A Roadmap to Key Pharmacologic Principles in Using Antipsychotics

The case examples and discussions in this ACADEMIC HIGHLIGHTS section were developed by Larry Culpepper, M.D., to illustrate clinical issues related to the treatment of psychosis and use of antipsychotics that clinicians in primary care are likely to encounter. The recommendations in this article are based on those in a recently published supplement on antipsychotic use by Peter J. Weiden, M.D.; Sheldon H. Preskorn, M.D.; Peter A. Fahnestock, M.D.; Daniel Carpenter, Ph.D.; Ruth Ross, M.A.; and John P. Docherty, M.D., titled Translating the Psychopharmacology of Antipsychotics to Individualized Treatment for Severe Mental Illness: A Roadmap.[1] *Dr. Culpepper acknowledges the authors of that supplement as well as the Roadmap Editorial Board (George S. Alexopoulos, M.D.; Shitij Kapur, M.D., Ph.D., F.R.C.P.C.; David C. Mamo, M.D., M.Sc., F.R.C.P.C.; Stephen R. Marder, M.D.; Joseph P. McEvoy, M.D.; John W. Newcomer, M.D.; Gary S. Sachs, M.D.), the experts who completed the survey, and Paola Vega of Expert Knowledge Systems for their invaluable help. Support for this project was provided by an educational grant from Bristol-Myers Squibb, Inc.*

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The treatment of severe mental illness has improved significantly in recent years because of advances in pharmacology and psychosocial interventions. One of the most important pharmacologic advances has been the introduction of the second generation "atypical" antipsychotics (SGAs), which are less likely to cause the neurologic movement disorders associated with older first generation antipsychotics, such as haloperidol. These neurologic side effects are usually called extrapyramidal symptoms (EPS) and include parkinsonian-type movements, rigidity, and tremor. However, with increasing new options have come new and more complex treatment decisions. In addition, some of the newer antipsychotics, while they are less likely to cause neurologic problems, are associated with weight gain and metabolic abnormalities that can increase health risks for patients.

Table 1 lists the antipsychotic medications that are most commonly used in the United States along with the disorders for which they have U.S. Food and Drug Administration labeling. Table 2 shows the Roadmap panel's dosing recommendations for a first-episode patient with no complicating conditions. Primary care physicians (PCPs) are likely to need accurate, up-to-date information on the pharmacology of antipsychotic medications and the treatment of psychotic disorders in a number of common situations, especially:

- When a patient who is being treated by a PCP for 1 or more medical conditions (diabetes, dyslipidemia, cardiovascular disease, hypertension, pulmonary illness) is also receiving antipsychotic medication from a psychiatrist for a serious mental illness.
- When a patient with a serious mental illness is being followed by a psychiatrist for periodic medication checks while a PCP provides more regular follow-up care in consultation with the psychiatrist.

Recently, a group of psychiatrists who are specialists on the use of antipsychotic medications developed a set of "Roadmap" recommendations to help clinicians with decisions involving the use of this class of medications.[1] These recommendations were based on a review of the literature, a roundtable meeting, and a survey of 27 experts on questions not adequately answered by the research literature. This ACADEMIC HIGHLIGHTS article presents a number of cases that illustrate the types of clinical questions PCPs are likely to encounter in using antipsychotics and discusses the guidance provided by the Roadmap on these questions.

Pharmacology of Antipsychotics

Whether a PCP is the primary prescriber of an antipsychotic or is providing care to a patient in collaboration with a psychiatrist, an understanding of the pharmacologic properties of available antipsychotics can be a great help in fine-tuning treatment decisions to achieve maximum efficacy while minimizing side effects. Therefore, as background for the case discussions that follow, a very brief overview of antipsychotic pharmacology is first presented. For a more detailed discussion of these issues, readers are referred to the full Roadmap supplement[1] as well as to a number of other useful

Table 1. FDA-Approved Labeling for Antipsychotic Medications[a]

Antipsychotic	Schizophrenia	Acute Bipolar Manic/ Mixed Episodes	Acute Bipolar Depression	Maintenance Treatment of Bipolar I Disorder
Chlorpromazine (Thorazine)	✓	✓		
Haloperidol (Haldol)	✓			
Perphenazine (Trilafon)	✓			
Clozapine[b] (Clozaril, FazaClo)	✓			
Aripiprazole[c,d] (Abilify)	✓	✓		✓
Olanzapine[c,d] (Zyprexa)	✓	✓	✓[e]	✓
Paliperidone (Invega)[f]	✓			
Quetiapine (Seroquel)	✓	✓	✓	
Risperidone (Risperdal)	✓	✓		
Ziprasidone[c] (Geodon)	✓	✓		

