100 times greater binding affinity for receptor X than receptor Y. This type of drug can completely saturate receptor X without binding to receptor Y to any physiologically meaningful degree. An example among available antipsychotics is haloperidol (Figure 3-1). Since concentration is dose divided by clearance, to achieve a concentration that would produce an effect on receptor Y, either the dose of a selective drug such as haloperidol would have to be increased 100 times or the clearance would have to be comparably reduced. While theoretically possible, this is not clinically possible because supersaturation of the D_2 receptor would very likely cause neuroleptic malignant syndrome and death before such a high concentration

Figure 3-5. Drug A with 3-fold difference in binding affinity for receptor X vs. receptor Y: e.g., most atypical antipsychotics



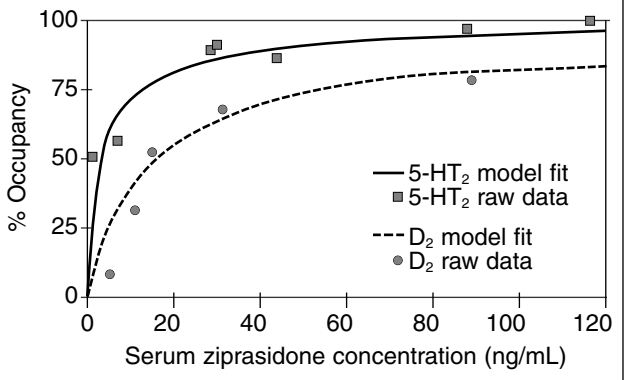
© *Preskorn 1999*[36]

Figure 3-6. Drug B with 10-fold difference in binding affinity for receptor X vs. receptor Y: e.g., ziprasidone



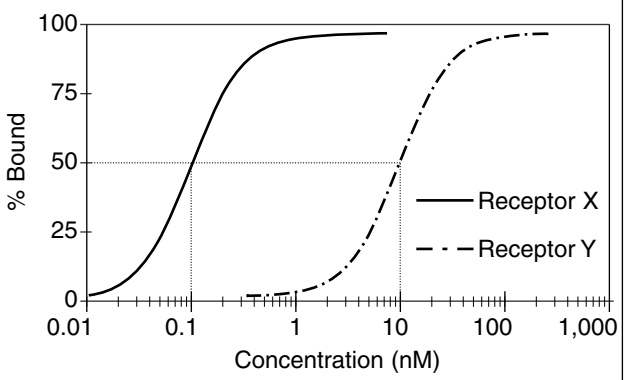
© *Preskorn 1999*[36]

Figure 3-7. 5-HT$_2$ and D$_2$ receptor occupancy



Sources: Fischman et al. 1996[38]*; Bench et al. 1996*[39]

Figure 3-8. Drug C with 100-fold difference in binding affinity for receptor X vs. receptor Y: e.g., haloperidol



© *Preskorn 1999*[36]

could be reached (illustrating the distinction between pharmacologic theory and reality and an important caveat when extrapolating from in vitro to in vivo studies).

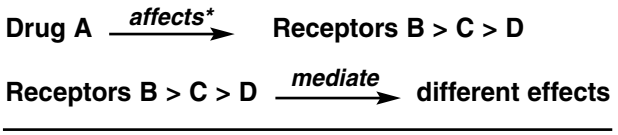
The difference in clinical effects of antipsychotics is due to their relative binding affinities. Figure 3-1, which compares relative binding affinities of six antipsychotics (haloperidol, clozapine, and the four atypicals developed using clozapine as a model), was created by taking each drug's most potent site of action (D_2 receptor for haloperidol) and dividing it into the drug's binding affinity for every other target shown. Thus, for haloperidol, the large separation between the D_2 circle and the 5-HT_{2A} triangle shows that the concentration of haloperidol would have to be increased almost 100 times to affect the 5-HT_{2A} receptor. As noted above, such an increase is theoretically but not clinically possible. In contrast, clozapine engages six targets over a 5-fold concentration range, which is practical to achieve with usual clinical dosing. In addition, at these concentrations, the 5-HT_{2A} target will have been engaged much more than the D_2 receptor.

Concentration is determined by two variables, dose and clearance. Concentration x affinity for site of action determines the effect of the drug. When dealing with nonselective drugs, it is important to remember that the pharmacology of a drug with multiple mechanisms of action (e.g., clozapine) can change with its dose. Thus, as dose and hence concentration increase, the effects of the drug will change as it sequentially engages the targets for which it has lower affinities.

CLINICAL IMPLICATIONS OF PHARMACODYNAMICS

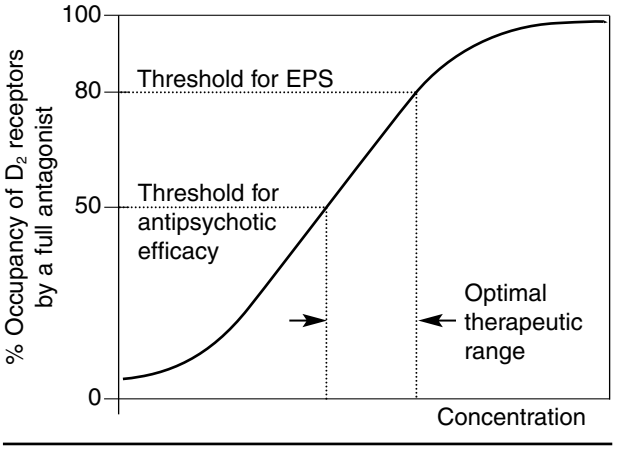
Figure 3-9 illustrates the relationship between a drug's receptor profile and clinical effects. If drug A affects receptor B more than receptor C, and affects receptor C more than receptor D, and receptors B, C, and D mediate different effects, then drug A will affect these targets in a dose-dependent, concentration-dependent manner.[25] As a caveat, binding affinity measures how avidly a drug binds to a target but does not tell us what the drug *does* to the target (i.e., agonism or antagonism or something between). That is an important distinction because the effect of a drug is a function of how much of it binds to the target *and* its intrinsic action on the target. The relationship between a psychiatric drug's action on specific receptors and its efficacy remains elusive. This point was reflected by the Roadmap expert panel, who expressed much more confidence about the role of dopamine,

Figure 3-9. How knowledge of a drug's effects on different receptors can be used to predict its clinical effects



*Could be agonism or antagonism © Preskorn 2003[25]

Figure 3-10. Relationship between D_2 receptor occupancy and D_2 receptor antagonist concentration: Narrow range between efficacy and behavioral toxicity



© Preskorn 1999[36]

histamine, muscarinic, and α-adrenergic than serotonin receptors in the effect profile of antipsychotics. While D_2 receptor blockade appears to be a universal characteristic of marketed antipsychotics and necessary for antipsychotic efficacy, there was no consensus among the experts on what role, if any, blockade of specific serotonin receptors plays in the efficacy of antipsychotics, particularly for negative or cognitive symptoms.

Figure 3-10, a gestalt based on the work of Nyberg and others,[37] illustrates effects of varying levels of D_2 receptor occupancy. It shows that a minimum threshold of 50% occupancy of the D_2 receptor appears to be required for antipsychotic efficacy while occupancy greater than 80% is associated with a marked increase in risk of acute EPS. (Note that a partial agonist with 30% of dopamine's intrinsic activity at the D_2 receptor cannot exceed 70% antagonism even if it binds to 100% of the D_2 receptors. Thus, it cannot exceed the 80% antagonism threshold associated with EPS, which was the rationale for developing partial D_2 agonists with 30% intrinsic activity such as aripiprazole.)

Figure 3-11, based on work of Frankle et al.,[42] shows distribution curves of percent of D_2 receptor occupancy in the striatum for risperidone 6 mg/day and olanzapine 10 mg/day. The X-axis is percent of D_2 receptor occupancy and the Y axis is number of people in the population. The first vertical bar indicates the minimum threshold of 50% occupancy needed to achieve antipsychotic efficacy, while the second bar represents the maximum 80% threshold above which there is an increased risk of EPS.

Effects of an Antipsychotic Dose Increase

A majority of patients receiving 10 mg/day of olanzapine will be in the correct occupancy range to achieve antipsychotic efficacy without EPS, but a sizable percentage will fall below the minimum 50% occupancy threshold for antipsychotic efficacy (Figure 3-11). That is consistent with the fact that 10 mg of olanzapine is not an effective antipsychotic dose for many patients and explains why a higher dose can produce a better response in individuals who fall on the left side of the curve by increasing their D_2 receptor occupancy (i.e., a higher dose shifts the curve to the right), as illustrated in the following case:

Mr. R, a patient with schizophrenia, was being treated with 10 mg of olanzapine but had not achieved a satisfactory response. The dose was raised to 20 mg and his response improved markedly without any occurrence of EPS.

Figure 3-12 shows a curve based on points extrapolated from data in Frankle et al.[42] assuming linear pharmacokinetics of olanzapine over the relevant dose ranges. Mr. R was in the group of patients who fell below the minimum 50% threshold on 10 mg/day of olanzapine but achieved approximately 60% D_2 receptor occupancy on 20 mg/day. This case illustrates the rationale for the practice of titrating the dose of olanzapine upward in the absence of therapeutic benefit and adverse effect. Thus, when clinicians assess antipsychotic efficacy and presence or absence of EPS in a patient, they are, in effect, performing a bioassay of the degree of D_2 receptor occupancy in the basal ganglia.

Effects of an Antipsychotic Dose Reduction

Figure 3-11 also illustrates why a larger number of individuals receiving 6 mg/day of risperidone than 10 mg/day of olanzapine achieve the appropriate amount of D_2 receptor occupancy to achieve antipsychotic efficacy. Nevertheless, a higher percentage will fall above the maximum 80% threshold for EPS. These data are consistent with clinical findings that 6 mg/day of risperidone has greater efficacy but a higher risk of EPS than 10 mg/day of olanzapine. Reducing the dose to risperidone 4 mg/day can often maintain efficacy while eliminating acute EPS in those who developed EPS on 6 mg/day, as illustrated in the following case:

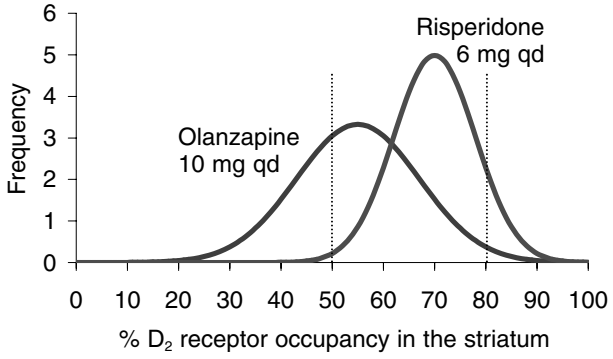
Ms. M, a patient with schizophrenia, experienced good amelioration of psychotic symptoms but developed distressing EPS on 6 mg/day of risperidone. When the dose was lowered to 4 mg/day, her response was maintained but EPS resolved.

Figure 3-13 shows a curve based on points extrapolated from data in Frankle et al.[42] assuming linear pharmacokinetics of risperidone over the relevant dose ranges. At a dose of 6 mg/day, Ms. M was above the 80% threshold for EPS; when the dose was lowered, the curve shifted to the left and Ms. M's percentage of receptor occupancy went down to approximately 60%—above the threshold for efficacy but below that associated with EPS.

Other Factors That Can Shift D_2 Occupancy Curves

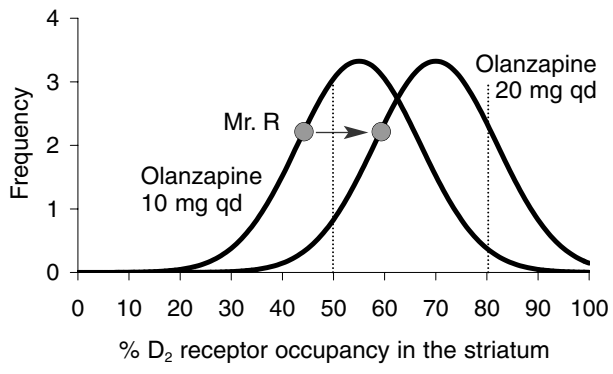
These occupancy curves can also be shifted without changing the dose by altering the drug's clearance, since dose divided by clearance is concentration, and concentration relative to the binding affinity of the drug for a receptor determines the occupancy

Figure 3-11. Distribution curves of % of D_2 occupancy as function of specific doses of 2 different antipsychotics



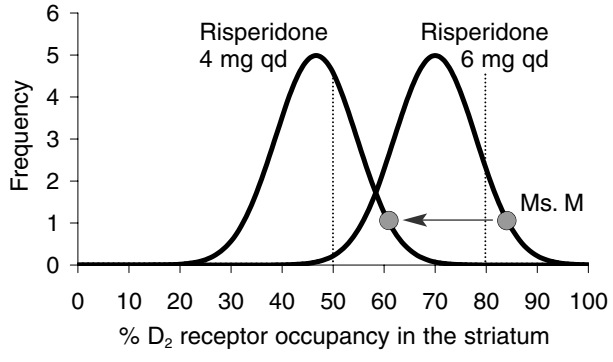
Reprinted with permission from Frankle et al. 2004[42]

Figure 3-12. Predicted change in distribution curves for olanzapine as a result of changing dose



Extrapolated by Preskorn from Frankle et al.[42] *© Preskorn 2007*

Figure 3-13. Predicted change in distribution curves for risperidone as a result of changing dose



Extrapolated by Preskorn from Frankle et al.[42] *© Preskorn 2007*

of that receptor. The occupancy curves can be shifted to the left (lower occupancy) or right (higher occupancy) when other drugs are added that increase or reduce the ability of the individual to clear the antipsychotic by inducing or inhibiting the cytochrome P450 (CYP) enzymes responsible for clearance of these drugs (see next section on Pharmacokinetics of Antipsychotics).

Clinicians should remember that some individuals are uniquely sensitive or insensitive (outliers) and do not follow usual expectations. For example, patients with subclinical Parkinson's disease (who have not lost enough dopamine neurons in the substantia nigra to exhibit EPS) may still be unable to tolerate even 50% D_2 receptor occupancy by a full antagonist without developing EPS because they lack sufficient dopamine reserves to compensate for that degree of dopamine antagonism. Note this effect would be predicted to be less likely if such a patient was treated with a partial agonist. The distribution curves shown in Figures 3-11 to 3-13 highlight the importance of evaluating the effect of a given dose of a drug in the *individual* patient, since response and side effects can vary widely from one person to another depending on concentration and receptor occupancy achieved. When clinicians titrate the antipsychotic dose and assess response, they are basically asking: "Did I engage the right site of action, to the right degree, in the right patient?" Each individual drug trial is in essence a bioassay.

Multiple Receptor Binding and Side Effects

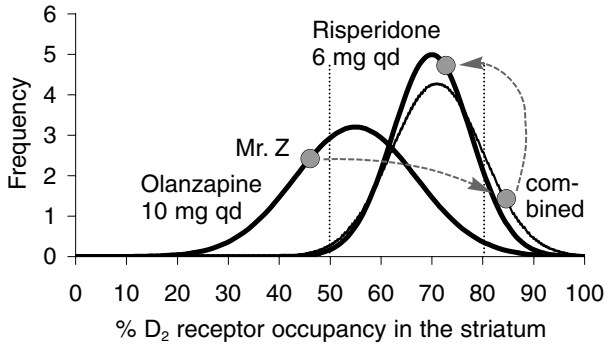
As noted above, the relationship between receptor binding profiles and adverse effects is better understood than the effect of receptor binding profiles on efficacy (Table 3-1).[24] The information in Table 3-1 used in conjunction with knowledge of the relative binding affinity of antipsychotics (Figure 3-1 and Table 3-2) provides guidance about types of side effects that may occur with different doses of different agents. For example, quetiapine binds most potently to H_1 and α_1 receptors, so that, to achieve D_2 occupancy, the dose and hence concentration of quetiapine has to be increased to a level 10 times higher than is needed to affect the H_1 and α_1 receptors. This is consistent with the observation that 50 mg of quetiapine is effective as a sedative dose for many patients but doses of 400–600 mg are usually needed for an antipsychotic effect. Thus, there is a correlation, though perhaps not perfect, between relative binding affinity and relative doses for different effects. With risperidone, the affinity for 5-HT_2 and D_2 is closer, explaining the increased incidence of EPS with doses above 6 mg/day. Ziprasidone's affinity for the 5-HT_{2A} receptor is 10 times more potent than its affinity for the D_2 receptor, so that low doses (e.g., 20 mg) block 5-HT_{2A} receptors, but have little effect on D_2 receptors, consistent with the fact that it is usually necessary to go up to a ziprasidone dose of 120–160 mg/day to achieve antipsychotic efficacy. (Keep in mind that, although Figure 3-1 illustrates how avidly a drug binds to a receptor, it does not indicate the drug's intrinsic activity at that receptor.)

Combining or Switching Antipsychotics

Figure 3-14 illustrates what might happen when a patient is receiving two antipsychotics at the same time, as frequently happens when switching from one agent to another.

Mr Z, being treated with 10 mg/day of olanzapine, was sedated but his psychotic symptoms were not responding. This result is

Figure 3-14. Extrapolation of possible % D_2 receptor occupancy from combined treatment



Extrapolated by Preskorn from Frankle et al. 2004.[42] Several assumptions made in generating this curve would need to be tested to determine whether they are accurate. *© Preskorn 2007*

consistent with olanzapine's higher affinity for the H_1 than the D_2 receptor (Figure 3-1). The clinician decided to switch Mr. Z from olanzapine to risperidone by first adding risperidone and then discontinuing olanzapine after a therapeutic dose of risperidone was reached. The dose of risperidone was gradually titrated up to 6 mg/day. At this point, Mr. Z, taking 10 mg/day of olanzapine and 6 mg/day of risperidone, was showing improved antipsychotic efficacy but developed significant distressing EPS. Some clinicians in this situation might have concluded that the EPS were due to the risperidone and have decided to discontinue it. However, the EPS were most likely the result of the combined D_2 receptor occupancy of both olanzapine and risperidone. The clinician was aware of this phenomenon and, since the patient was showing symptomatic response, decided to stick with risperidone a little longer and discontinue olanzapine. Within a week, the EPS resolved, the patient's improved antipsychotic efficacy was maintained, and he was no longer sedated.

The extrapolation in Figure 3-14 illustrates how changes in D_2 receptor occupancy levels could account for this clinical scenario. When the patient was receiving 10 mg/day of olanzapine, D_2 receptor occupancy was just under the 50% therapeutic threshold—inadequate for efficacy but sufficient to cause sedation due to the more potent effects on the H_1 receptor. When the patient reached a dose of 10 mg/day of olanzapine *plus* 6 mg/day of risperidone, percentage of D_2 receptor occupancy had shifted to the right above the 80% threshold for EPS. When olanzapine was discontinued, D_2 receptor occupancy shifted back to the left, bringing the patient below the 80% threshold. The patient was no longer sedated due to the reduction in H_1 blockade secondary to the discontinuation of olanzapine. It is important to consider these types of pharmacologic principles when two antipsychotics are being used simultaneously. One caveat is that the curve representing the effect of combined olanzapine and risperidone (Figure 3-14) is only extrapolated and hypothetical. The number of receptors is not infinite and two drugs with different binding affinities compete for binding. Combined effects will also not be strictly additive when two antipsychotics with substantially different affinities for the same receptor are combined since the higher affinity drug can antagonize the binding of the other by competing for the same receptor. Complementary effects can also occur when two drugs from the same therapeutic class but different pharmacodynamic classes are used simultaneously, but a discussion of this is beyond the scope of this publication. Nevertheless, this case illustrates that it is more important to consider pharmacodynamic and pharmacokinetic profiles than therapeutic class when deciding to use two psychiatric drugs together.

While a detailed discussion of polypharmacology is beyond the scope of this publication, a few words are warranted given its pervasive use. Most drugs are given to patients to change their biology.[43] Drugs are thus a source of potentially important biological variance among patients and can increase the likelihood that patients will experience greater toxicity as well as improved efficacy. The frequency and complexity of multiple medication use are enormous[44–46] and pose significant challenges for clinicians in following the adage: "First do no harm." There can be considerable difference of opinion among experts as to whether the level of multiple medication use in psychiatry is excessive or appropriate. It is thus very important that clinicians carefully weigh the risk-benefit ratio when adding medications to a patient's regimen and provide conscientious, close, and thoughtful (i.e., pharmacologically based) follow-up.[32]

A principle to keep in mind when stopping an antipsychotic or switching between agents is that the brain adapts to most psychiatric medications as a result of compensatory mechanisms. These mechanisms typically involve changes that are the opposite of the drug's acute activity (e.g., upregulation of a receptor in response to treatment with a drug that antagonizes that receptor; downregulation of a receptor in response to treatment with an agonist for that receptor). If such adaptation is not taken into account when changing drugs, the patient may have withdrawal effects. For example, chronic treatment with a D_2 antagonist can lead to upregulation of D_2 receptors. When D_2 receptor blockade is reduced, the patient can develop distressing withdrawal dyskinesia. Such reduction in D_2 receptor blockade can occur when one completely discontinues a drug that is a D_2 blocker, switches to a drug with significantly lower D_2 occupancy (e.g., low-dose ziprasidone), or switches from a full D_2 antagonist to a partial D_2 agonist (e.g., aripiprazole). An example from a different medication class is the syndrome that can occur when a serotonin reuptake inhibitor is stopped, which can present in many ways, including as worsening of depression or onset of mania. When withdrawal dyskinesia or the serotonin discontinuation syndrome occurs, the patient, or even the clinician, may misattribute the symptoms to the new drug (if the switch was abrupt) rather than correctly attributing the problem to discontinuation of the prior drug.

When switching between antipsychotics, occupancy of D_2 receptors (or other receptors depending on the antipsychotics) will increase or decrease as a function of the relative affinity of those drugs for those receptors and their residual time in the body (e.g., half-life). Unless the prescriber takes these factors into account in cross-titrating drugs, additive or withdrawal effects may occur, depending on whether receptor occupancy is

increased or decreased. For example, in switching from an antipsychotic with potent antihistaminic properties to one that does not block histamine receptors, such as aripiprazole or ziprasidone, abrupt discontinuation of the first drug may result in the patient experiencing "activation," which may be erroneously attributed to the second antipsychotic (i.e., aripiprazole or ziprasidone) rather than to withdrawal from the more sedating antipsychotic. When switching from an antipsychotic with potent anticholinergic properties to one that does not block muscarinic cholinergic receptors (e.g., aripiprazole, ziprasidone), abrupt discontinuation of the first drug may cause "cholinergic rebound" that may be erroneously attributed to the second antipsychotic rather than to withdrawal of the first antipsychotic.

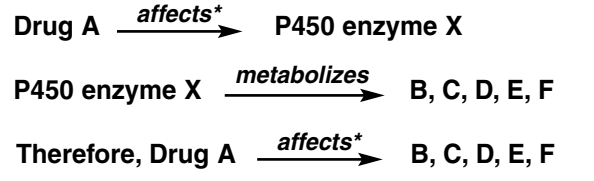
PHARMACOKINETICS OF ANTIPSYCHOTICS

Most drugs (except anti-infectives that change the biology of infectious agents) treat disease by changing the patient's biology. Drugs are thus an acquired source of biological variance that produce a state-dependent change in the patient's biology (Figure 3-2) that can change the patient's response to concomitantly prescribed drugs.[43] One drug can interact with another pharmacodynamically (Figures 3-9 and 3-14) or pharmacokinetically or both. A drug can affect the *pharmacokinetics* of another, usually by acting on its biotransformation and/or clearance, thus increasing or decreasing the drug's accumulation in the body. The most common type of pharmacokinetic drug interactions involve effects on phase one (oxidative) metabolism[47] (Figure 3-15): if drug A affects enzyme X and enzyme X metabolizes drug B, then adding drug A will change the level of drug B in the body.[25] The effect can involve induction or inhibition of the enzyme, just as the drug's effect on the receptor can involve agonism or antagonism.

Table 3-3 lists key pharmacokinetic parameters of the atypical antipsychotics and Table 3-4 shows commonly prescribed drugs that substantially inhibit CYP enzymes at usual clinical doses.[48] The key information for predicting potential interactions is the enzyme principally responsible for the antipsychotic's metabolism in the usual patient. When a drug that affects that enzyme is given in combination with that antipsychotic, it changes the accumulation (concentration) of the antipsychotic in the body and thus the effect it produces in that patient (Figure 3-2).

A naturalistic trial in a state hospital by de Leon et al.[49] illustrated how pharmacokinetic drug interactions can affect antipsychotic treatment in routine practice. They examined whether deficiency in CYP2D6, whether due to genetics or to coadministration of a substantial CYP2D6 inhibitor (bupropion, fluoxetine, or paroxetine) would increase risk of acute EPS in patients treated with risperidone. As noted earlier, when the dose of risperidone is increased above 6 mg/day, a higher percentage of patients achieve more than 80% D_2 occupancy and incidence of EPS goes up, requiring anticholinergic drug treatment or reduction in the risperidone dose. de Leon et al.[49] compared the percentage of patients in whom risperidone was discontinued because of adverse effects in three populations receiving exactly the same dose. They found that the odds ratio for experiencing acute EPS, resulting in discontinuation of risperidone, was three to four times higher in both patients who had a genetic deficiency in CYP2D6 (making them poor risperidone metabolizers) and in genetically normal metabolizers functionally deficient in CYP2D6 because of co-administration of a substantial CYP2D6 inhibitor. Extensive CYP2D6 metabolizers not receiving substantial 2D6 inhibitors had a discontinuation rate of 30%, compared with 64% in those genetically deficient in 2D6 and 55% in normal metabolizers treated with a substantial 2D6 inhibitor at a dose that would predictably convert such patients into a phenocopy of genetic deficiency. This illustrates how two different types of biological variance can affect concentration at the site of action and hence clinical effect. This example has immediate clinical relevance, since patients who experience acute EPS as a result of a drug interaction such as described here may not adhere to their medication, which can lead to psychotic relapse.[50]

Figure 3-15. How knowledge of P450 enzymes will simplify understanding of pharmacokinetic interactions



**inhibition or induction* © Preskorn 2003[25]

Table 3-3. Pharmacokinetic parameters

Drug	*Principal enzyme*	*$t_{1/2}$ (hours)*	*Bioavailability*	*T_{max}*
Aripiprazole	2D6 ⩾ 3A	75	87%	3–5
Clozapine	1A2	16	70%	1–4
Olanzapine	1A2	30	60%	6
Risperidone	2D6	3	70%	1–2
Quetiapine	3A	7	< 20%	1–2
Ziprasidone	aldehyde oxidase >> 3A	7	60%	5

Source: Preskorn and Flockhart 2006[48]

Table 3-4. Drugs that substantially inhibit CYP450 enzymes

CYP2D6: bupropion, fluoxetine, paroxetine, terbinafine

CYP3A3/4: clarithromycin, erythromycin, fluconazole, itraconazole, ketoconazole, nefazodone, indinavir, nelfinavir, ritonavir

CYP1A2: fluvoxamine, omeprazole

CYP2C: fluoxetine, fluvoxamine, omeprazole

Source: Preskorn and Flockhart 2006[48]

IV. Disease and Symptom Factors That Influence Treatment Decisions

DIAGNOSIS

Antipsychotic medications are indicated for treatment of a number of different conditions (Table 4-1) and are available in a wide range of formulations and dosage strengths (Table 4-2). This section presents information to help clinicians select the most appropriate medication for the individual patient based on diagnosis and symptomatic presentation. We asked the experts about the appropriateness of different antipsychotics for treating an acute psychotic episode in patients with different diagnoses. We specified that the patient was a healthy young man with normal weight, lipid levels, and fasting glucose; that information on

Table 4-1. FDA-approved labeling for antipsychotic medications

Antipsychotic	*Schizophrenia*	*Acute bipolar manic/ mixed episodes*	*Acute bipolar depression*	*Maintenance treatment of bipolar I disorder*
Chlorpromazine (Thorazine)	X	X		
Haloperidol (Haldol)	X			
Perphenazine (Trilafon)	X			
Clozapine[a] (Clozaril, FazaClo)	X			
Aripiprazole[b,c] (Abilify)	X	X		X
Olanzapine[b,c] (Zyprexa)	X	X	X[d]	X
Paliperidone (Invega)[e]	X			
Quetiapine (Seroquel)	X	X	X	
Risperidone (Risperdal)	X	X		
Ziprasidone[b] (Geodon)	X	X		

[a]*Labeled only for treatment-resistant schizophrenia or for patients with recurrent suicidal behavior*
[b]*IM formulation labeled for treatment of acute agitation in schizophrenia*
[c]*IM formulation labeled for treatment of acute agitation in bipolar disorder*
[d]*In combination product with fluoxetine, labeled for treatment of acute bipolar depression*
[e]*Extended-release formulation of major active metabolite of risperidone. Not included in survey since approved after survey was completed.*
Sources: www.fda.gov/cder/drug/infopage/antipsychotics/default.htm and package inserts for the different agents

Table 4-2. Available formulation and dosage strengths

Antipsychotic	*Tablet/capsules*	*Liquid*	*Short-acting IM*	*Orally disintegrating*	*Long-acting injectable*[c]
Aripiprazole	2, 5, 10, 15, 20, 30 mg	yes	yes	10, 15, 20, 30 mg	
Chlorpromazine[a]	10, 25, 50, 100, 200 mg	yes	yes	20, 75, 150 mg	
Clozapine	25, 100 mg			25, 100 mg	
Haloperidol	0.5, 1, 2, 5, 10, 20 mg	yes	yes		50, 100 mg
Olanzapine	2.5, 5, 7.5, 10, 15, 20 mg		yes	5, 10, 15, 20 mg	
Paliperidone	3, 6, 9 mg (extended release)				
Perphenazine	2, 4, 8, 16 mg	yes	yes		Outside U.S.
Quetiapine[b]	25, 50, 100, 200, 300, 400 mg				
Risperidone	0.25, 0.5, 1, 2, 3, 4 mg	yes		0.5, 1, 2, 3, 4 mg	25, 37.5, 50 mg
Ziprasidone	20, 40, 60, 80 mg (caps)	yes	yes		

[a]*Also available as 25 or 100 mg suppositories and as an extended release spansule*
[b]*Extended release (XR) available in 50, 200, 300, and 400 mg tabs*
[c]*Fluphenazine decanoate also available in the United States; several other long-acting depot FGAs available in Europe*
Sources: www.fda.gov/cder/drug/infopage/antipsychotics/default.htm and package inserts for the different agents

previous treatment was not available; and that the patient was not currently on medication. As shown in the results of the section of Question 30 on schizophrenia, the panel preferred the second generation antipsychotics (SGAs) over the first generation antipsychotics (FGAs), which is consistent with recommendations in the American Psychiatric Association's treatment guidelines[51] and other guidelines.[52] The confidence intervals for the SGAs overlap, indicating no significant differences between ratings of the different SGAs. The results for schizoaffective disorder, bipolar disorder (mania or depression with psychosis), unipolar psychotic depression, and psychosis not otherwise specified (not shown here) were very similar, with only some minor, statistically nonsignificant differences in order of preference for different diagnoses. Again, the preference for SGAs over FGAs in these conditions reflects recommendations in available treatment guidelines.[53,54] There was little support for using FGAs and clozapine, except that haloperidol was rated as sometimes appropriate for schizophrenia and schizoaffective disorder. (Although clinicians tend to think in terms of therapeutic indications, it is important to keep in mind that the pharmacodynamic and pharmacokinetic profiles of psychoactive medications do play a role in clinical treatment decisions [see Section III, p. 10].)

PHASE OF ILLNESS

Because many complex challenges arise in selecting the most appropriate treatment strategies for patients at different phases of illness (e.g., a first episode of psychosis), issues related to specific phases of illness are discussed in Section VII (p. 34).

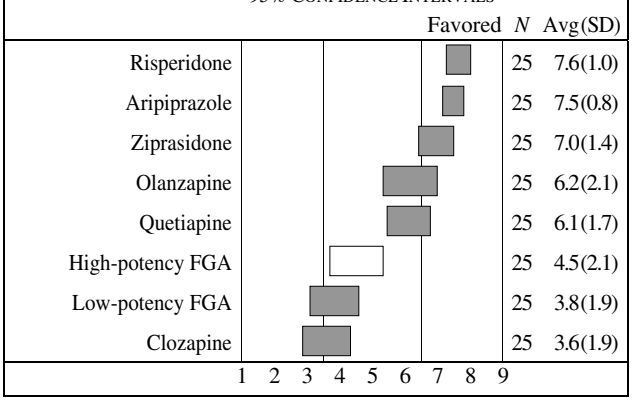
TREATMENT HISTORY

In selecting an antipsychotic medication, clinicians should consider the patient's treatment history. Important factors that influence choice of specific medication as well as dosing and switching/crossover strategies are discussed below. For an overview of clinical issues to consider in deciding to make a change of antipsychotics, see Sections III (p. 10) and VII (p. 34).

Current Medication

As shown in Question 16, two thirds of the experts indicated they would be equally willing to consider an elective switch of antipsychotics whether a patient was taking an FGA or SGA and that their willingness would not be affected by whether the person was taking a long-acting or oral agent. However, about a third of the panel said they would be less willing to switch if the person was taking an SGA rather than an FGA, or depot rather than oral haloperidol. In selecting the most appropriate dose and speed for a switch, clinicians need to consider the medication the patient is currently taking in order to minimize withdrawal or rebound effects (see Section III, p. 17, for a discussion of crossover problems that can occur when switching between agents with different receptor profiles).

Question 30. Acute psychotic episode with primary diagnosis of schizophrenia. Please indicate the appropriateness of using each of the following antipsychotics to treat a healthy young man with schizophrenia who has normal weight, lipid levels, and fasting glucose and is having an acute psychotic episode. Assume information on previous treatment and response is not available and the patient is currently not on medication.



Question 16. Factors affecting decision to switch, part 1. We asked the experts how a number of factors would affect their willingness to make an elective switch of antipsychotics to achieve improved efficacy or reduced side effects in a stable patient.

	Effect on decision to switch antipsychotics		
	Less willing	No difference	More willing
On SGA rather than FGA	32%	64%	4%
On depot haloperidol	27%	69%	4%
Early episode treated with antipsychotics for 6 months–1 year	8%	31%	62%
1 unsuccessful attempt to switch antipsychotics*	21%	75%	4%
2 unsuccessful attempts to switch antipsychotics*	77%	19%	4%
1 failed switch trial (not successfully completed)	27%	69%	4%
Adherence questionable	50%	12%	38%
Active substance abuse	38%	38%	23%

**Assume a fully completed switch trial*

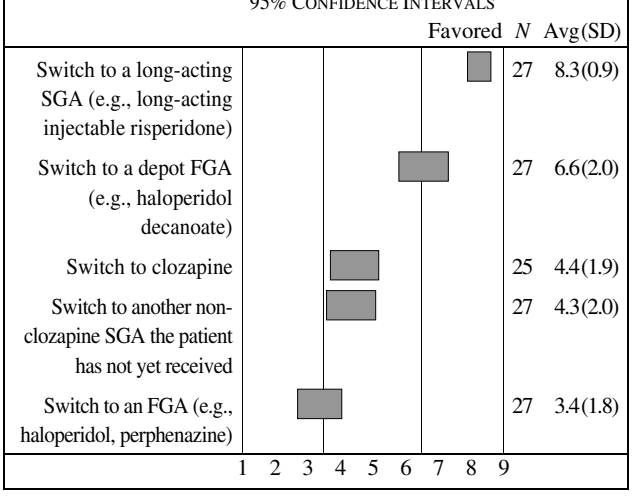
History of Response

The majority of the panel indicated that they would be just as likely to consider an elective switch of antipsychotics to achieve a better response or reduced side effects if the patient had had one previous unsuccessful attempt to switch as if there had been none (Question 16). However, if the patient had failed to respond after two switching attempts involving fully completed antipsychotic trials (see definition below), three quarters of the panel would be less willing to attempt an elective switch.

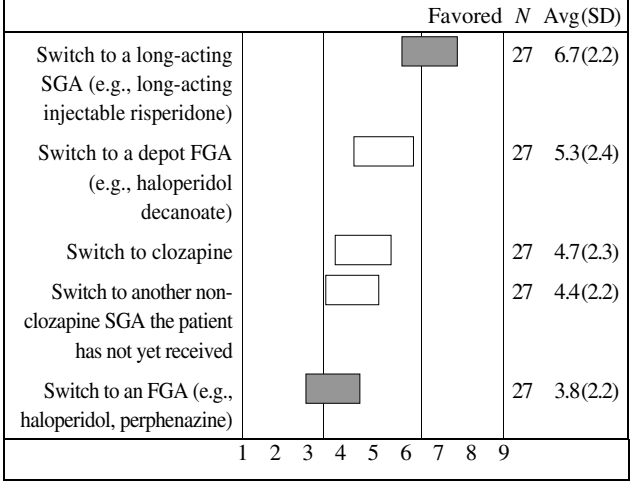
In making an elective switch of antipsychotics for a patient who has a history of being very sensitive to side effects, the experts recommend making the switch more slowly and aiming

Question 18. Factors affecting switching strategy, part 1. Assuming you have decided to switch to a different antipsychotic (AP), how much would each of the following factors influence your switching strategy (e.g., dose selection, speed of the switch).	**Target dose**			**Speed of switch**		
	Lower	**Same**	**Higher**	**Slower**	**Same**	**Faster**
History of extreme sensitivity to side effects	86%	14%	0%	89%	7%	4%
Little or no response to current AP	0%	52%	48%	0%	38%	62%
Partial response to current AP	0%	78%	22%	11%	78%	11%
Responded only to high dose of current AP	4%	26%	70%	31%	65%	4%
Wants to stop current AP immediately because of side effects	24%	56%	20%	0%	19%	81%
Active substances abuse	14%	82%	4%	19%	54%	27%

Question 5. Patient #2: Treatment-resistant first episode patient complicated by noncompliance. You discover that Mr. D's mother is not able to supervise his medication taking, and she reports that the patient often does not take his medication. How would this affect your choice of treatment strategy? Please rate the appropriateness of the same treatment options in this situation. There is no evidence of substance abuse.



Question 6. Patient #2: Treatment-resistant first episode patient complicated by active substance abuse. Further history reveals that Mr. D has been actively abusing cocaine. On each occasion he was hospitalized, his urine drug screen was positive for cocaine and the patient admitted to smoking crack cocaine. The patient says he is compliant with his medication but has difficulty remembering what happens during periods of intoxication. Please rate the appropriateness of the same treatment options in this situation.



Fully completed antipsychotic switch trial. To be considered to have completed a full trial of an antipsychotic in the context of a medication switch, the patient must

- Reach a therapeutic dose (within FDA-approved range) of the new post-switch antipsychotic
- Have completely discontinued taking the pre-switch antipsychotic
- Remain on the post-switch antipsychotic at a therapeutic dose for at least 6 weeks after the previous antipsychotic is completely discontinued.

for a lower target dose (Question 18). Conversely, if the patient has a history of only responding to a very high dose of the current antipsychotic, the experts would aim for a higher dose of the new agent. If the patient has had little or no response to the current medication or wants to stop the current medication immediately because of side effects, two thirds of the experts would make a faster switch to a different agent.