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

Table 2. Initial Dose and Titration Schedule for a First-Episode Patient With No Complicating Conditions Affecting Dosing[a]

Antipsychotic	Usual Starting Dose (mg/day) Avg (range)	Interval Between Dose Increases	Usual Dose Increment	Usual Initial Target Dose Range (mg/day) Low Avg (range)	High Avg (range)
Aripiprazole	10 (5–15)	1 week	5 (or 10) mg	10 (5–15)	25 (20–30)
Olanzapine	10 (5–15)	1 week	5 mg	10 (7.5–12.5)	22.5 (20–30)[b]
Quetiapine[c]	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)[d]	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)

[a]The doses in this table are based on responses from the Roadmap expert survey with mean doses and standard deviations from survey results converted to "real world" doses. Note there are some differences from information in the package inserts for these agents.
[b]Safety of doses above 20 mg/day has not been evaluated in clinical trials.
[c]Package insert recommends the following: initial doses of 50 mg/day for bipolar depression, increasing to 300 mg by day 4; initial doses of 100 mg/day for bipolar mania, increasing to 400 mg/day by day 4, with a final target dose of no higher than 800 mg/day; and initial doses of 50 mg/day for schizophrenia, increasing to 300–400 mg/day by day 4, with a final target dose of no higher than 750 mg/day.
[d]Package insert recommends initial dose of 40 mg/day for schizophrenia and 80 mg/day for bipolar mania.

Figure 1. Three Variables That Determine Response to Any Drug[a]

Clinical response = Affinity for the site of action (pharmacodynamics) × Drug concentration at site of action (pharmacokinetics) (ADME) × Underlying biology of patient (GADE)

- Drug concentration: Absorption; Distribution; Metabolism; Elimination
- Underlying biology: Genetics; Age; Disease; Environment

[a]Reprinted with permission from Preskorn.[7]

publications on the pharmacology of antipsychotics and other psychiatric drugs.[2–6]

Determinants of Clinical Response

The equation in Figure 1 shows the 3 major variables that determine a drug's effect in a specific patient.[7] A drug's pharmacodynamics (the effects it has on receptors) and its pharmacokinetics (how it is metabolized and cleared from the body) ultimately determine the good and bad effects it will produce in an individual. As part of the Roadmap project, the expert panel was asked how the factors in Figure 1 can help guide medication choices over and above data provided by clinical trials. Such questions are particularly relevant for antipsychotics. Despite the fact that all these agents are approved to treat psychotic symptoms, they differ considerably in other pharmacologic properties. These differences can be especially important in predicting side effects and avoiding withdrawal and additive effects when drugs are titrated, tapered, or added to each other.

Pharmacodynamics. A drug's effects are a function of which site(s) of action it affects, how many sites it occupies, and its actions at the site(s) (e.g., agonism, antagonism) (as well as the actions of any active metabolites the drug may have). *Agonists* act like the endogenous neurotransmitter to fully activate a receptor. *Antagonists* produce no activation, taking the receptor "out of play." Drugs can also

Table 3. Common Adverse Effects Caused by Receptor Blockade[a]

Receptors	Effects
Histamine 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
Dopamine D_2	Extrapyramidal side effects, prolactin elevation

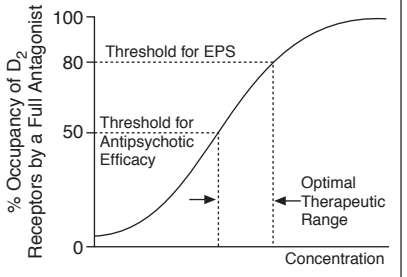
[a]Based on Gardner et al.[6]
Abbreviations: α_1 = alpha-1 norepinephrine, M_1 = muscarinic acetylcholine-1.