History of Adherence Problems

If lack of response to an SGA appears to be due to adherence problems, the panel recommended switching to a long-acting SGA (e.g., long-acting injectable risperidone) (Question 5), and would also consider a depot FGA (e.g., haloperidol or fluphenazine decanoate). The panel also recommended considering a long-acting SGA for patients with poor insight or denial of illness (Question 3, not shown), probably because these problems are associated with a lack of adherence. The panel indicated that the presence of adherence problems would affect their willingness to make an elective change of antipsychotics. Half of the experts would be less willing to make an elective switch of antipsychotics in a patient with adherence problems, probably reflecting the belief that changing medications will not improve the situation if the patient is not taking the medication as prescribed in the first place. However, nearly 40% would be more likely to switch antipsychotics for a patient with adherence prob-

lems, possibly reflecting the belief that, if the new medication has a better side effect profile, the patient may be more willing to take it, or reflecting a willingness to switch to a long-acting injectable formulation (see Question 5). Research also indicates that the least complex dosing regimens are associated with improved adherence. Therefore, if a long-acting formulation is not an option, clinicians may want to consider using an antipsychotic that can be dosed on a once daily basis.[55]

History of Substance Abuse Problems

If lack of response to an antipsychotic medication occurs in the context of consistent substance abuse, the panel supported switching to a long-acting antipsychotic, preferably an SGA (e.g., long-acting injectable risperidone), probably reflecting concern that patients are less likely to take their medications as prescribed when intoxicated. We also asked the panel how the presence of active substance abuse would affect their willingness to make an elective switch of antipsychotic medication to try to achieve a better response or reduced side effects: the panel was split on this issue, with over a third saying the presence of substance abuse would make them less willing to make an elective switch or that it would make no difference in their decision to make a switch, while slightly fewer than a quarter indicated that they would be more willing to make a switch if the patient is abusing substances. Treatment guidelines for serious mental illness generally recommend that, when patients have active substance abuse problems, the substance abuse should be targeted in integrated treatment programs.[56,57]

Summary

Table 4-3 summarizes areas in which disease and symptom factors influence treatment decisions.

Table 4-3. Disease and symptom factors that influence treatment decisions*

Characteristic	*Choice of antipsychotic*	*Dosing and titration*	*Comments*
Diagnosis	SGAs preferred over FGAs for all psychotic illnesses		
Phase of illness	SGAs preferred over FGAs for all phases	Lower doses generally recommended for first-episode	
Treatment history	Consider side effects and response to current medication (e.g., if serious problems with weight gain or EPS, choose agent with lower liability for these problems)	Consider pharmacodynamics and pharmacokinetics of current medication in choosing cross-titration schedule to minimize withdrawal or rebound effects	Experts less willing to switch in a patient who has had two or more unsuccessful previous switches
	Clozapine indicated for treatment resistance	Lower doses and slower switches recommended when patient very sensitive to side effects	
		Higher doses recommended when patient has responded only to high doses of other antipsychotics	
		Faster switch recommended for patients who have had little or no response to current agent or who are likely to stop immediately anyway because of side effects	
Adherence problems	Long-acting injectable SGA, with depot FGA another option to consider		Experts divided as to whether to switch agents when adherence is a problem
Substance abuse	Long-acting injectable SGA, with depot FGA another option to consider		Literature supports treatment for substance use problems in integrated dual diagnosis programs[56,57]

**Recommendations are based on the Roadmap expert survey unless otherwise indicated*

V. Demographic Characteristics That Influence Treatment Decisions

This section presents information to help clinicians select the most appropriate antipsychotic medication to treat patients with psychotic disorders depending on individual patient characteristics, such as age, sex, gender, psychosocial status, and environmental situation. Such characteristics can affect:

- Response to medication
- Ability to tolerate medication
- Long-term safety of medication for the individual
- Ability to adhere to prescribed treatment.

This section discusses how to match patient profiles to the pharmacology of different antipsychotics to optimize the probability of good outcomes. In formulating the recommendations presented here and in Section VI, we drew on clinical trial data; recommendations in existing practice guidelines, such as the APA *Practice Guidelines for the Treatment of Patients with Schizophrenia*,[51] and *Bipolar Disorder*[53]; consensus recommendations concerning use of antipsychotic drugs, obesity, and diabetes developed by the American Diabetes Association, the APA, the American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity[58]; published expert consensus guidelines[52,54]; and results of the Roadmap expert survey.

AGE

Adolescents

Use of antipsychotics in children and adolescents has been increasing in recent years. Olfson et al.[59] reported that the estimated number of office visits by youth in the United States that included antipsychotic treatment increased from approximately 201,000 in 1993 to 1,224,000 in 2002. Between 2000 and 2002, over 90% of prescriptions for this population involved second generation antipsychotics (SGAs), which were prescribed for a wide range of disorders, including disruptive behavior disorders (37.8%), mood disorders (31.8%), pervasive developmental disorders or mental retardation (17.3%), and psychotic disorders (14.2%). A review of data from three state Medicaid programs also found increasing rates of SGAs being prescribed to children and adolescents.[60] However, in part because of constraints on undertaking controlled trials in this population, empirical data on use of antipsychotics in children and adolescents are limited.[61] Kapetanovic and Simpson[62] recently reviewed 77 clinical trials of antipsychotics in children and adolescents published over the past 10 years. They noted that only four first generation antipsychotics (FGAs) (chlorpromazine, thioridazine, haloperidol, and pimozide) and none of the SGAs have to date been labeled by the FDA for use in pediatric patients. In addition, the majority of controlled trials in this population have focused on Tourette's disorder, disruptive behavior disorders, and autistic disorders or mental retardation with disruptive behavior. Kapetanovic and Simpson reviewed 8 short-term studies in pediatric schizophrenia and found that, although none of these studies was placebo controlled, findings suggested that haloperidol,[63] clozapine,[64] olanzapine,[60–66] and risperidone[63,67,68] were effective in treating schizophrenia in children and adolescents. They also reviewed studies showing that clozapine appeared to be more efficacious than haloperidol[69] or olanzapine[64,70] for treatment-refractory illness in this population, although it was associated with more adverse effects. Kapetanovic and Simpson also noted promising findings in youth with schizophrenia for longer-term treatment with clozapine[70,71] and olanzapine.[72,73] In addition to the studies described above, one small open-label trial in 10 adolescents with psychotic disorders[74] found that quetiapine was effective and well tolerated, and a recent open-label trial comparing 12 weeks of treatment with risperidone or olanzapine in 25 children with childhood-onset schizophrenia[75] found that both agents produced significant improvement in symptoms and also caused a significant increase in weight.

When the Roadmap experts were asked about choice of antipsychotic for an adolescent patient with acute psychotic symptoms, their ratings closely resembled those for a healthy young adult with schizophrenia or other psychotic disorder (see Question 30, p. 21), with aripiprazole, ziprasidone, and risperidone receiving the highest ratings and little support for use of an FGA. There was somewhat less support for using olanzapine in an adolescent than in an adult patient with schizophrenia. Given that limited studies have been published concerning the use of any of these agents in the treatment of pediatric psychosis, the ratings appear to reflect concern about side effects and safety, in particular weight gain, given recent reports of an epidemic of obesity in youth in the United States and findings concerning weight gain with olanzapine[63,72,73,75,76] and risperidone[63,67,75] in this population. A number of studies have also reported that children and adolescents appear more sensitive than adult patients to side effects such as weight gain and EPS.[63,77] Based on their review of safety data, Kapetanovic and Simpson recommended careful routine monitoring of body weight, body mass index (BMI), and metabolic status in adolescent patients being treated with antipsychotics.[62] They also recommend that suicide risk be assessed at every visit and that visit frequency be increased after starting or switching to a different antipsychotic or increasing dose, given the hypothesis that akathisia may contribute to increased suicidality in youths treated with selective serotonin reuptake inhibitors.[62]

When asked if the patient's age would affect their willingness to make an elective change of antipsychotics to achieve better symptom control or reduced side effects in a stable patient, the experts indicated that whether a patient was in his or her 30s or 40s would not affect this decision. However, two thirds of the expert panel said they would be ***more*** willing to make an elective change of antipsychotic in an adolescent patient (Question

16). The greater willingness to make a change in younger patients to achieve better outcomes may reflect the hypothesis that early effective interventions in schizophrenia may lead to better long-term outcomes and reduced overall deterioration.[78]

Older Patients

In diagnosing primary psychotic disorders, such as schizophrenia, bipolar disorder with psychosis, delusional disorder, and psychotic depression, in older patients, it is important to distinguish these symptoms from those of delirium, psychosis induced by medications or medical illness, and dementia, which are more common among older patients.[79]

When dosing and titrating antipsychotic medications in older patients, the APA Practice Guideline for the Treatment of Patients with Schizophrenia recommends using starting doses that are a quarter to a half the usual starting dose for healthy younger adults.[51] This is because older patients may metabolize these drugs more slowly and may also be more sensitive to side effects, in particular sedation, anticholinergic side effects, and postural hypotension.

When asked about appropriateness of different antipsychotics to treat acute psychotic symptoms in patients 65 years of age and older, the experts' ratings were again very similar to those for a healthy younger adult (Question 30, p. 21), with all the non-clozapine SGAs favored over FGAs and highest ratings given to aripiprazole and risperidone, followed by ziprasidone.

In selecting a specific agent to treat psychotic disorders in an older patient, it is important to consider the comorbid medical conditions that occur much more commonly in this population, such as cardiovascular disease, diabetes, urinary retention, as well as other medications the patient may be taking. Studies have shown that the number of medications patients are likely to be taking increases significantly with age.[44,80,81] Thus, clinicians should be especially alert for potential drug-drug interactions in selecting antipsychotics for older patients (see discussion of drug combinations and pharmacokinetic drug-drug interactions, p. 19). Clinicians should also keep in mind that the labeling for all the SGAs contains a black box warning concerning an increased rate of mortality in elderly patients with dementia-related psychosis, primarily due to cardiovascular or infectious causes. Although none of the SGAs are approved for the treatment of dementia-related psychosis, clinicians should keep this finding in mind when using these agents to treat other types of psychosis in elderly patients. (For more discussion of management of dementia-related psychosis, readers are referred to the *Expert Consensus Guidelines on the Treatment of Dementia and Its Behavioral Disturbances*.[82])

Question 16. Factors affecting decision to switch, part 2. We asked the experts how a number of factors would affect their willingness to make an elective switch of antipsychotics to achieve improved efficacy or reduced side effects in a stable patient.	**Effect on decision to switch antipsychotics**		
	Less willing	**No difference**	**More willing**
Age: adolescent	4%	35%	62%
Age: 40s compared with 30s	4%	92%	4%
Gender: male	8%	92%	0%

The panel was also asked how the patient's age would affect their strategy in switching antipsychotics. Not surprisingly, 85% of the panel indicated that they would use a lower target dose and a slower dose titration schedule in older patients, in keeping with the clinical adage "to start low and go slow" in older patients (Question 18), which reflects the increased sensitivity and slower metabolism common in older patients.

GENDER

Even after body weight is factored in, women often require lower overall antipsychotic doses than men.[51,83,84] Among the SGAs, higher plasma levels in women have only been demonstrated to date with olanzapine and clozapine.[85] Some studies have reported that women experience more neurologic side effects, including acute dystonia, parkinsonism, akathisia, and tardive dyskinesia,[51,86] while other studies have not found such differences.[85] Women do appear to be more vulnerable to weight gain, cardiometabolic side effects, and hyperprolactinemia.[51,82–87] The APA *Practice Guideline for the Treatment of Patients with Schizophrenia*[51] notes that it is important for clinicians to be alert for prolactin-related effects on women's menstrual cycles and fertility (for a discussion of elevated prolactin levels, see p. 31).

When asked if the patient's gender would affect their willingness to make an elective change of antipsychotics to achieve better symptom control or reduced side effects in a stable patient, over 90% of the expert panel indicated that the patient's gender would not influence this decision (Question 16).

Question 18. Factors affecting switching strategy, part 2. Assuming you have decided to switch to a different antipsychotic, how much would each of the following factors influence your switching strategy (e.g., dose selection, speed of the switch).	**Target dose**			**Speed of switch**		
	Lower	**Same**	**Higher**	**Slower**	**Same**	**Faster**
Age over 65 years	86%	14%	0%	85%	15%	0%
Less availability of social supports to help during the switch	11%	81%	7%	38%	27%	35%
Low level of medical support available	22%	74%	4%	54%	42%	4%
Patient is reluctant/fearful about switch	33%	67%	0%	89%	11%	0%

PSYCHOSOCIAL/ENVIRONMENTAL FACTORS

The panel was asked about the appropriateness of the different antipsychotics for a first episode patient with a number of different psychosocial or environmental problems. The editors note that recommendations would in many cases be the same for a patient with an acute recurrence of psychosis, except for the need to consider the patient's treatment history.

Homelessness/Limited Social Support

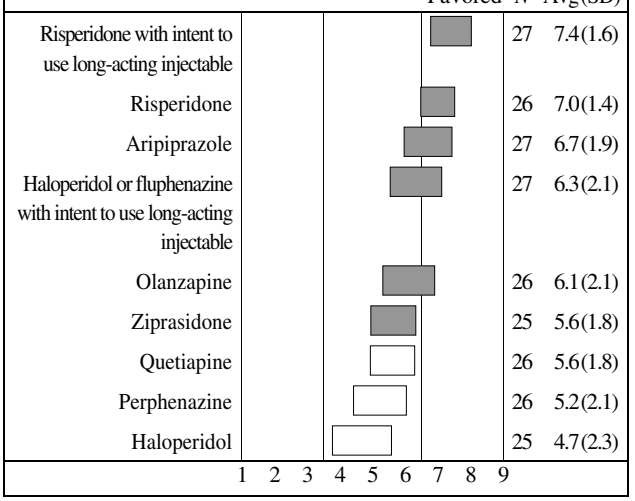
The literature provides only limited guidance concerning choice of antipsychotic agent or dosing in patients who are homeless or lack social support. The expert panel gave highest ratings to using a long-acting SGA (e.g., long-acting injectable risperidone) for such patients (Question 3). These recommendations probably reflect findings that medication nonadherence is significantly associated with homelessness in individuals with schizophrenia[88,89] and bipolar disorder.[90]

Clinicians should also keep in mind the need to target the multiple problems homeless patients are likely to have, in order to try to achieve the best outcomes. The APA *Practice Guideline for Schizophrenia*[51] recommends that treatment for homeless individuals with schizophrenia should include:

- Access to medical services
- Provision of appropriate housing
- Treatment of substance use disorders
- Income support and benefits
- Rehabilitation and employment assistance.

In making an elective switch for a patient for whom only a low level of medication support is available, half the experts recommend making the switch more slowly (Question 18). If the patient is reluctant or fearful about making an elective change of medications, nearly all the experts recommend making the switch more slowly (Question 18).

Question 3. Factors affecting choice of agent for a first episode patient. Please rate the appropriateness of each antipsychotic for a first episode patient who is homeless.



Other Psychosocial/Environmental Factors

Other psychosocial factors that can influence treatment decisions are discussed in Section VII (p. 34).

Summary

Table 5-1 summarizes areas in which demographic characteristics may influence treatment decisions.

Table 5-1. Areas in which demographic characteristics may influence treatment decisions*

Characteristic	*Choice of antipsychotic*	*Dosing and titration*	*Comments*
Adolescent patient			Greater willingness to switch for better efficacy or reduced side effects in adolescent patients
Elderly patient		Slower switch with lower target dose recommended	
Female patient	May be more vulnerable to prolactin-related effects	May require lower doses of certain agents even when body weight factored in	
Homeless patient	Consider long-acting injectable antipsychotic		

**Recommendations are based on the Roadmap expert survey unless otherwise indicated*

VI. Medical Issues That Influence Treatment Decisions

This section discusses how a patient's medical conditions, whether related to antipsychotic treatment or not, may affect decisions concerning antipsychotic medications. In this area especially clinicians must often do risk/benefit analyses and balance competing objectives (e.g., when a patient has achieved a good symptomatic response to a medication but has developed serious side effects that pose a risk to long-term health). A number of medical problems can complicate treatment with antipsychotic medications, and antipsychotics themselves are associated with a variety of side effects, ranging from those that are uncomfortable but not dangerous to conditions that are life-threatening. While a detailed discussion of general medical care for patients with psychosis is beyond the scope of the Roadmap, we highlight medical issues with special bearing on choice of antipsychotic medications and dosing strategies.

WEIGHT AND CARDIOMETABOLIC RISK

Overview of the Problem

Patients with serious mental illnesses have elevated rates of a number of risk factors for cardiovascular disease (CVD) unrelated to medication treatment; yet these patients often do not receive adequate preventive care. This problem is compounded by the fact that some antipsychotics used to treat these illnesses can themselves cause weight gain and metabolic abnormalities, further increasing health risks for these patients. Recent data from the Centers for Disease Control show that U.S. patients with a major mental illness die 25–30 years earlier than the general population.[2] This excess mortality is caused more by CVD than any other factor.[2] Elevated rates of CVD have been found in patients with schizophrenia, in particular,[91,92] a multifactorial problem that seems largely due to an increased prevalence of modifiable risk factors (e.g., smoking, hypertension, overweight/obesity, dyslipidemia, and diabetes mellitus). All these risk factors were present at elevated rates among patients with schizophrenia even ***before*** the advent of the SGAs,[93,94] with data showing that cardiovascular mortality in schizophrenia increased from 1976 to 1995.[95] Rates of obesity, smoking, and diabetes are 1.5–3 times higher in patients with schizophrenia than in the general population.[93,96,97] Studies have shown that 45%–55% of patients with schizophrenia[96] and 26% of those with bipolar disorder[98] are obese; 10%–14% of patients with schizophrenia[97] and 10% of those with bipolar disorder[99] have diabetes mellitus; 50%–80% of patients with schizophrenia[93] and 55% of those with bipolar disorder[100] smoke; and 18% of those with schizophrenia[101] and 15% of those with bipolar disorder[98] have hypertension. Data from the 1989 National Health Interview Survey and other sources examined by Allison et al.[93] showed that patients with schizophrenia were overrepresented in every Body Mass Index (BMI) range above 26 kg/m^2, particularly the range greater than 34 kg/m^2.

Two studies compared baseline data from 689 subjects in the Clinical Trials of Antipsychotic Treatment Effectiveness (CATIE) Schizophrenia Trial with age-, race-, and gender-matched controls from the National Health and Nutrition Examination Survey (NHANES) III, a survey of 40,000 individuals in the general U.S. population. Goff et al.[102] reported the 10-year CVD risk was significantly elevated in male (9.4% vs. 7.0%) and female (6.3% vs. 4.2%) patients with schizophrenia compared with controls. McEvoy et al.[103] found men in the CATIE sample were 138% more likely and females 251% more likely to have the metabolic syndrome (see definition below) than their NHANES matched sample (with differences in BMI controlled for, CATIE males were still 85% more likely and females 137% more likely to have the metabolic syndrome).

To understand how SGAs can contribute to this problem, one must look at the interplay between modifiable risk factors. Data from the Framingham risk study (a cohort study of residents of Framingham, Massachusetts conducted by the National Heart, Lung, and Blood Institute) show that the estimated 10-year risk of CVD increases with the addition of each of the following factors: diabetes mellitus, hypertension, elevated total cholesterol, low HDL cholesterol, and cigarette smoking.[104–106]

Overweight/obesity seems to contribute to this risk equation primarily through development of insulin resistance. As visceral (i.e., intra-abdominal) adiposity increases, insulin sensitivity decreases.[107] Individuals with increased visceral adiposity therefore tend to have correspondingly decreased tissue sensitivity to insulin action. Normally functioning pancreatic beta cells compensate for this decreased sensitivity by secreting more insulin (a compensatory hyperinsulinemia). However, this compensation tends to be time-limited. If an insulin-resistant individual develops even modest deficiency in beta cell insulin production, the pancreas is unable to sustain compensatory hyperinsulinemia, and hyperglycemia results, leading to prediabetes or frank type 2 diabetes mellitus.

"Prediabetes" is clinically characterized by impaired fasting glucose or impaired glucose tolerance. *Impaired fasting glucose* is defined as a fasting plasma glucose level above normal but below the diabetes threshold (i.e., 100–125 mg/dL, with 126 mg/dL the current cutoff for diabetes mellitus). *Impaired glucose tolerance* is defined as abnormally elevated plasma glucose, below the diabetes threshold, 2 hours after oral consumption of 75 g of glucose (140–199 mg/dL, with 200 mg/dL the current cutoff for diabetes mellitus). Most individuals with prediabetes go on to develop type 2 diabetes mellitus within 10 years, and those with prediabetes already have an increased risk for atherosclerosis and a risk of CVD 1.5 times greater than those with normal fasting glucose and glucose metabolism.[108–110]

Given the typical delay between onset of insulin resistance and development of detectable impairments in fasting glucose or glucose tolerance, and the contribution of other factors such as hypertension, expanded definitions of risk have been devised to include those who do not show frank diabetes. One widely

Table 6-1. Metabolic syndrome: 3 or more risk factors required for definition

Risk Factor	*Defining Level*
Abdominal obesity	Waist circumference
Men	> 102 cm (> 40 in)
Women	> 88 cm (> 35 in)
Fasting plasma triglycerides	= 150 mg/dL or drug treatment
High-density lipoprotein (HDL) cholesterol	
Men	< 40 mg/dL
Women	< 50 mg/dL
Blood pressure	= 130/85 mm Hg or drug treatment
Fasting plasma glucose*	= 110 mg/dL

**Note that a fasting plasma glucose of 100 mg/dL is now gaining acceptance as a better cutoff point than 110 mg/dL.*

Source: NCEP 2002[111]

used formulation is the metabolic syndrome. The National Cholesterol Education Program (NCEP), in its third Adult Treatment Panel (ATP III), defined the metabolic syndrome in terms of five risk factors (Table 6-1).[111] This definition excludes smoking, which the Framingham study identified as an important risk factor for CVD.[104] For this project, the ATP III criteria were updated with the new definition of prediabetes and smoking was added to the list of risk factors (Table 6-2). This set of risk factors, representing a synthesis of the best available data, was used in the questions we posed to the experts in our survey.

Overweight/obesity interacts with other factors to increase cardiometabolic risk. Although data suggest that the SGAs may generate rapid peripheral insulin resistance[112] or acute beta cell dysfunction through some direct effect,[112,113] the SGAs increase cardiometabolic risk primarily through their differential tendency to cause weight gain.[114–118] SGAs can produce weight gain of varying magnitude[94,118] with the most weight gain seen with clozapine[94,119,120] and olanzapine,[121,122] and the least with ziprasidone[94,123] and aripiprazole.[124] In phase 1 of the CATIE study, 30% of patients taking olanzapine gained > 7% of their baseline body weight over 18 months compared with 16% of those on quetiapine, 14% of those on risperidone, and 7% of those on ziprasidone.[125] CATIE Phase 2 had similar results.[126] (Aripiprazole was not FDA-approved in time to be included in the CATIE study.)

Monitoring and Evaluating Cardiovascular Risk Factors

Recommendations from an American Diabetes Association (ADA) Consensus Development Conference on antipsychotics and cardiometabolic vascular risk were published in 2004,[58] in a paper sponsored by the ADA, the APA, the American Association of Clinical Endocrinologists (AACE), and the North American Association for the Study of Obesity (NAASO). This review found "compelling evidence" for the differential effects of SGAs on adiposity and cardiometabolic risk, with clozapine and olanzapine conferring the greatest risk. Relative weight gain liability and risk of diabetes and dyslipidemia of the SGAs as presented in the consensus statement are shown in Table 6-3.

Table 6-2. Risk factors for cardiovascular disease (CVD)

1. Abdominal obesity: waist circumference > 40 in. in men, >35 in. in women
2. Fasting plasma triglycerides: > 150 mg/dL
3. Low HDL cholesterol: < 40 mg/dL in men, < 50 mg/dL in women
4. Elevated blood pressure: > 130/85 mm Hg
5. Elevated fasting plasma glucose: > 100 mg/dL
6. Cigarette smoking

Source: NCEP 2002[111] and Framingham Heart Study[104] (www.nhlbi.nih.gov/about/framingham/index.html)

Table 6-3. SGAs and metabolic abnormalities[58]

Drug	*Weight gain*	*Risk for diabetes*	*Worsening lipid profile*
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole*	+/–	–	–
Ziprasidone*	+/–	–	–

+ = increase effect; – = no effect; D = discrepant results.

**Newer drugs with limited long-term data.*

The conference recommended the screening and monitoring regimen shown in Table 6-4. To carry out these procedures, clinicians need to have a scale, a tape measure to assess waist circumference, a tape measure or height bar to assess height (first visit), and a blood pressure cuff. To calculate BMI, divide weight in kilograms by square of the patient's height in meters. Conversion equations are pounds/2.2 = kg and inches x 0.025 = m. Clinicians can access a BMI calculator on the National Institute of Health's Heart, Lung, and Blood Institute website (www.nhlbisupport.com/bmi). Waist circumference should be checked with the tape encircling the patient's abdomen at the level of the iliac crests. The best type of tape measure to use for this purpose is a non-stretch tape measure with a tensioning devise such as the "Gulick." To obtain fasting laboratory values, instruct patients to abstain from food or drink except water from midnight (at the latest) the night before until blood samples are drawn.

Table 6-4. Monitoring protocol for patients on SGAs*[58]

	Baseline	*4 weeks*	*8 weeks*	*12 weeks*	*Quarterly*	*Annually*	*Every 5 years*
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X		X†	X

**More frequent assessments may be warranted based on clinical status*

†Revised to reflect current consensus on annual monitoring

Measuring Change in CVD Risk Factors

The Roadmap experts developed definitions based on evidence-based guidelines to help clinicians evaluate changes in weight and metabolic parameters in their patients. These apply whether or not the risk factors are related to treatment.

Clinically meaningful improvement in overweight/obesity: Successful treatment decreases BMI, defined as weight/height^2 in kg/m^2, ideally to normal range, but with recognition that any reduction produces some reduction in CVD risk.[111,127]

Normal: 18.5–24.9 kg/m^2
Overweight: 25.0–29.9 kg/m^2
Obese: > 30 kg/m^2

Clinically meaningful improvement in dyslipidemia: Successful treatment reduces lipid values as much as possible, with recognition that any improvement will be beneficial, even if "optimal" level is not achieved (Table 6-5).[111]

Clinically meaningful improvement in metabolic syndrome indices: Successful treatment reduces the index in question (Table 6-1) as much as possible, with recognition that any improvement will be beneficial, even if "optimal" level is not achieved. Risk for CVD increases with each criterion present, so that intervention is indicated for any single criterion.[111]

Table 6-5. Fasting lipid levels (mg/dL)

	Optimal/ desirable	*Near optimal*	*Borderline high*	*High/ undesirable*	*Very high*
Total cholesterol	< 200		200–239	> 240	
LDL	< 100	100–129	130–159	160–189	> 190
HDL	> 60			< 40	
Triglycerides	< 150		150–199	200–499	> 500*

**Requires immediate pharmacotherapeutic intervention.*

Source: NCEP 2002[111]

Clinically meaningful improvement of prediabetes/diabetes mellitus: Successful treatment reduces fasting plasma glucose level or 2-hour postload glucose level (if oral glucose tolerance test is used), with the recognition that any improvement will be beneficial, even if an "optimal" level within the normal range is not achieved.

Role of therapeutic lifestyle changes: The NCEP's ATP III[111] recommends therapeutic lifestyle changes for patients with prediabetes,[128] hypertension,[129] 0–1 CVD risk factor and LDL >160 mg/dL, 2+ CVD risk factors and LDL >130, and metabolic syndrome. Such changes involve smoking avoidance/cessation, modifications in diet, weight control, and increased exercise. Clinicians may also want to consider such changes for patients with subsyndromal metabolic syndrome.[130] Follow-up at 6- to 12-week intervals to monitor response[111] is recommended. Pharmacotherapy is recommended if lifestyle changes do not produce improvement after 3 months, unless lipid, blood pressure, or glucose values require immediate drug treatment.

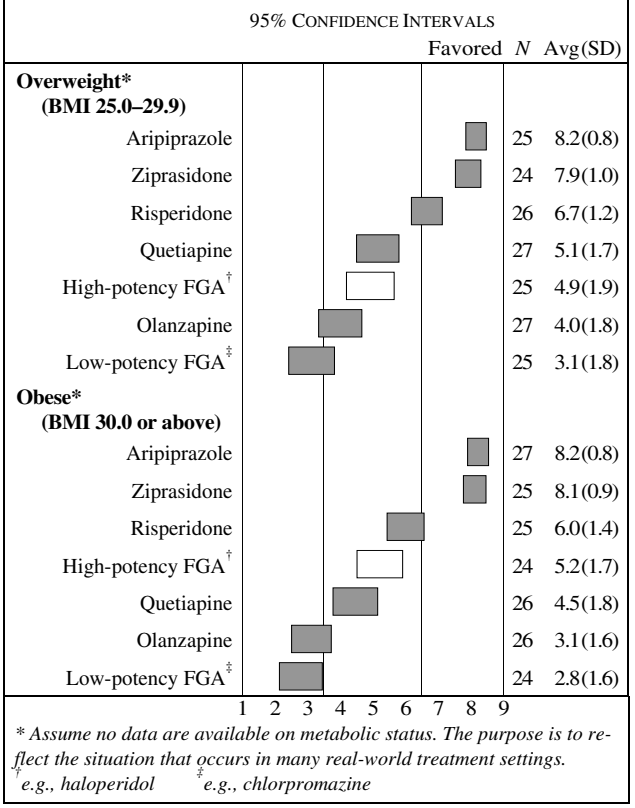
Effect of Weight/Metabolic Status on Antipsychotic Choice

We asked the experts about initiating treatment with different antipsychotics when the only CVD risk information available is the weight, reflecting the situation in many real-world settings, as well as when they have more complete information. When asked about most appropriate antipsychotics for a patient who is overweight or obese, the panel gave highest ratings to aripiprazole and ziprasidone, followed by risperidone, and indicated they would generally avoid olanzapine and low-potency first generation antipsychotics (FGAs). Ratings were almost exactly the same when the panel was asked about risk factors for CVD, with support for using aripiprazole or ziprasidone increasingly strong as the number of risk factors increased (Question 7a).

Weight and Metabolic Status and Use of Clozapine

Patients are generally being treated with clozapine either because they have failed to respond to adequate trials of several other antipsychotics or because they are believed to be at increased risk for suicide. Under these circumstances, the risk-benefit equation becomes considerably more difficult. The panel considered it appropriate to initiate clozapine in such a patient

Question 7a. Effect of weight/metabolic status on choice of antipsychotic. Please rate the appropriateness of initiating treatment with each antipsychotic in a patient with the presentations shown below, taking into account both safety and efficacy. Assume the patient has not had prior exposure to the antipsychotic asked about, that the weight gain is not related to the previous antipsychotic the patient was receiving, and that the switch is not being made because of concern about weight gain.



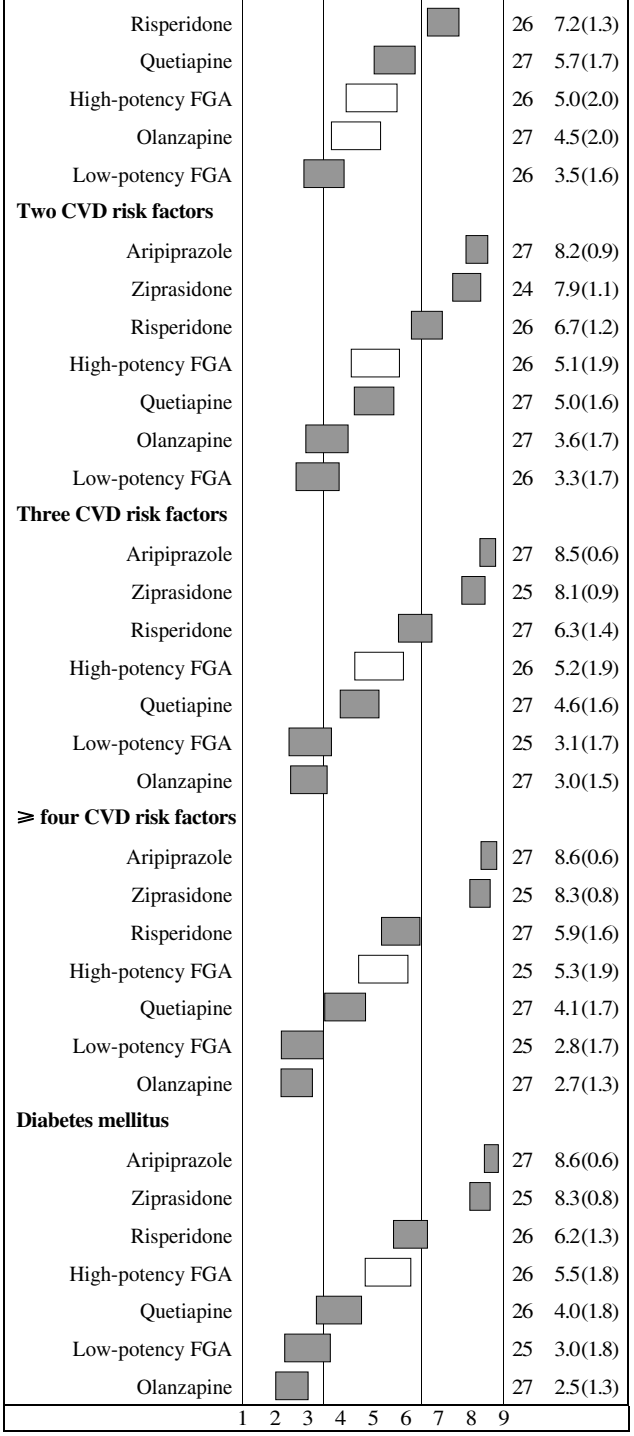
** Assume no data are available on metabolic status. The purpose is to reflect the situation that occurs in many real-world treatment settings.*
† e.g., haloperidol ‡ e.g., chlorpromazine

even if he or she has weight problems or CVD risk factors, although there was somewhat less support for using clozapine in a patient who is obese or has multiple CVD risk factors or actual diabetes. The editors note that, if it is decided that clozapine is needed to treat psychosis in such a patient, the patient's weight and metabolic parameters should be carefully monitored and appropriate medical interventions should be initiated to try to control weight and reduce CVD risk factors. For a discussion of strategies for patients who gain weight or develop metabolic abnormalities *while* being treated with an antipsychotic, see Section VII (p. 37).

EPS AND TARDIVE DYSKINESIA

Although reduced incidence of EPS with the SGAs has been a step forward in treatment of psychotic disorders, the SGAs, like the FGAs, do affect the D_2 receptor and can still cause EPS, although EPS with SGAs tend to be less frequent and severe. The incidence of EPS differs among the SGAs, with risperidone associated with the most and clozapine and quetiapine with the fewest EPS. The likelihood of developing EPS with one of the SGAs also depends on rapidity of the dose escalation, target dose, and patient's vulnerability to EPS. The CATIE study found that perphenazine was associated with a higher rate of EPS and discontinuation due to EPS, even though patients with tardive dyskinesia (TD) at baseline were excluded from the perphenazine

Question 7a. continued



group.[125,131] A reanalysis of data from CATIE showed that, of 553 patients who discontinued medication due to intolerability or lack of efficacy as agreed on by patient and clinician, EPS accounted for 10% of all medication discontinuations and over 25% of all discontinuations due to side effects. More than twice as many discontinuations due to EPS occurred in the group receiving perphenazine as in those receiving SGAs, even though the patients received relatively low doses of perphenazine and patients with TD, expected to be more vulnerable to EPS, were not assigned to perphenazine. Data from the first 12 months of the Schizophrenia Outpatient Health Outcome (SOHO) study,[132] a naturalistic study of schizophrenia treatment in 10,972 adult outpatients from 10 European countries, indicated that SGAs as a class were associated with a lower frequency of EPS and anticholinergic use than FGAs, with frequency of EPS lowest in the patients treated with clozapine, quetiapine and olanzapine (around 10%). SGAs were also found to have a lower risk of TD than FGAs. Nevertheless, since EPS can still occur with SGAs, clinicians should continue to assess for these side effects, including their more subtle manifestations. Readers are referred to a review by Weiden for discussion of EPS profiles of the SGAs,[133] to Section II (p. 15) for guidance on pharmacodynamic principles involved in minimizing EPS while achieving therapeutic doses, and to Section VII (p. 40) for a discussion of early onset akathisia.

Now that some of the SGAs have been available for over a decade, researchers are evaluating whether the risk of TD is lower with the newer agents. Although more research and longer-term data are needed,[134] the limited available evidence suggests that the SGAs have a decreased liability of TD of approximately 1% compared with 5% for FGAs.[135] Baseline data from 1,460 patients with schizophrenia in the CATIE trial confirmed the established relationships between TD and age, duration of antipsychotic treatment, treatment with an FGA, treatment with anticholinergics, the presence of EPS and akathisia, and substance abuse.[136] Unfortunately, due to short treatment duration, the CATIE study did not have the assay sensitivity to detect differences in TD risk among any of the drugs during the course of the study.[133] Data from the first 12 months of the SOHO study showed that the SGAs had a lower risk for TD than the FGAs.[132]

In selecting an antipsychotic for a patient with a history of EPS or who has TD, clinicians should, if possible, choose an agent with low EPS liability. Clinicians should also keep in mind that patients with bipolar disorder may be especially vulnerable to EPS and TD.[137]

ELEVATED PROLACTIN LEVELS

Elevated prolactin levels (hyperprolactinemia) is a major neuroendocrine-related cause of reproductive disturbances in men and women.[138] Pituitary D_2 blockade induces prolactin elevation. Because of their potent effects on the D_2 receptor, a number of antipsychotics can cause hyperprolactinemia, although the development of progressively more selective dopaminergic drugs has increased our ability to avoid or reverse hyperprolactinemia. Elevated prolactin levels may be asymptomatic, but they can also cause amenorrhea (menstrual disturbance, cessation of menses) and galactorrhea (abnormal lactation) in women and gynecomastia (enlargement of male mammary glands) and sexual dysfunction (decreased libido, impotence, ejaculatory dysfunction) in men. FGAs (e.g., haloperidol) and risperidone are associated with the most prolactin elevation, which tends to occur more often in women than in men.[138] Aripiprazole, clozapine, and quetiapine appear to be associated with the least prolactin elevation (some studies have found that aripiprazole lowers prolactin levels), while ziprasidone and olanzapine appear to fall in between.[139] A recent study comparing prolactin levels in 28 patients receiving clozapine, 29 patients receiving olanzapine, and 18 patients receiving risperidone found that 89% of those treated with risperidone had elevated prolactin levels compared with 24% treated with olanzapine and none treated with clozapine.[140] This study also found that patients receiving risperidone had the most prolactin-related symptoms, while the incidence of such symptoms was modest in the olanzapine group and nonexistent in the clozapine group. The SOHO study found that prolactin-related and sexual adverse events were frequent at baseline, with amenorrhea in approximately one third of the women, impotence in approximately 40% of the men, and loss of libido in 50% of both male and female patients.[132] After 6 months of treatment, the patients treated with olanzapine, clozapine, and quetiapine were significantly less likely to have sexual/endocrine-related dysfunctions than those treated with FGAs and risperidone.

Before initiating treatment with an antipsychotic, especially an FGA or risperidone, clinicians should take a careful history and ask about signs or symptoms of elevated prolactin. As part of their annual examination, clinicians should ask female patients being treated with an antipsychotic about changes in menstrual pattern or libido and about galactorrhea, and male patients about libido and erectile and ejaculatory function.[140] If a clinician suspects hyperprolactinemia, serum prolactin levels should be measured. If elevated and the patient is distressed by the symptoms, changing to a medication less likely to elevate prolactin levels (aripiprazole, olanzapine, quetiapine, or ziprasidone) should be considered. Female patients being switched to an antipsychotic less likely to cause prolactin elevation should be counseled that their menses are likely to resume in a few weeks to months and that they should use appropriate methods of birth control if they are sexually active.

Female patients treated with an antipsychotic that can cause hyperprolactinemia should be advised to let their gynecologist or primary care doctor know to avoid needless work-ups for pituitary abnormalities. At the same time, if hyperprolactinemia does not resolve with a medication change, this could indicate the presence of a serious problem such as a pituitary tumor and the patient should be referred for medical follow-up.[140]

The APA *Practice Guideline on the Treatment of Patients with Schizophrenia* recommends that, if symptomatic prolactin elevation occurs, the clinician should try to lower the dose or switch antipsychotics.[51] When a change of antipsychotic is not possible, use of dopamine agonists such as bromocriptine (2–10 mg/day) or amantadine may reduce prolactin levels.[51]

COMORBID MEDICAL CONDITIONS

Mental Retardation/Developmental Delay

The experts' recommendations for initial antipsychotic treatment for patients with mental retardation/developmental delay did not differ from those for uncomplicated schizophrenia (p. 21).

Epilepsy or Seizure Disorder

The experts' recommendations for initial antipsychotic treatment for patients with epilepsy or seizure disorder did not differ from those for uncomplicated schizophrenia (p. 21).

Dementia in Elderly Patients

As noted in Section V on the treatment of elderly patients, the labeling for all the SGAs contains a black box warning concerning an increased rate of mortality in elderly patients with dementia-related psychosis, primarily due to cardiovascular or infectious causes. Although none of the SGAs are approved for the treatment of dementia-related psychosis, clinicians should keep this finding in mind when using these agents to treat psychosis in elderly patients. (For more information on treatment of dementia-related psychosis, see Alexopoulos et al.[79,82])

Human Immunodeficiency Virus and Hepatitis C

Serious mental illness is associated with a higher risk of HIV infection.[141] One study found that patients with a schizophrenia spectrum disorder were 1.5 times as likely to have HIV infection, while those with a major affective disorder were 3.8 times as likely to have HIV.[142] Many individuals with schizophrenia have co-occurring substance use disorders, which can contribute to increased risk of infection with HIV, hepatitis B and C, and other sexually transmitted diseases.[57] A study of 931 patients with severe mental illness in the Northeastern United States found the prevalence of HIV infection (3.1%) to be approximately 8 times that estimated for the general U.S. population, while the prevalences of HBV (23.4%) and HCV (19.6%) were approximately 5 and 11 times the estimated rates in the general population, respectively.[143]

The effective management of psychiatric illness in patients with HIV can improve the patient's quality of life and may improve adherence to antiretroviral therapy.[144] However, in using antipsychotics to treat patients with HIV, clinicians need to be alert for the possibility of pharmacokinetic drug-drug interactions involving cytochrome P450 (CYP) enzymes, which are involved in the metabolism of many antipsychotics as well as the protease inhibitors and the nonnucleoside reverse-transcriptase inhibitors,[144–146] so that dosages can be adjusted appropriately. A detailed discussion of side effects and potential drug interactions involving antiretroviral agents is beyond the scope of this monograph. Clinicians treating patients with HIV with antipsychotic medications are referred to the American Psychiatric Association's 2000 *Practice Guideline for the Treatment of Patients with HIV/AIDS*[145] and especially to the 2006 *Guideline Watch*[146] for a discussion of potential interactions between antiretrovirals and psychotropic medications as well as central nervous system side effects of antiretrovirals that may complicate treatment of patients with psychosis. However, these drug-drug interactions occur only with a few combinations of medications and this should by no means discourage physicians from assuring that their patients with schizophrenia receive the same treatment for HIV as any other HIV positive patient. This is important because individuals with severe mental illness are often not screened for HIV and, despite widespread access to antiretroviral treatment in the United States, HIV outcomes among mentally ill individuals continue to be poor.[147] Yet it has been shown that patients with schizophrenia and HIV can respond well to antiretroviral treatment and can adhere to the required complex treatment regimens as long as they receive well-coordinated, sustained multidisciplinary support.[148,149] Improved screening and prevention efforts for HIV and hepatitis B and C as well as interventions to educate patients about high-risk behaviors and promote better adherence to treatment in those infected are needed in this population.[57]

Respiratory Disorders

Schizophrenia can complicate diagnosis and treatment of respiratory disorders such as asthma, chronic obstructive pulmonary disease (COPD), and obstructive sleep apnea (OSA). For a detailed discussion of diagnosis and management of respiratory disorders in patients with schizophrenia, see Weiden et al.[150] Note that morning headache, daytime sleepiness, and snoring may suggest the need to evaluate for the presence of OSA. In this section, we focus on issues related to using antipsychotic medications in patients with respiratory disorders. Medications that cause sedation or reduce capacity of respiratory muscles can exacerbate problems related to hypoventilation (e.g., OSA) or increased work of breathing (e.g., asthma).[151,152] IV administration of a sedating antipsychotic with a benzodiazepine has been reported as a cause of respiratory arrest in schizophrenia.[153] Sedating antipsychotics should also be used cautiously in patients with COPD and those with poor lung function tests, since they can blunt the respiratory drive.[150]

Obesity increases risk for aspiration pneumonia, pulmonary thromboembolism, and respiratory failure, is the most common precipitant for OSA, and causes obesity hypoventilation syndrome.[154] There is a very high prevalence of OSA in obese individuals and a high prevalence of obesity in patients with OSA.[155] Since patients with schizophrenia have high rates of overweight and obesity, they also have high rates of OSA.[156,157] Since obesity increases risk for OSA and sedating medications increase the risk of hypoventilation in patients with OSA, caution should be exercised when prescribing sedating antipsychotics and antipsychotics that are likely to increase weight in patients with OSA. When choosing an antipsychotic for a patient with OSA, the expert panel gave highest ratings to antipsychotics associated with the least sedation and weight gain, aripiprazole, ziprasidone, and risperidone, and indicated that they would avoid olanzapine. Because certain types of EPS can interfere with respiratory function (e.g., dystonic reactions involving the larynx

or pharynx, dystonic movements affecting respiratory muscles), antipsychotics that increase EPS risk should be avoided in patients who have a history of respiratory dystonia or dyskinesia. A number of antipsychotics can also affect the metabolism of medications used to treat asthma or COPD.

SMOKING

As noted above, a very high percentage of patients with schizophrenia and bipolar disorder smoke, and many are heavy smokers.[93,100,158] Of 689 patients evaluated at baseline in the CATIE study, 68% smoked compared with 35% of age-, race-, and gender-matched controls from the NHANES-III population.[102] Patients with schizophrenia also have been found to smoke "harder" than smokers in the general population, extracting significantly more nicotine per cigarette.[159,160] Studies have suggested that nicotine may ameliorate certain cognitive deficits associated with schizophrenia, perhaps because of abnormalities in nicotinic receptors in patients with the disorder[159,161] or may reduce agitation[162] or akathisia[163] in patients with schizophrenia, but more research is needed.

Cigarette smoking has been shown in several studies to induce the metabolism of the CYP1A2 substrates clozapine and olanzapine, with one study reporting that a daily consumption of 7–12 cigarettes is probably sufficient for maximum induction of clozapine and olanzapine metabolism.[164] The Roadmap expert panel suggested that clinicians consider using a higher dose of these antipsychotics and/or use therapeutic drug monitoring to monitor plasma levels in patients who smoke. In patients who successfully quit smoking, doses may need to be lowered to avoid toxicity due to increased plasma levels. Conversely, patients stabilized on an antipsychotic during an inpatient stay during which smoking was not permitted may need a dose increase when they resume smoking upon discharge.

Motivational interviewing techniques have been found helpful in encouraging patients with schizophrenia to try to quit smoking.[165] Studies have shown that patients with schizophrenia can participate in smoking cessation programs involving cognitive behavioral therapy plus nicotine replacement therapy (NRT) or bupropion, that psychotic symptoms do not worsen, and that some patients do successfully stop smoking.[166,167] Another pharmacologic aid for smoking cessation, varenicline, was approved in 2006, although it has not yet been studied in patients with serious mental illness. Patients who smoke should be encouraged to try to reduce the amount even if they cannot quit, since this can reduce lung cancer risk; NRT may be helpful in reducing cigarette use.[168] Earlier studies[169] had reported that some patients switched to clozapine appeared to spontaneously reduce or discontinue smoking, however, a more recent study did not find that clozapine had any major effect on smoking, although they could not rule out a small decrease in smoking with clozapine in some subjects.[170]

Summary

Table 6-6 summarizes areas in which medical conditions and problems may influence treatment decisions.

Table 6-6. Areas in which medical conditions and problems may influence treatment decisions*

Characteristic	*Choice of antipsychotic*	*Dosing and titration*	*Comments*
Weight and cardiometabolic risk	Choose/switch to agent with lower weight gain liability and metabolic risk if possible	Dose reductions unlikely to help with weight and metabolic problems	Greater the CVD risk, stronger the recommendation to try to switch APs. Less willingness to switch if prominent risk of harm
Distressing side effects due to prolactin elevation	Lower dose or switch to prolactin sparing antipsychotic	Dose reduction may be helpful if response can be maintained	Educate patients about potential side effects as well as risk of pregnancy after a switch
HIV positive		May need to adjust dose due to interaction with antiretrovirals	
Respiratory disease	Use sedating APs cautiously		Avoid drugs with weight liability in patients with OSA
Smoking		Increased dose of clozapine and olanzapine may be needed	

**Recommendations are based on the Roadmap expert survey unless otherwise indicated*

VII. Clinical Challenges in Applying the Roadmap

THE FIRST-EPISODE PATIENT

Studies have found that duration of untreated psychosis is a predictor of poorer short- and long-term outcomes.[171–174] This highlights the importance of providing the most effective treatment as early as possible for patients with a first episode of psychosis.[173,175] "First-episode" is a clinical term for patients who have recently been evaluated and treated for the first time in the mental health system and have been diagnosed with probable or definite schizophrenia. Because psychotic symptoms are likely to be the focus of treatment in this situation, the primary pharmacologic question will be choice of antipsychotic.

While treating first-episode patients usually occupies only a small part of most practitioners' time, the issues that arise have important ramifications. Since many first-episode patients have never received psychopharmacologic treatment when they present for evaluation, it is important to record baseline data on the person's physical and mental status before starting medication. A record of baseline weight, BMI, and metabolic parameters (e.g., glucose, prolactin, and lipids) will be very important for future decisions should these parameters be affected by antipsychotic medications that are subsequently prescribed.

It is also important to remember that response to antipsychotic medication does not clarify the psychiatric diagnosis. Antipsychotics will treat acute psychotic symptoms regardless of whether the diagnosis will ultimately turn out to be schizophrenia, bipolar disorder, or substance-induced psychosis. Thus, before starting an antipsychotic, clinicians should assess for factors that suggest it might be appropriate to delay initiation of medication (e,g., possible pregnancy, behavioral or neurologic toxicity from recent antipsychotic exposure, or need for a careful neurologic examination unaffected by possible side effects of antipsychotic medication).

Case Example

We presented the following case to the panel:

Patient #1: First episode of psychosis, not yet stabilized. *Mr. Q is a 19-year-old man in his second semester of college. In his last years of high school, his family noted he was "depressed" for months at a time with decreased activity and voluntary isolation; these symptoms did not respond to antidepressant medications or psychotherapy. After starting college, he began to believe his classmates were watching and "controlling" him. His behavior became increasingly bizarre, and he recently returned home to his parents. During the past week, he reported onset of auditory hallucinations, was diagnosed by his primary care physician with schizophrenia, and was referred to your care. He has never received antipsychotic medications, and has no other known health problems.*

Key features and assumptions in this case:

- Patient showed good intellectual and social functioning before onset of schizophrenia prodrome.
- Patient will be adherent to recommended treatment.
- No history of or current substance abuse.
- Good psychosocial support.
- No problems with medication access.
- Normal body mass index (BMI) and normal fasting glucose and lipid profile.

Choice of Antipsychotic Agent for a First Episode

First-episode patients are more likely than chronic patients to achieve a good medication response, so that clinicians should aim for excellent results when treating a first-episode patient. Similar but slightly different issues related to efficacy, safety, and tolerability arise with first-episode compared with more

Table 7-1. Initial dose and titration schedule for a first-episode patient with no complicating conditions affecting dosing*

	Usual starting dose (mg/day) Avg (range)	*Interval between dose increases*	*Usual dose increment*	*Usual initial target dose range (mg/day)*	
				Low	*High*
				Avg (range)	*Avg (range)*
Aripiprazole	10 (5–15)	1 week	5 (or10 mg)	10 (5–15)	25 (20–30)
Olanzapine	10 (5–15)	1 week	5 mg	10 (7.5–12.5)	22.5 (20–30)
Quetiapine	150 (50–250)	3 days (but wide range)	150 mg (but wide range)	300 (but wide range)	800 (600–1000)
Risperidone	1.5 (1–2)	1 week (but wide range)	1.5 mg (but wide range)	2 (1–3)	6 (5–8)
Ziprasidone	60 (40–100)	4 days	40 or 60 mg	100 (60–140)	200 (160–240)
Haloperidol	3 (1–4)	1 week	2–4 mg	5 (2–8)	10 (10–15)

**Mean doses and standard deviations from survey results converted to "real world" doses*

persistently ill patients. First and most obvious, lack of prior treatment trials means that pharmacologic history is not available to help guide medication choice. Because of the stress and opposition to treatment that is common in first-episode patients, any distressing or unexpected medication reaction is more likely to result in a long-term rejection of further treatment and may create a sense of distrust and alienation from mental health services. In choosing the first medication for a patient, it is important to try to minimize risk of sudden, unexpected adverse events that could lead to long-term avoidance of medications. This is especially important since first-episode patients tend to be more sensitive to side effects of antipsychotics than more chronic patients and may have more severe side effects, faster onset of side effects, or greater distress due to the same side effect. Clinicians should keep in mind that there is nothing "good" about having any side effect (the old idea that EPS might be a marker for antipsychotic efficacy has now been clearly disproved).

Choice of medication for psychosis has shifted overwhelmingly to preferential use of second generation antipsychotics (SGAs) over first generation antipsychotics (FGAs). While short-term response rates to FGAs and SGAs are approximately equivalent, SGAs are generally recommended over FGAs for first-episode patients.[51,52] One of the most compelling reasons to favor the newer agents is their lower EPS liability, which translates to fewer neurologic events that could "turn the patient off" to long-term treatment. There is also less need for coprescription of anticholinergic agents (e.g., benztropine) with the SGAs, reducing the incidence of peripheral anticholinergic effects and additional cognitive dysfunction. To date, there is no consensus or definitive evidence that any of the SGAs is preferable to the others, except that, because of side effects, use of clozapine is reserved for patients who fail to respond to adequate trials of other medications or who display active suicidal ideation.

The expert panel indicated that the initial antipsychotic for a patient with a first episode of psychosis, such as Mr. Q in Case #1, should be chosen based on the individual patient's symptoms and risk factors for adverse effects.[175] Reflecting recommendations for treatment of first-episode psychosis in current treatment guidelines,[51,52] the experts recommended an SGA over an FGA for this patient, no matter what information was provided about initial presentation. Studies involving risperidone,[176–178] olanzapine,[178–180] quetiapine,[181,182] and aripiprazole[183] have reported that each of these agents was effective in first-episode schizophrenia, with lower rates of EPS compared with haloperidol, although greater increases in weight and cholesterol levels were seen with olanzapine than with haloperidol.[180] More studies are available for those agents that have been available the longest. No studies of ziprasidone in first-episode patients have yet been published. Results from the European First Episode Schizophrenia Trial (EUFEST), comparing amisulpride, quetiapine, olanzapine, and ziprasidone with a low dose of haloperidol in patients with a first episode of schizophrenia, should be available soon.[184] The following sections summarize the experts' responses concerning how variations in the case presentation above would affect their choice of initial pharmacologic treatment.

Substance abuse: Many patients with a first episode of psychosis present with active substance abuse, which can complicate the diagnostic picture and worsen the prognosis.[185,186] Just as for uncomplicated schizophrenia (p. 21), the experts recommended using an SGA for a first episode of psychosis complicated by substance abuse. They also gave strong support to use of a long-acting injectable formulation in this situation, probably because of concern about poorer adherence to treatment in a patient with active substance abuse.[187]

Homelessness, poor social support, and poor insight: The experts supported use of a long-acting injectable antipsychotic (SGA preferred over FGA) for first-episode patients who are homeless/have poor social support (p. 26) or have poor insight/denial of illness (p. 22), probably reflecting concern about adherence to treatment. Studies have found that denial of illness/lack of insight is one of the strongest predictors of nonadherence to antipsychotic medications.[188,189]

Comorbid psychiatric symptoms: For patients with a first episode of psychosis characterized by prominent anxiety or agitation, the experts gave the most support to quetiapine and olanzapine, probably reflecting the more sedating profile of these agents. For first-episode patients with prominent depressive symptoms, the experts would use one of the SGAs and would avoid haloperidol, probably reflecting the dysphoric qualities associated with this agent.[190]

Dosing

The panel's dosing recommendations for a first-episode patient with no complicating condition are shown in Table 7-1 (mean values and standard deviations were converted to real-world dose equivalents). The recommended doses are very similar to those endorsed in a 2003 expert survey[52] and reflect recommendations to begin with somewhat lower doses for a first episode of illness.[175]

Use of Adjunctive Agents

When starting an antipsychotic, it is important to manage early side effects (see definition below) so the patient can achieve an adequate trial. We asked the experts about including a prophylactic benzodiazepine or anticholinergic when starting different antipsychotics. The experts were very comfortable adding a benzodiazepine to nonsedating antipsychotics such as aripiprazole or ziprasidone, but would not usually consider this strategy with antipsychotics such as olanzapine or quetiapine that are already sedating. The panel would often include a prophylactic anticholinergic when beginning treatment with haloperidol and sometimes with risperidone but did not support use of prophylactic anticholinergics with ziprasidone, aripiprazole, olanzapine, or quetiapine. One of the advantages of starting with one of the SGAs is that, with the possible exception of risperidone, adding an anticholinergic agent is not a routine procedure. For a discussion of pharmacodynamic properties underlying these side effect profiles, see Section III (pp. 11, 15–18).

Early side effect:
Appears within days to weeks of starting or raising the dose of an antipsychotic medication. May be transient and time limited so that there is a good chance that it will abate or disappear after the first month of antipsychotic treatment

Nonpharmacologic Interventions

Although the focus of the Roadmap is pharmacologic treatment, clinicians should keep in mind that medication treatment alone is not sufficient to achieve the best outcomes in a patient with a first episode of psychosis. It is also important to provide patients and families/caregivers with psychoeducation, social support, and case management and to refer patients for appropriate treatment of associated problems (e.g., dual diagnosis treatment if substance abuse is present), help with financial and housing problems, and vocational and rehabilitation services.[175] Studies of psychological interventions, in particular cognitive-behavioral therapy and family interventions, in the treatment of early psychosis have promising early findings, but more controlled research with these strategies in first-episode patients is needed.[191,192] Families and patients can also benefit from referral to programs such as the National Alliance on Mental Illness (NAMI) "Family-to-Family" program.[193] Some excellent books are also available to help patients and families better understand psychotic illness and available treatments.[194–197]

Strategies for Ensuring Continuity of Treatment

Antipsychotic medication is often initiated during an inpatient admission. The experts recommended the following strategies to help ensure continuity of treatment and avoid potential disruptions of care after discharge:

- Provide enough medication at discharge to last several days to allow for time to have a prescription filled.
- Ask how the patient will obtain the medication on an outpatient basis.
- Find out if the patient has insurance coverage and if it will cover the medication being considered.
- If insurance will not cover the medication, ask about patient's/family's ability to pay out of pocket.
- Choose a medication that the patient will be able to afford or obtain free of charge.
- If patient cannot pay for the medication you believe is indicated, contact the pharmaceutical company to see if they will supply medication free of charge or at reduced cost.

FAILURE TO ACHIEVE ADEQUATE ANTIPSYCHOTIC RESPONSE

Sometimes the usual pharmacologic approach fails to achieve an adequate response. The experts were asked about the most appropriate strategies for a first-episode patient who remains floridly psychotic despite two adequate trials of an SGA, with the assumption that the dose and duration of each trial were more than sufficient. The "basic" version of the case involves a 19-year-old man with excellent family supports, who does not have any adherence or substance abuse problems. This is followed by case variations in which the situation is complicated by persistent nonadherence or substance abuse.

Patient #2: Treatment-resistant first episode. *Mr. D, a 19-year-old man diagnosed with psychosis 6 months earlier, was first treated with a nonclozapine SGA. This agent was titrated up to a therapeutic dose but produced little or no response. He was switched to a different nonclozapine SGA, which was titrated up to a therapeutic dose and has been continued at that dose for 10 weeks (or however long you consider an adequate trial). The patient continues to be floridly psychotic (i.e., has auditory hallucinations, hyperreligious delusions, is unable to care for himself). Mr. D's family are no longer willing to have him at home and he was just admitted to the inpatient service for the fourth time in 3 months. When the patient is home, his mother supervises him in taking his antipsychotic.*

Key features and assumptions in this case

- Patient has shown unsatisfactory response to trials of two nonclozapine SGAs (e.g., aripiprazole, olanzapine, risperidone, quetiapine, ziprasidone)
- Trials were at therapeutic dose and of adequate duration
- Patient will be adherent with recommended treatment
- No history of or current substance abuse
- No problems with medication access
- Normal BMI, normal fasting glucose and lipid profile

We also asked about two variants of this clinical situation.

Patient #2 but complicated by lack of adherence: *You discover Mr. D's mother is not able to supervise his medication and she reports the patient often does not take it. How does this affect your choice of treatment strategy, assuming no evidence of substance abuse?*

Patient #2 but complicated by active substance abuse: *Further history reveals Mr. D has been actively abusing cocaine. Each time he has been hospitalized, his urine drug screen was positive for cocaine and he admitted to smoking crack. The patient says he usually takes his medication as prescribed but has trouble remembering what happens when he is intoxicated. How does this affect your treatment strategy?*

The goal of these cases is to answer the following questions:

1. How soon should one consider clozapine for a first-episode patient who is clearly not responding to non-clozapine SGAs? How much support is there for nonclozapine options, such as using an FGA or a combination of antipsychotics?
2. What role do long-acting antipsychotics have in the treatment of first-episode patients, especially if there is a pattern of nonadherence or substance abuse?

As shown in Table 7-2, the panel strongly supported (93% first line ratings) switching a patient such as Mr. D to clozapine even early in the course of the illness, as long as there are not problems with adherence or substance abuse. There was much

Table 7-2. Strategies for treatment resistance recommended in the expert survey

Clinical presentation	*Recommended*	*Also consider*	*Not recommended*
Patient #2 as described	Switch to clozapine		Switch to a depot FGA
Treatment resistance complicated by noncompliance	Switch to long-acting SGA	Switch to a depot FGA	Switch to FGA
Treatment resistance complicated by active substance abuse		Switch to long-acting SGA	Switch to FGA

less enthusiasm for using an FGA or combining antipsychotics. If clozapine is not an option, then the experts recommend continuing with successive treatment trials of other SGAs.

When failure to stabilize was attributed to a pattern of nonadherence, then a long-acting antipsychotic was recommended, with a long-acting injectable SGA preferred to a depot FGA medication. It is important to note that the panel did not hesitate to recommend a long-acting injectable route of administration once a pattern of nonadherence is established, even early in the course of illness.

The experts gave similar recommendations, albeit somewhat less strongly endorsed, when failure to stabilize was associated with substance abuse. The panel may have felt a long-acting regimen would be more reliable during medication gaps related to substance abuse. They gave only limited support to clozapine here, perhaps because they felt the complexities of a clozapine regimen may not be compatible with the chaotic life of an actively psychotic patient with uncontrolled substance abuse.

When asked how the presence of adherence problems would affect their willingness to make an elective switch of antipsychotics, half the panel indicated they would be less willing to switch, perhaps reflecting the belief that changing medications will not improve the situation if the patient is not taking medication as prescribed in the first place. However, nearly 40% indicated that they would be more likely to switch antipsychotics in a patient with adherence problems, possibly reflecting the belief that, if new medication has a better side-effect profile, the patient may be more willing to take it. Or this recommendation may reflect a plan to change to a long-acting injectable formulation (Table 7-2).

PATIENTS WHO ARE UNSTABLE BECAUSE OF WEIGHT GAIN OR METABOLIC COMPLICATIONS

Weight Gain and Metabolic Problems With a Nonclozapine Antipsychotic

A dilemma clinicians increasingly face is a patient who has responded well to an antipsychotic medication but has gained weight or developed metabolic problems that are a cause for concern. We presented the following case to the panel:

Patient #3: A patient who gains weight and develops metabolic risk factors during treatment. *Mr. B is a 21-year-old man who was diagnosed with schizophrenia and started on an antipsychotic. He has been maintained on this medication for 6 months; his symptoms are well controlled with only occasional auditory hallucinations he is generally able to ignore. The patient and family report that Mr. B has better control of his behavior and are pleased with how the medication is working. However, Mr. B has gained 30 lb since beginning this antipsychotic, his BMI has increased from 25 to 29, and his fasting triglyceride level has gone from 130 mg/dL to over 300 mg/dL.*

As shown in Question 8, the panel strongly endorsed switching to a different antipsychotic in this situation, with support increasing as the number of risk factors for CVD rises. In this

Question 8. **Weight gain and metabolic side effects in patients who are symptomatically stable.** Assume you are treating a patient who has achieved a satisfactory response to an antipsychotic and is stable and achieving functional improvements. Unfortunately, the patient is experiencing one of the following side effects that you believe is clearly related to the antipsychotic. Assume you have initiated psychosocial interventions (e.g., nutritional counseling, exercise program) but the problem continues. Please rate the appropriateness of each of the following options as your *initial* strategy in this situation. Refer to the list of CVD risk factors above in answering the items that ask about the presence of a certain number of CVD risk factors. Assume there would be no pressing need to change antipsychotics except for this side effect.

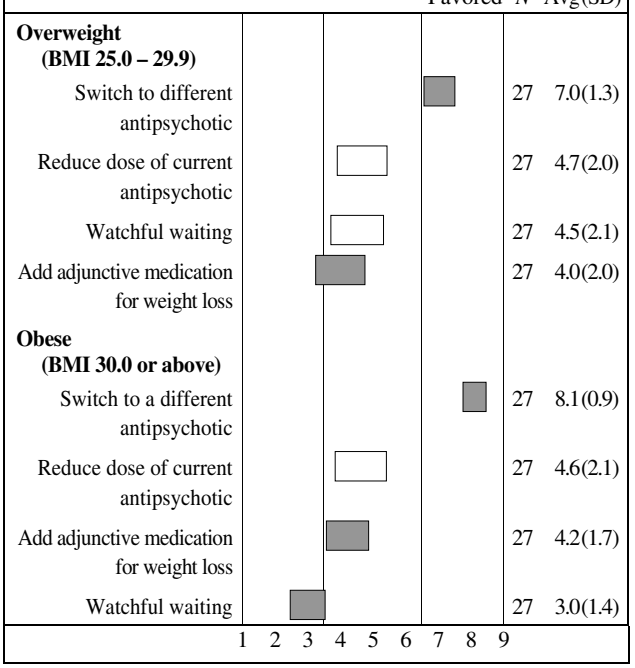


Table 7-3. Switching antipsychotics because of weight gain or metabolic problems

Before switching, evaluate	Is the problem related to current medication? Patient report not always reliable Check pre-treatment weight and/or BMI Are factors that would not respond to medication change contributing (e.g., marijuana use, other medications)?
Consider switching antipsychotics for weight or metabolic problems when	There is clear relationship between antipsychotic medication and a change in health risk (e.g., obesity, sleep apnea, diabetes) Patient has stopped or is about to stop antipsychotic because of weight gain
Cautions to consider and discuss with patient before switching because of weight or metabolic problems	Patient has bulimia or is abusing weight loss drugs Change of antipsychotic will only be effective for weight gain related to antipsychotic medication and will not help with obesity unrelated to antipsychotic exposure If patient has had good response to current antipsychotic, no guarantee next medication will be as effective

situation, the panel recommended choosing an agent with lower liability to cause weight gain and metabolic problems, keeping in mind the patient's treatment history and other medical factors (see Section VI, p. 27 and Table 7-3).

Weight Gain and Metabolic Problems With Clozapine

More complicated issues arise when clozapine is involved. Since most patients being treated with clozapine have a history of nonresponse to other medications or may have been placed on clozapine because of suicidal ideation or behavior, a change of medications must be approached much more cautiously. We presented the panel with the following question:

A patient has gained significant weight and gone from 0 to 3 CVD risk factors after beginning treatment with clozapine. Please rate the appropriateness of trying to switch from clozapine to another antipsychotic in the following situations.

The panel's recommendations were as follows:

Switching from clozapine recommended

- Persistent positive symptoms successfully treated with clozapine. Before clozapine, patient had trials of only two older SGAs (e.g., risperidone, olanzapine, quetiapine).

Switching from clozapine sometimes appropriate

- Able to live independently and hold down part-time job prior to clozapine treatment, but complained of occasional auditory hallucinations and was switched to clozapine.
- Lived independently and occasionally attended psychosocial rehabilitation but had frequent distressing auditory hallucinations and persecutory delusions before clozapine.

Continue clozapine treatment

- Unable to live independently due to persistent psychosis and disorganization until treated with clozapine.
- Consistent history of violence associated with psychosis including assault of family members during entire course of illness until switched to clozapine, which greatly reduced psychotic symptoms and violence.
- History of frequent suicidal ideation with three suicide attempts by ingestion. Markedly reduced suicidal ideation and no suicide attempts with clozapine.

If a patient being treated with clozapine develops metabolic abnormalities and switching from clozapine is not an option, the next step is to treat the metabolic symptoms. For example, metformin could be prescribed for type 2 diabetes; lipid lowering agents could be prescribed for elevated lipid levels. Patients can also be encouraged to make lifestyle changes related to diet, exercise, and smoking. Obviously, addition of more medications does increase the risk for nonadherence and drug interactions as well as the cost of care.

Summary

- Patients with major mental illness are commonly at risk for diabetes and CVD.
- In the setting of increased cardiometabolic risk, the panel recommended choosing/switching to an antipsychotic with lower metabolic risk when clinically possible (p. 28).
- Increases in cardiometabolic risk factors were associated with increased clinical concern.
- Increasing weight gain and increased number of CVD risk factors were associated with increasing strength of the recommendation to attempt a switch.
- Severe psychopathology with prominent risk of harm was associated with increased reluctance to change psychiatric medication for metabolic benefit.

REDUCING BURDEN OF ILLNESS AFTER ACHIEVING STABILITY

A common challenge clinicians face is whether to make a pharmacologic intervention to try to further reduce symptoms or side effects after a patient has achieved psychiatric stability (see definition below). Many patients with psychotic disorders who are "stable" and much improved compared to their worst periods are still far from "well" or "recovered," if defined as a complete absence of symptoms or functional limitations. Some patients may have responded to pharmacologic interventions, such as a

change of medication, but, while doing better than on previous medications, seem unable to achieve further gains; or they may have persistent side effects that are distressing or jeopardize their future health.

An overall treatment approach needs to be established with the patient before it is possible to make specific pharmacologic decisions. The Roadmap survey asked about difficult situations involving potential risk and trade-offs. For example, is it worth trying a new medication in a stable patient who continues to have persistent positive symptoms? What about targets for which a complete response is unlikely, such as persistent negative or cognitive symptoms? Is it better to switch antipsychotics or add an antidepressant for persistent depressive symptoms? Is it worth risking a relapse to switch medications in a patient who has gained weight on the current medication? Often there is no single "right" answer. The following section provides an overview of the experts' responses to these kinds of difficult situations. They were first presented with the following case.

Patient #4: Stable with persistent problems. *Ms. A is a 32-year-old woman ill with schizophrenia since the age of 20. She experienced repeated relapses and hospitalizations during the first 5 years of her illness but has not been hospitalized for the past 6 years since she began taking her medication as prescribed. She is currently taking haloperidol 5 mg twice daily and benztropine 2 mg every morning. Ms. A spends most of her time alone or with family members, especially her mother, who is very involved with her care. Ms. A can shop at stores she knows well and help with cleaning but cannot cook because the directions "confuse and frustrate her." Ms. A says she often feels depressed about her illness and "not worth very much as a person." Ms. A's mother says it is sad to see her daughter lead such an empty life but "I guess we're both used to it now." Ms. A admits that, although the haloperidol "gets rid of the voices" she has felt "stiff and restless" since she has been taking it. When asked about goals, Ms. A says that she had hoped to get married and have a family but believes this will never happen because of her illness and because she no longer has menstrual periods. She says she would like to take courses at the community college but is afraid she won't be able to follow the lectures. She has some dry mouth and blurry vision but says these don't bother her much. When asked if she would consider trying a new medication to see if it would help her lead a more active life, Ms. A expresses worry that her symptoms will return, especially since previous attempts to lower her haloperidol dose caused her symptoms to worsen. Ms. A's mother expresses concern about "rocking the boat."After more discussion and being given information about the newer medications, Ms. A and her mother decide they would be willing to try a new medicine to see if it might improve things.*

Key features and assumptions in this case

- Revolving door course early in illness but now stable (no imminent risk of relapse)
- Some persistent (mainly negative and cognitive) symptoms that seem to have plateaued with current treatment
- Some persistent distressing side effects (e.g., amenorrhea, extrapyramidal symptoms, anticholinergic side effects)
- Has only been treated with haloperidol
- Excellent compliance
- No evidence of substance abuse
- Good psychosocial support
- No problems accessing medication and psychiatric care

Question 10. *Please rate appropriateness of trying to switch Ms. A from haloperidol to a nonclozapine SGA (aripiprazole, olanzapine, risperidone, quetiapine, ziprasidone).*

Nearly all of the experts (96%) considered it very appropriate to switch Ms. A from haloperidol to a nonclozapine SGA.

Definition of Psychiatric Stability

- Patient can remain in current living environment
- Absence of worsening psychiatric symptom that threatens patient's ability to function at current level
- Absence of psychiatric symptom that poses danger to self or others
- Absence of potentially life-threatening medical condition
- No anticipated change in psychosocial support or treatment access that threatens ability to continue as above

Pharmacologic Options for Persistent Symptoms

When considering a pharmacologic intervention for persistent symptoms, it is helpful to consider the following questions:

1. Is the problem amenable to a pharmacologic intervention?
2. Are there other problems or complications (e.g., substance abuse, medication nonadherence) that are interfering with the pharmacologic response to the current agent that might be better addressed through psychosocial (nonpharmacologic) strategies?
3. If this is a pharmacologic problem, what is the best approach to try? Raising or lowering the dose of the current antipsychotic? Adding an adjunctive medication? Combining antipsychotics? Switching to another antipsychotic? Which options are most helpful for which target symptoms?

The experts' recommendations for a patient similar to Ms. A but with a variety of different presentations are summarized in Table 7-4. The panel was relatively enthusiastic about switching antipsychotics for persistent symptoms rather than "leaving well enough alone." Thus it appears they are willing to take some risks in pursuit of a recovery-oriented treatment plan.

Pharmacologic Options for Persistent Side Effects

Many of the same issues arise in approaching persistent side effects. When is it appropriate to "do nothing" and try to wait it out? When it is appropriate to intervene? In making such decisions, clinicians often need to differentiate between side effects that are distressing but not dangerous and those that could jeopardize the future health and well-being of the patient. When a pharmacologic intervention for side effects is warranted, adjusting the dosage and/or adding an adjunctive agent tend to be

more important strategies than when dealing with insufficient efficacy. A key question is when is it appropriate to *switch* antipsychotics because of side effects. Clinicians need to consider whether it is appropriate to intervene for side effects that are distressing but not dangerous. They also need to decide on the best approach for side effects that can lead to serious medical consequences but do not bother the patient, such as elevated lipid levels (i.e., should the psychiatrist act as a medical "advocate" and encourage the patient to accept a pharmacologic intervention for dyslipidemia?).

Table 7-4. Strategies for managing residual symptoms in patients who are stable

Patient stable on haloperidol plus benztropine but has predominant:	*Recommended*	*Also consider*
Positive symptoms	Switch to nonclozapine SGA	(Switch to clozapine)
Negative symptoms	Switch to nonclozapine SGA	Refer to psychosocial treatment Lower the dose of haloperidol
Cognitive symptoms	Lower the dose of benztropine Switch to nonclozapine SGA	Refer to psychosocial treatment Lower the dose of haloperidol
Affective symptoms	Switch to nonclozapine SGA Refer to psychosocial treatment	Add an antidepressant

When switching antipsychotics, clinicians need to consider the potential for long-term complications. As in the short-term, haloperidol is most likely to cause long-term EPS and TD, while clozapine and quetiapine are associated with the fewest EPS. Quetiapine, olanzapine, and clozapine may continue to cause sedation, while haloperidol, ziprasidone, and aripiprazole may continue to cause insomnia. Haloperidol and risperidone are associated with the greatest incidence of prolactin-related side effects (e.g., sexual dysfunction, amenorrhea, galactorrhea). Clozapine is associated with an increased risk of seizures. The panel indicated that quetiapine, clozapine, and olanzapine, followed by risperidone, are associated with the greatest incidence of long-term weight gain and glucose and lipid abnormalities while aripiprazole and ziprasidone are associated with the fewest.

The panel's recommendations for managing side effects in patients who are stable are summarized in Tables 7-3 and 7-5. For a discussion of the pharmacodynamic mechanisms involved in the side effect profiles of the different antipsychotics, see Section III (pp. 11, 15–18). For more detailed discussion of weight and metabolic problems, see Section VI (p. 27) and the case of Mr. B earlier in this section (p. 37). As shown in Table 7-5, whether a dose adjustment or a change of antipsychotics is recommended depends on the specific side effect. For example, EPS and sedation may respond to a dose adjustment, so that lowering the dose if possible is the first strategy recommended for these problems. In contrast, switching antipsychotics is recommended for problems less likely to be amenable to a dose change, such as prolactin-related side effects, weight gain, or persistent anticholinergic problems.

SWITCHING TECHNIQUES

Managing Problems During an Antipsychotic Switch

If it is decided to make an elective change of antipsychotics to try to achieve better symptomatic response or reduce side effects, it is important to try to minimize side effects during the switch so the patient can have an adequate trial of the new medication to see if it will be of benefit.[198–200] We asked the expert panel to rate different antipsychotics in terms of complexity of use and potential to cause a variety of short-term problems.

Complexity in Switching

The panel indicated that clozapine poses the most difficulties in switching and reaching a therapeutic dose, followed by ziprasidone and quetiapine, and that it is easiest to reach a therapeutic dose of olanzapine.

Laboratory Monitoring

Because of the need for regular blood monitoring for agranulocytosis, clozapine obviously requires the most complicated laboratory monitoring. The experts indicated that the antipsychotics associated with the most liability for weight gain and elevated lipid and glucose levels (clozapine and olanzapine, followed by risperidone and quetiapine) require the most monitoring of glucose and lipid levels.

Short-Term Side Effects During Switching

We asked the experts about the potential for a number of short-term side effects with different antipsychotics.

EPS. The panel indicated that haloperidol has the greatest propensity to cause EPS (akathisia, parkinsonian symptoms) while clozapine and quetiapine are associated with the fewest EPS. The experts supported including a prophylactic anticholinergic agent in the treatment regimen when initiating treatment with haloperidol and would sometimes use a prophylactic anticholinergic when initiating treatment with risperidone.

Early activation/insomnia. The experts rated olanzapine, quetiapine, and clozapine as most likely to cause sedation early in treatment, and aripiprazole and ziprasidone as most likely to cause early insomnia or activation (see definition below). To minimize early insomnia or activation, the experts would sometimes include a benzodiazepine in the regimen, especially when starting aripiprazole or ziprasidone. Early activation and insomnia with ziprasidone are associated with lower doses and can be minimized by rapidly titrating the dose up to at least 80 mg/day and preferably 120 mg/day (60 mg bid), which is also associated with greater therapeutic response.[198] It is believed that activation at lower doses of ziprasidone is related to the serotonin 5-HT_{1A} activation occurring at lower doses, an effect that is mitigated by D_2 receptor antagonism at higher doses (see pp. 14

Table 7-5. Strategies for managing side effects in patients who are stable

Side effect	*Recommended*	*Also consider*
Parkinsonian symptoms or akathisia	Dose adjustment	Add adjunctive medication Switch to different antipsychotic
Tardive dyskinesia	Switch to different antipsychotic	Dose adjustment
Persistent sedation	Dose adjustment	Switch to different antipsychotic
Persistent insomnia		Add adjunctive medication Dose adjustment Switch to different antipsychotic
Prolactin-related side effects (e.g., amenorrhea, galactorrhea)	Dose adjustment Switch to different antipsychotic	
Sexual difficulties judged to be due to the antipsychotic		Switch to a different antipsychotic Dose adjustment
Anticholinergic side effects of antipsychotic	Dose adjustment Switch to a different antipsychotic	
Anticholinergic side effects related to adjunctive anticholinergic agent	Dose adjustment of anticholinergic Switch to antipsychotic with lower EPS liability with plan to then discontinue anticholinergic agent	Dose adjustment of antipsychotic

and 17). Conversely, early activation and insomnia with aripiprazole are believed to be associated with dopamine agonism and are more common at higher doses (see p. 14). Since aripiprazole appears to have a "flat" dose response curve between 15 and 30 mg/day, early activation can be minimized by aiming for a target dose at the lower end of that range.[198]

Early "activation"

A term that is often used, but with little clinical specificity, to refer to unwanted feelings of excess energy, restlessness, or insomnia associated with beginning treatment with an antipsychotic medication. This nonspecific term is often used because it is very difficult to differentiate the contribution of akathisia, agitation, and lack of sedation to "activation."

Nausea. The experts consider aripiprazole and ziprasidone most likely to be associated with early nausea, which usually subsides after about 2 weeks. It is helpful to take the medication with meals (note that ziprasidone must be taken with food to achieve adequate levels). Nausea is a dose-sensitive side effect and responds to dose lowering.[198]

CONCLUSION

This Roadmap publication has reviewed key issues in the use of antipsychotics in order to facilitate clinical decision-making, with the ultimate goal of improving outcomes for patients with serious psychiatric disorders. The approach used here is somewhat different from that of other psychopharmacology reviews. We emphasize the importance of identifying the treatment model to be used for the individual patient. We simplified this complex area into two basic approaches: the maintenance model, emphasizing stability, and the recovery model, emphasizing the goal of regaining health and self. The challenge clinicians face is how to best achieve the treatment objectives they have identified with the patient, given the range of currently available antipsychotic medications. The Roadmap approach is based on the belief that it is often possible to achieve better outcomes by integrating clinical evidence with what is known about the pharmacologic properties of antipsychotics. An understanding of the pharmacodynamic and pharmacokinetic characteristics of the different agents—as well as differences among the antipsychotics in these characteristics—can help guide treatment selection and dosing decisions, and enable the clinician to minimize acute and long-term complications.

Because pharmacodynamic principles can supplement—but not substitute for—evidence-based data from clinical trials, we integrated these approaches in this publication and provided guidance based on expert opinion about common clinical situations clinicians face in treating serious mental illness. There will of course be times when treatment objectives conflict or there is uncertainty about which of several competing objectives should take priority. The Roadmap survey asked the experts about these types of difficult situations, and their answers are reviewed here. But this is not and cannot be the final word. All patients are unique. Undoubtedly, as our treatments continue to improve, we will face new dilemmas and still more complex decisions. As much as possible, the best expert to consult is your patient. As stressed by the President's New Freedom Commission report,[1] a major component of the recovery model is a process in which the patient is actively involved in both defining his or her goals and working to achieve them.

REFERENCES

1. The President's New Freedom Commission on Mental Health. Achieving the Promise: Transforming Mental Health Care in America. Final Report. Department of Health and Human Services Publication No. SMA-03-3832. Rockville, MD, July 2003 (available at www.mentalhealthcommission.gov/reports/finalreport/fullreport-02.htm)
2. Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. Prev Chronic Dis 2006;3:A42
3. Casey DE, Haupt DW, Newcomer JW, Henderson DC, Sernyak MJ, Davidson M, and others. Antipsychotic-induced weight gain and metabolic abnormalities: implications for increased mortality in patients with schizophrenia. J Clin Psychiatry 2004;65(suppl 7):4–18
4. West JC, Wilk JE, Olfson M, et al. Patterns and quality of treatment for patients with schizophrenia in routine psychiatric practice. Psychiatric Serv 2005;56:283–291
5. Preskorn SH. Relating clinical trials to psychiatric practice: Part II: The gap between the usual patient in registration trials and in practice. J Psychiatr Pract 2003;9:455–461
6. Zimmerman M, Mattia JI, Posternak MA. Are subjects in pharmacological treatment trials of depression representative of patients in routine clinical practice? Am J Psychiatry 2002;159:469–473
7. Zimmerman M, Chelminski I, Posternak MA. Exclusion criteria used in antidepressant efficacy trials: consistency across studies and representativeness of samples included. J Nerv Ment Dis 2004;192:87–94
8. Storosum JG, Fouwels A, Gispen-de Wied CC, et al. How real are patients in placebo-controlled studies of acute manic episode? Eur Neuropsychopharmacol 2004;14:319–323
9. Mulder RT, Frampton C, Joyce PR, et al. Randomized controlled trials in psychiatry. Part II: their relationship to clinical practice. Aust N Z J Psychiatry 2003;37:265–269
10. Zarin DA, Young JL, West JC. Challenges to evidence-based medicine: a comparison of patients and treatments in randomized controlled trials with patients and treatments in a practice research network. Soc Psychiatry Psychiatr Epidemiol 2005;40:27–35
11. Brook RH, Chassin MR, Fink A, et al. A method for the detailed assessment of the appropriateness of medical technologies. Int J Tech Assess Health Care 1986;2:53–63
12. McNeil B, Pauker SG, Sox HC Jr., et al. On the elicitation of preferences for alternative therapies. N Engl J Med 1982;306:1259–1262
13. Slovic P. The construction of preference. Am Psychol 1995;50:364–371
14. Nasrallah HA, Targum SD, Tandon R, et al. Defining and measuring clinical effectiveness in the treatment of schizophrenia. Psychiatr Serv 2005;56:273–282.
15. Bellack AS. Scientific and consumer models of recovery in schizophrenia: concordance, contrasts, and implications. Schizophr Bull 2006;32: 432–442
16. Diamond RJ. Recovery from a psychiatrist's viewpoint. Postgrad Med 2006; Sep (Spec No):54–62
17. Tandon R, Targum SD, Nasrallah HA, et al. Strategies for maximizing clinical effectiveness in the treatment of schizophrenia. J Psychiatr Pract 2006;12:348–363
18. Davidson L, O'Connell M, Tondora J, Styron T, Kangas K. The top ten concerns about recovery encountered in mental health system transformation. Psychiatr Serv. 2006;57(5):640–645.
19. Andresen R, Oades L, Caputi P. The experience of recovery from schizophrenia: towards an empirically validated stage model. Aust N Z J Psychiatry. 2003;37:586–594
20. Meltzer HY, Matsubara S, Lee JC. Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin2 pKi values. J Pharmacol Exp Ther 1989;251:238–246
21. Kane JM, Marder SR, Schooler NR, et al. Clozapine and haloperidol in moderately refractory schizophrenia: a 6-month randomized and double-blind comparison. Arch Gen Psychiatry 2001;58:965–972
22. Meltzer HY, Alphs L, Green AI, et al. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). Arch Gen Psychiatry 2003;60:82–91
23. McEvoy JP, Lieberman JA, Stroup TS, et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. Am J Psychiatry 2006;163:600–610
24. Gardner DM, Baldessarini RJ, Waraich P. Modern antipsychotic drugs: a critical overview. CMAJ 2005;172:1703–1711
25. *Preskorn SH. Classification of neuropsychiatric medications by principal mechanism of action: a meaningful way to anticipate pharmacodynamically mediated drug interactions (part I). J Psychiatr Pract 2003;9:376–384
26. *Preskorn SH. Clinical application of the concept of relative potency: An example involving chlorpromazine and haloperidol. J Psychiatr Pract 2005;11:258–261
27. Richelson E. Pharmacology of antidepressants: characteristics of the ideal drug. Mayo Clinic Proceedings 1994;69:1069–1081
28. Abilify package insert. Bristol-Meyers Squibb
29. Arnt J, Skarsfeldt T. Do novel antipsychotics have similar pharmacological characteristics? A review of the evidence. Neuropsychopharmacology 1998;18:63–101
30. Bymaster FP, Hemrick-Luecke SK, Perry KW, et al. Neurochemical evidence for antagonism by olanzapine of dopamine, serotonin, alpha 1-adrenergic and muscarinic receptors in vivo in rats. Psychopharmacology (Berl) 1996;124(1-2):87–94
31. Seeger TF, Seymour PA, Schmidt AW, et al. Ziprasidone (CP-88,059): a new antipsychotic with combined dopamine and serotonin receptor antagonist activity. J Pharmacol Exp Ther 1995;275:101–113
32. *Preskorn SH. The slippery slide. J Pract Psychiatry Behav Health 1999; 5:50–55
33. Burris KD, Molski TF, Xu C, et al. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. J Pharmacol Exp Ther 2002;302:381–389.
34. Yokoi F, Grunder G, Biziere K, et al. Dopamine D2 and D3 receptor occupancy in normal humans treated with the antipsychotic drug aripiprazole (OPC 14597): a study using positron emission tomography and [11C]raclopride. Neuropsychopharmacology 2002;27:248–259
35. Ross EM, Kinakin TP. Pharmacodynamics: mechanisms of drug action and the relationship between drug concentration and effect.. In: Hardman JG, Limbird LE, Gilman AG, eds. Goodman & Gilman's The Pharmacologic Basis of Therapeutics, 10th edition. New York: McGraw-Hill; 2001:31–44
36. *Preskorn SH. Defining "is." J Pract Psychiatry Behav Health 1999;5: 224–228
37. Nyberg S, Farde L, Halldin C. Test-retest reliability of central [11C]raclopride binding at high D2 receptor occupancy: a PET study in haloperidol-treated patients. Psychiatry Res 1996;67:163–171
38. Fischman AJ, Bonab AA, Babich JW, et al. Positron emission tomographic analysis of central 5-hydroxytryptamine2 receptor occupancy in healthy volunteers treated with the novel antipsychotic agent, ziprasidone. J Pharmacol Exp Ther 1996;279(2):939–947
39. Bench CJ, Lammertsma AA, Grasby PM, et al. The time course of bind-

*Can be accessed at www.preskorn.com

ing to striatal dopamine D2 receptors by the neuroleptic ziprasidone (CP-88,059-01) determined by positron emission tomography. Psychopharmacology (Berl) 1996;124:141–147
40. Goff DC, Posever T, Herz L, et al. An exploratory haloperidol-controlled dose-finding study of ziprasidone in hospitalized patients with schizophrenia or schizoaffective disorder. J Clin Psychopharmacol 1998;18:296–304
41. Roberts H, Warrington L, Loebel A, et al. Ziprasidone in the treatment of schizophrenia: evidence for a linear dose-response relationship. Schizophr Bull 2007;33:477 (abstract)
42. Frankle WG, Gil R, Hackett E, et al. Occupancy of dopamine D2 receptors by the atypical antipsychotic drugs risperidone and olanzapine: theoretical implications. Psychopharmacology (Berl) 2004;175(4):473–480
43. *Preskorn SH. Drugs are an acquired source of biological variance among patients. J Psychiatr Pract 2006;12:391–396
44. Preskorn SH, Silkey B, Shah R, et al. Complexity of medication use in the Veterans Affairs healthcare system: part I: Outpatient use in relation to age and number of prescribers. J Psychiatr Pract 2005;11:5–15
45. Silkey B, Preskorn SH, Golbeck A, et al. Complexity of medication use in the Veterans Affairs healthcare system: part II: Antidepressant use among younger and older outpatients. J Psychiatr Pract 2005;11:16–26
46. *Preskorn SH. Multiple medication use in patients seen in the Veterans Affairs healthcare system: so what? J Psychiatr Pract 2005;11:46–50
47. Levy RH, Thummel KE, Trager WF, et al. Metabolic Drug Interactions. Philadelphia: Lippincott, Williams & Wilkins; 2000
48. Preskorn SH. Flockhart DA. 2006 guide to psychiatric drug interactions. Primary Psychiatry 2006;13:35–64
49. de Leon J, Susce MT, Pan RM, et al. The CYP2D6 poor metabolizer phenotype may be associated with risperidone adverse drug reactions and discontinuation. J Clin Psychiatry 2005;66:15–27.
50. Preskorn S, Werder S. Detrimental antidepressant drug-drug interactions: are they clinically relevant? Neuropsychopharmacology. 2006;31: 1605–1612; discussion 1613
51. Lehman AF, Lieberman JA, Dixon LB, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. Am J Psychiatry 2004;161(2 Suppl):1–56
52. Kane JM, Leucht S, Carpenter D, et al. The Expert Consensus Guideline Series: Optimizing pharmacologic treatment of psychotic disorders. J Clin Psychiatry 2003;64(suppl 12):1–100
53. American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder (revision). Am J Psychiatry 2002;159(4 Suppl):1–50
54. Keck PE, Perlis RH, Otto MW, et al. The Expert Consensus Guideline Series: treatment of bipolar disorder 2004. Postgrad Med Spec Rep 2004; December: 1–120
55. Diaz E, Neuse E, Sullivan MC, et al. Adherence to conventional and atypical antipsychotics after hospital discharge. J Clin Psychiatry 2004;65:354–360
56. Ziedonis DM. Integrated treatment of co-occurring mental illness and addiction: clinical intervention, program, and system perspectives. CNS Spectr 2004;9:892–904, 925
57. Ziedonis DM, Smelson D, Rosenthal RN, et al. Improving the care of individuals with schizophrenia and substance use disorders: consensus recommendations. J Psychiatr Pract 2005;11:315–339
58. American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. J Clin Psychiatry 2004;65:267–272
59. Olfson M, Blanco C, Liu L, et al. National trends in the outpatient treatment of children and adolescents with antipsychotic drugs. Arch Gen Psychiatry 2006;63:679–685
60. Patel NC, Crismon ML, Hoagwood K, et al. Trends in the use of typical and atypical antipsychotics in children and adolescents. J Am Acad Child Adolesc Psychiatry 2005;44:548–556
61. AACAP Official Action. Practice Parameter for the Assessment and Treatment of Children and Adolescents With Schizophrenia. J Am Acad Child Adolesc Psychiatry 2001;40(7 Suppl):4S–23S
62. Kapetanovic S, Simpson GM. Review of antipsychotics in children and adolescents. Expert Opin Pharmacother 2006;7:1871–1885
63. Sikich L, Hamer RM, Bashford RA, et al. A pilot study of risperidone, olanzapine, and haloperidol in psychotic youth: a double-blind, randomized, 8-week trial. Neuropsychopharmacology 2004;29:133–145
64. Kumra S, Jacobsen LK, Lenane M, et al. Childhood-onset schizophrenia: an open-label study of olanzapine in adolescents. J Am Acad Child Adolesc Psychiatry 1998;37:377–385
65. Findling RL, McNamara NK, Youngstrom EA, et al. A prospective, open-label trial of olanzapine in adolescents with schizophrenia. J Am Acad Child Adolesc Psychiatry 2003;42:170–175
66. Sholevar EH, Baron DA, Hardie TL. Treatment of childhood-onset schizophrenia with olanzapine. J Child Adolesc Psychopharmacol 2000;10: 69–78
67. Zalsman G, Carmon E, Martin A, et al. Effectiveness, safety, and tolerability of risperidone in adolescents with schizophrenia: an open-label study. J Child Adolesc Psychopharmacol 2003;13:319–327
68. Armenteros JL, Whitaker AH, Welikson M, et al. Risperidone in adolescents with schizophrenia: an open pilot study. J Am Acad Child Adolesc Psychiatry 1997;36:694–700
69. Kumra S, Frazier JA, Jacobsen LK, et al. Childhood-onset schizophrenia. A double-blind clozapine-haloperidol comparison. Arch Gen Psychiatry 1996;53:1090–1097
70. Shaw P, Sporn A, Gogtay N, ete al. Childhood-onset schizophrenia: A double-blind, randomized clozapine-olanzapine comparison. Arch Gen Psychiatry 2006;63:721–730
71. Kranzler H, Roofeh D, Gerbino-Rosen G, et al. Clozapine: its impact on aggressive behavior among children and adolescents with schizophrenia. J Am Acad Child Adolesc Psychiatry 2005;44:55–63
72. Mozes T, Greenberg Y, Spivak B, et al. Olanzapine treatment in chronic drug-resistant childhood-onset schizophrenia: an open-label study. J Child Adolesc Psychopharmacol 2003;13:311–317
73. Ross RG, Novins D, Farley GK, et al. A 1-year open-label trial of olanzapine in school-age children with schizophrenia. J Child Adolesc Psychopharmacol 2003;13:301–309
74. McConville BJ, Arvanitis LA, Thyrum PT, et al. Pharmacokinetics, tolerability, and clinical effectiveness of quetiapine fumarate: an open-label trial in adolescents with psychotic disorders. J Clin Psychiatry 2000;61:252–260
75. Mozes T, Ebert T, Michal SE, et al. An open-label randomized comparison of olanzapine versus risperidone in the treatment of childhood-onset schizophrenia. J Child Adolesc Psychopharmacol 2006;16:393–403
76. McGlashan TH, Zipursky RB, Perkins D, et al. Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. Am J Psychiatry 2006;163:790–799
77. Arango C, Parellada M, Moreno DM. Clinical effectiveness of new generation antipsychotics in adolescent patients. Eur Neuropsychopharmacol. 2004;14(suppl 4):S471–479
78. Harrigan SM, McGorry PD, Krstev H. Does treatment delay in first-episode psychosis really matter? Psychol Med 2003;33:97–110
79. Alexopoulos GS, Strein J, Carpenter D, et al. The expert consensus guideline series: using antipsychotic medications in older patients. J Clin

Psychiatry 2004;65(suppl 2):1–105
80. Bjerrum L, Sogaard J, Hallas J, et al. Polypharmacy: correlations with sex, age and drug regimen: a prescription database study. Eur J Clin Pharmacol 1998;54:197–202
81. Rosholm JU, Bjerrum L, Hallas J, et al. Polypharmacy and the risk of drug-drug interactions among Danish elderly: a prescription database study. Dan Med Bull 1998;45:210–213
82. Alexopoulos GS, Jeste DV, Chung H, et al. The expert consensus guideline series: treatment of dementia and its behavioral disturbances. Postgrad Spec Rep January 2005:1–108
83. Szymanski S, Lieberman JA, Alvir JM, et al. Gender differences in onset of illness, treatment response, course, and biologic indexes in first-episode schizophrenic patients. Am J Psychiatry 1995;152:698–703
84. Kelly DL, Conley RR, Tamminga CA. Differential olanzapine plasma concentrations by sex in a fixed-dose study. Schizophr Res 1999;40: 101–104
85. Aichhorn W, Whitworth AB, Weiss EM, et al. Second-generation antipsychotics: is there evidence for sex differences in pharmacokinetic and adverse effect profiles? Drug Saf 2006;29:587–598
86. Leung A, Chue P. Sex differences in schizophrenia, a review of the literature. Acta Psychiatr Scand Suppl 2000;401:3–38
87. Kinon BJ, Gilmore JA, Liu H, et al. Hyperprolactinemia in response to antipsychotic drugs: characterization across comparative clinical trials. Psychoneuroendocrinology 2003;28(Suppl 2):69–82
88. Olfson M, Mechanic D, Hansell S, et al. Predicting medication noncompliance after hospital discharge among patients with schizophrenia. Psychiatr Serv 2000;51:216–222
89. Opler LA, White L, Caton CL, et al. Gender differences in the relationship of homelessness to symptom severity, substance abuse, and neuroleptic noncompliance in schizophrenia. J Nerv Ment Dis 2001;189: 449–456
90. Sajatovic M, Valenstein M, Blow FC, et al. Treatment adherence with antipsychotic medications in bipolar disorder. Bipolar Disord 2006;8: 232–241
91. Harris EC, Barraclough B. Excess mortality of mental disorder. Br J Psychiatry 1998;173:11–53
92. Osby U, Correia N, Brandt L, et al. Mortality and causes of death in schizophrenia in Stockholm county, Sweden. Schizophr Res 2000;45: 21–28
93. Allison DB, Fontaine KR, Heo M, et al. The distribution of body mass index among individuals with and without schizophrenia. J Clin Psychiatry 1999;60:215–220
94. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156: 1686–1696
95. Osby U, Correia N, Brandt L, et al. Time trends in schizophrenia mortality in Stockholm county, Sweden: cohort study. BMJ 2000;321:483–484
96. Davidson S, Judd F, Jolley D, et al. Cardiovascular risk factors for people with mental illness. Aust N Z J Psychiatry 2001;35:196–202
97. Dixon L, Postrado L, Delahanty J, et al. The association of medical comorbidity in schizophrenia with poor physical and mental health. J Nerv Ment Dis 1999;187:496–502
98. McElroy SL, Frye MA, Suppes T, et al. Correlates of overweight and obesity in 644 patients with bipolar disorder. J Clin Psychiatry 2002;63: 207–213
99. Cassidy F, Ahearn E, Carroll BJ. Elevated frequency of diabetes mellitus in hospitalized manic-depressive patients. Am J Psychiatry 1999;156: 1417–1420
100. Ucok A, Polat A, Bozkurt O, et al. Cigarette smoking among patients with schizophrenia and bipolar disorders. Psychiatry Clin Neurosci 2004;58:434–437
101. Herran A, de Santiago A, Sandoya M, et al. Determinants of smoking behaviour in outpatients with schizophrenia. Schizophr Res 2000;41: 373–381.
102. Goff DC, Sullivan LM, McEvoy JP, et al. A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. Schizophr Res 2005;80:45–53
103. McEvoy JP, Meyer JM, Goff DC, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. Schizophr Res 2005;80:19–32
104. Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97:1837–1847 (http://www.nhlbi.nih.gov/about/framingham/riskabs.htm)
105. Sattar N, Gaw A, Scherbakova O, et al. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. Circulation. 2003;108:414–419
106. Ridker PM, Buring JE, Cook NR, et al. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. Circulation 2003;107: 391–397
107. Banerji MA, Lebowitz J, Chaiken RL, et al. Relationship of visceral adipose tissue and glucose disposal is independent of sex in black NIDDM subjects. Am J Physiol 1997;273:E425–432
108. Haffner SM. Pre-diabetes, insulin resistance, inflammation and CVD risk. Diabetes Res Clin Pract 2003;61(Suppl 1):S9–S18
109. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2004;27(Suppl 1):S5–S10
110. American Diabetes Association. Screening for type 2 diabetes. Diabetes Care 2004;27(Suppl 1):S11–14
111. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143–3421
112. Houseknecht KL, Robertson AS, Johnson DE, et al. Diabetogenic effects of some atypical antipsychotics: rapid, whole body insulin resistance following a single dose. Diabetologia 2005;48(Suppl 1):A212 (abstract).
113. Ader M, Kim SP, Catalano KJ, et al. Metabolic dysregulation with atypical antipsychotics occurs in the absence of underlying disease: a placebo-controlled study of olanzapine and risperidone in dogs. Diabetes 2005;54:862–871
114. Koller EA, Doraiswamy PM. Olanzapine-associated diabetes mellitus. Pharmacotherapy 2002;22:841–852
115. Koller EA, Cross JT, Doraiswamy PM, et al. Risperidone-associated diabetes mellitus: a pharmacovigilance study. Pharmacotherapy 2003;23: 735–744
116. Koller EA, Weber J, Doraiswamy PM, et al. A survey of reports of quetiapine-associated hyperglycemia and diabetes mellitus. J Clin Psychiatry 2004;65:857–863
117. Newcomer JW, Haupt DW, Melson AK, et al. Fasting plasma lipids, glucose and insulin, and c-reactive protein are related to adiposity in schizophrenia. Schizophr Res 2003;60:363
118. Newcomer JW, Haupt DW. The metabolic effects of antipsychotic medications. Can J Psychiatry 2006;51:480–491
119. Collaborative Working Group on Clinical Trial Evaluations. Adverse effects of the atypical antipsychotics. J Clin Psychiatry 1998;59(Suppl

12):17–22
120. Leadbetter R, Shutty M, Pavalonis D, et al. Clozapine-induced weight gain: prevalence and clinical relevance. Am J Psychiatry 1992;149:68–72
121. Gupta S, Droney T, Al-Samarrai S, et al. Olanzapine-induced weight gain. Ann Clin Psychiatry 1998;10:39
122. Kraus T, Haack M, Schuld A, et al. Body weight and leptin plasma levels during treatment with antipsychotic drugs. Am J Psychiatry 1999;156:312–314
123. Simpson GM, Glick ID, Weiden PJ, et al. Randomized, controlled, double-blind multicenter comparison of the efficacy and tolerability of ziprasidone and olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. Am J Psychiatry 2004;161:1837–1847
124. Jody D, Saha AR, Iwamoto T. Meta-analysis of weight effects with aripiprazole. Int J Neuropsychopharmacol 2002;5(suppl 1):S186
125. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; 353:1209–1223
126. Stroup TS, Lieberman JA, McEvoy JP, et al. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. Am J Psychiatry 2006;163:611–622
127. Klein S, Wadden T, Sugerman HJ. AGA technical review on obesity. Gastroenterology 2002;123:882–932
128. Standards of medical care in diabetes-2006. Diabetes Care 2006;29(suppl 1):S4–42
129. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206–1252
130. Kahn R, Buse J, Ferrannini E, et al. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2005;28:2289–2304
131. Casey DE. Implications of the CATIE trial on treatment: extrapyramidal symptoms. CNS Spectr 2006;11(7 Suppl 7):25–31
132 Haro JM, Salvador-Carulla L. The SOHO (Schizophrenia Outpatient Health Outcome) study: implications for the treatment of schizophrenia. CNS Drugs 2006;20:293–301
133. Weiden PJ. EPS profiles: the atypical antipsychotics are not all the same. J Psychiatr Pract 2007;13:13–24
134. de Leon J. The effect of atypical versus typical antipsychotics on tardive dyskinesia: a naturalistic study. Eur Arch Psychiatry Clin Neurosci 2007; 257:169–172
135. Remington G. Tardive dyskinesia: eliminated, forgotten, or overshadowed? Curr Opin Psychiatr 2007;20:131–137
136. Miller DD, McEvoy JP, Davis SM, et al. Clinical correlates of tardive dyskinesia in schizophrenia: baseline data from the CATIE schizophrenia trial. Schizophr Res 2005;80:33–43.
137. Gentile S. Extrapyramidal adverse events associated with atypical antipsychotic treatment of bipolar disorder. J Clin Psychopharmacol 2007;27:35–45
138. Ben-Jonathan N, Hnasko R. Dopamine as a prolactin (PRL) inhibitor. Endocr Rev 2001;22:724–763
139. El-Sayeh HG, Morganti C, Adams CE. Aripiprazole for schizophrenia. Systematic review. Br J Psychiatry 2006;189:102–108
140. Covell NH, Jackson CT, Weissman EM. Health monitoring for patients who have schizophrenia: Summary of the Moount Sinai Conference recommendations. In: Weiden PJ, Ross R, eds. New Directions in Psychopharmacology and Recovery in Schizophrenia. Postgrad Med September 2006;Spec No:20–26
141. Cournos F, McKinnon K. HIV seroprevalence among people with severe mental illness in the United States: a critical review. Clin Psychol Rev 1997;17:259–269
142. Blank MB, Mandell DS, Aiken L, et al. Co-occurrence of HIV and serious mental illness among Medicaid recipients. Psychiatr Serv 2002; 53:868–873
143. Rosenberg SD, Goodman LA, Osher FC, et al. Prevalence of HIV, hepatitis B, and hepatitis C in people with severe mental illness. Am J Public Health 2001;91:31–37
144. Thompson A, Silverman B, Dzeng L, et al. Psychotropic medications and HIV. Clin Infect Dis 2006;42:1305–1310
145. American Psychiatric Association Work Group on HIV/AIDS.. Practice guideline for the treatment of patients with HIV/AIDS. Am J Psychiatry 2000;157(11 Suppl):1–62 (avaiable at www.psychiatryonline.com/content.aspx?aID=43997).
146. Forstein M, Cournos F, Douaihy A, et al. American Psychiatric Association Practice Guidelines: Guideline Watch: Practice Guideline for the Treatment of Patients With HIV/AIDS, updated April 2006 (available at www.psychiatryonline.com/content.aspx?aID=147976)
147. Weiser SD, Wolfe WR, Bangsberg DR. The HIV epidemic among individuals with mental illness in the United States. Curr HIV/AIDS Rep 2004;1:186–1192
148. Walkup JT, Sambamoorthi U, Crystal S. Use of newer antiretroviral treatments among HIV-infected medicaid beneficiaries with serious mental illness. J Clin Psychiatry 2004;65:1180–1189
149. Wagner GJ, Kanouse DE, Koegel P, Sullivan G. Adherence to HIV antiretrovirals among persons with serious mental illness. AIDS Patient Care STDS 2003;17:179–186
150. Weiden PJ, Weiden MD, Aneja J. When schizophrenia is complicated by respiratory symptoms: implications for psychopharmacologic therapy. In: Dewan NA, Nasrallah HA, Keck PE, Jr. Schizophrenia: The Clinician's Guide to Pharmacotherapy for Patients with Co-occurring Medical Conditions. Current Psychiatry 2005:31–43 (available at www.currentpsychiatry.com/pages_supplementarchive.asp)
151. Mouallem M, Wolf I. Olanzapine-induced respiratory failure. Am J Geriatr Psychiatry 2001;9:304–305
152. Joseph KS. Asthma mortality and antipsychotic or sedative use. What is the link? Drug Saf 1997;16:351–354
153. Hatta K, Takahashi T, Nakamura H, et al. Prolonged upper airway instability in the parenteral use of benzodiazepine with levomepromazine. J Clin Psychopharmacol 2000;20:99–101
154. Koenig SM. Pulmonary complications of obesity. Am J Med Sci 2001;321:249–279
155. Gami AS, Caples SM, Somers VK. Obesity and obstructive sleep apnea. Endocrinol Metab Clin North Am 2003;32:869–894
156. Winkelman JW. Schizophrenia, obesity, and obstructive sleep apnea. J Clin Psychiatry 2001;62:8–11
157. Wirshing DA, Pierre JM, Wirshing WC. Sleep apnea associated with antipsychotic-induced obesity. J Clin Psychiatry 2002;63:369–370
158. McCreadie RG; on behalf of the Scottish Schizophrenia Lifestyle Group. Diet, smoking and cardiovascular risk in people with schizophrenia: descriptive study. Br J Psychiatry 2003;183:534–539
159. Sacco KA, Termine A, Seyal A, et al. Effects of cigarette smoking on spatial working memory and attentional deficits in schizophrenia: involvement of nicotinic receptor mechanisms. Arch Gen Psychiatry 2005;62: 649–659
160. Williams JM, Ziedonis DM, Abanyie F, et al. Increased nicotine and cotinine levels in smokers with schizophrenia and schizoaffective disorder is not a metabolic effect. Schizophr Res 2005;79:323–335
161. Myers CS, Robles O, Kakoyannis AN, et al. Nicotine improves delayed recognition in schizophrenic patients. Psychopharmacology (Berl)

2004;174:334–340
162. de Leon J, Diaz FJ, Aguilar MC, et al. Does smoking reduce akathisia? Testing a narrow version of the self-medication hypothesis. Schizophr Res 2006;86:256–68
163. Barnes M, Lawford BR, Burton SC, et al. Smoking and schizophrenia: is symptom profile related to smoking and which antipsychotic medication is of benefit in reducing cigarette use? Aust N Z J Psychiatry 2006;40:575–580
164. Haslemo T, Eikeseth PH, Tanum L, et al. The effect of variable cigarette consumption on the interaction with clozapine and olanzapine. Eur J Clin Pharmacol. 2006;62:1049–1053
165. Steinberg ML, Ziedonis DM, Krejci JA, et al. Motivational interviewing with personalized feedback: a brief intervention for motivating smokers with schizophrenia to seek treatment for tobacco dependence. J Consult Clin Psychol 2004;72:723–728
166. Ziedonis D, Williams JM, Smelson D. Serious mental illness and tobacco addiction: a model program to address this common but neglected issue. Am J Med Sci 2003;326:223–230
167. Evins AE, Cather C, Rigotti NA, et al. Two-year follow-up of a smoking cessation trial in patients with schizophrenia: increased rates of smoking cessation and reduction. J Clin Psychiatry 2004;65:307–311
168. Godtfredsen NS, Prescott E, Osler M. et al. Effect of smoking reduction on lung cancer risk. JAMA 2005;294:1505–1510
169. McEvoy JP, Freudenreich O, Wilson WH. Smoking and therapeutic response to clozapine in patients with schizophrenia. Biol Psychiatry 1999;46:125–129
170. de Leon J, Diaz FJ, Josiassen RC, et al. Does clozapine decrease smoking? Prog Neuropsychopharmacol Biol Psychiatry 2005;29:757–762
171. Harrigan SM, McGorry PD, Krstev H. Does treatment delay in first-episode psychosis really matter? Psychol Med 2003;33:97–110
172. Perkins D, Lieberman J, Gu H, et al. Predictors of antipsychotic treatment response in patients with first-episode schizophrenia, schizoaffective and schizophreniform disorders. Br J Psychiatry 2004;185:18–24
173. Harris MG, Henry LP, Harrigan SM, et al. The relationship between duration of untreated psychosis and outcome: an eight-year prospective study. Schizophr Res 2005;79:85–93
174. Marshall M, Lewis S, Lockwood A, et al. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. Arch Gen Psychiatry 2005;62:975–983
175. Buckley PF, Evans D. First-episode schizophrenia: a window of opporunity for optimizing care and outcomes. Postgrad Med Spec Rep 2006;Sept:5–19
176. Merlo MC, Hofer H, Gekle W, et al. Risperidone, 2 mg/day vs. 4 mg/day, in first-episode, acutely psychotic patients: treatment efficacy and effects on fine motor functioning. J Clin Psychiatry 2002;63:885–891
177. Schooler N, Rabinowitz J, Davidson M, et al. Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. Am J Psychiatry 2005;162:947–953.
178. Robinson DG, Woerner MG, Napolitano B, et al. Randomized comparison of olanzapine versus risperidone for the treatment of first-episode schizophrenia: 4-month outcomes. Am J Psychiatry 2006;163: 2096–2102
179. Keefe RS, Seidman LJ, Christensen BK, et al. Comparative effect of atypical and conventional antipsychotic drugs on neurocognition in first-episode psychosis: a randomized, double-blind trial of olanzapine versus low doses of haloperidol. Am J Psychiatry 2004;161:985–995
180. Green AI, Lieberman JA, Hamer RM, et al. Olanzapine and haloperidol in first episode psychosis: two-year data. Schizophr Res 2006;86:234–243
181. Tauscher-Wisniewski S, Kapur S, Tauscher J, et al. Quetiapine: an effective antipsychotic in first-episode schizophrenia despite only transiently high dopamine-2 receptor blockade. J Clin Psychiatry 2002;63:992–997
182. Good KP, Kiss I, Buiteman C, et al. Improvement in cognitive functioning in patients with first-episode psychosis during treatment with quetiapine: an interim analysis. Br J Psychiatry 2002;43(suppl):s45–49
183. Saha AR, Brown D, McEvoy J, et al. Tolerability and efficacy of aripiprazole in patients with first-episode schizophrenia: an open-label pilot study. Schizophr Res 2004;67:310
184. Fleischhacker WW, Keet IP, Kahn RS; EUFEST Steering Committee. The European First Episode Schizophrenia Trial (EUFEST): rationale and design of the trial. Schizophr Res 2005;78:147–56
185. Green AI, Canuso CM, Brenner MJ, et al. Detection and management of comorbidity in patients with schizophrenia. Psychiatr Clin North Am 2003;26:115–139
186. Buhler B, Hambrecht M, Loffler W, et al. Precipitation and determination of the onset and course of schizophrenia by substance abuse: a retrospective and prospective study of 232 population-based first illness episodes. Schizophr Res 2002;54:243–251
187. Janssen B, Gaebel W, Haerter M, et al. Evaluation of factors influencing medication compliance in inpatient treatment of psychotic disorders. Psychopharmacology (Berl) 2006;187:229–236
188. Day JC, Bentall RP, Roberts C, et al. Attitudes toward antipsychotic medication: the impact of clinical variables and relationships with health professionals. Arch Gen Psychiatry 2005;62:717–724
189. Kikkert MJ, Schene AH, Koeter MW, et al. Medication adherence in schizophrenia: exploring patients', carers' and professionals' views. Schizophr Bull 2006;32:786–794
190. King DJ, Burke M, Lucas RA. Antipsychotic drug-induced dysphoria. Br J Psychiatry 1995;167:480–482
191. Penn DL, Waldheter EJ, Perkins DO, et al. Psychosocial treatment for first-episode psychosis: a research update. Am J Psychiatry 2005;162: 2220–2232
192. Haddock G, Lewis S. Psychological interventions in early psychosis. Schizophr Bull 2005;31:697–704
193. Dixon L, Lucksted A, Stewart B, et al. Outcomes of the peer-taught 12-week family-to-family education program for severe mental illness. Acta Psychiatr Scand 2004;109:207–215
194. Amador X. I am not sick: I don't need help! Vida; 2006
195. Green MF. Schizophrenia Revealed: From Neurons to Social Interactions. New York: Norton; 2001
196. Torrey EF. Surviving Schizophrenia: A Manual for Families, Patients and Providers, 5th edition. New York: Harper Collins; 2006
197. Weiden PJ, Schaeffer PL, Diamond RJ, et al. Breakthroughs in Antipsychotic Medications: A Guide for Consumers, Families, and Clinicians. New York: Norton; 1999
198. Weiden PJ. Switching in the era of atypical antipsychotics. Post Grad Med Spec Rep 2006; September:27–44
199. Weiden PJ, Young AH, Buckley PF. The art and science of switching of antipsychotic medications, part 1. J Clin Psychiatry 2006;67:e15
200. Weiden PJ, Miller AL, Lambert TJ, et al. The art and science of switching antipsychotic medications, part 2. J Clin Psychiatry 2007;68:e02