Table 4. Binding Affinity of Selected Antipsychotics for Specific Neuroreceptors[a,b]

Antipsychotic	D_2	5-HT_{1A}	5-HT_{2A}	5-HT_{2C}	α_1	H_1	M_1
Aripiprazole	0.34[c]	1.7[c]	3.4[c]	15	57	61[c]	> 1000
Clozapine	126	875	16	16	7	6	1.9
Haloperidol	0.7	1100	45	> 10,000	6	440	> 1500
Olanzapine	11	> 10,000	4	23	19	7	1.9
Quetiapine	160	2800	295	1500	7	11	120
Risperidone	4	210	0.5	25	0.7	20	> 10,000
Ziprasidone	5	3	0.4	1	11	50	> 1000

[a]From Preskorn,[4] with permission, based on Richelson,[8] Abilify package insert,[9] Arnt and Skarsfeldt,[10] Bymaster et al.,[11] and Seeger et al.[12]
[b]Data represented as K_i (nM).
[c]Data with cloned human receptors.
Abbreviations: 5-HT = serotonin, α_1 = alpha-1 norepinephrine, D = dopamine, H_1 = histamine 1, M_1 = muscarinic acetylcholine-1.

Figure 2. Narrow Range Between Efficacy and Behavioral Toxicity With D_2 Receptor Antagonists[a,b]



[a]Reprinted with permission from Preskorn.[14]
[b]D_2 antagonism ≥ 50% appears needed for antipsychotic efficacy, while antagonism > 80% is associated with increased risk of acute extrapyramidal side effects (EPS).[13] This curve explains the narrow window between efficacy and EPS with full D_2 antagonists (the curve would differ for partial D_2 agonists).

fall between these reference points (e.g., partial agonists). A drug can affect just 1 site of action (i.e., be selective) at clinically relevant concentrations or more than 1 site of action as a function of its relative binding affinity for more than 1 regulatory protein. When a drug affects *multiple* receptors, its pharmacology can change with its dose, as the drug sequentially engages different target receptors in a dose-dependent, concentration-dependent manner.[4] Binding affinity does not indicate the effect (e.g., agonism or antagonism) a drug has on its target.

The relationship between receptor binding profiles and adverse effects is better understood than the effect of receptor binding profiles on efficacy. All available antipsychotics block dopamine-2 (D_2) receptors to some extent but vary in the degree to which they affect the D_2 receptor relative to other clinically meaningful receptors. These differences in receptor binding affinities generally explain differences in the clinical profile of these drugs (e.g., side effects)[6] (Tables 3 and 4). The Roadmap panel was therefore asked about the relative importance of pharmacodynamic differences in choice of medication, side effects, withdrawal effects, and cross-titration techniques when switching from one antipsychotic to another. The panel expressed more confidence about the role of dopamine, histamine, muscarinic, and α-adrenergic than serotonin receptors in the effects of antipsychotics.

Pharmacokinetics refer to the ways in which drugs enter and leave the body and hence the biological sites they affect. All antipsychotics have to cross the blood-brain barrier and find their way to the synapse; they are then eventually cleared from the synapse and eventually from the body. Differences in the way antipsychotics are metabolized and cleared from the body are relevant to questions about use of long-acting antipsychotics (e.g., depot haloperidol, long-acting risperidone), effects of other coprescribed medications on clearance, and how quickly to cross-taper drugs when switching antipsychotics.

Biological variability. There is significant variation in how the same medication at the same dose may affect different individuals. Some of this variation is due to factors such as age, gender, or individual genetic variability in receptor activity or metabolic pathways. Other medications the person is taking may also cause variation in response as a result of drug-drug interactions due to pharmacodynamic or pharmacokinetic mechanisms. Some variations in response cannot be predicted given the current level of knowledge (e.g., clinically important but unknown genetic differences).

Effects of D_2 Antagonism

Figure 2 shows that a minimum threshold of 50% antagonism or blockade of the D_2 receptor appears to be required for antipsychotic efficacy, while blockade greater than 80% is associated with a markedly increased risk of acute extrapyramidal side effects (EPS).[13,14] This figure explains the relatively narrow window between antipsychotic efficacy and risk of acute EPS associated with unopposed D_2 antagonism.

The EPS that can occur with antipsychotics include parkinsonian tremor, muscular rigidity, and akinesia;

dystonia (abnormal positioning or spasm of the muscles of the head, neck, limbs, or trunk); and akathisia (subjective complaints of restlessness accompanied by observable movements such as fidgety movements of the legs, rocking from foot to foot, pacing, or the inability to sit or stand still).[15]

Effects of D_2 Partial Agonism

Until recently, all available antipsychotics were D_2 antagonists. However, a new class of antipsychotics that are D_2 partial agonists has recently been introduced. Because clinicians may not be as familiar with the concept of partial agonism in relation to antipsychotics, it may be helpful to clarify how partial agonists affect the D_2 receptor. As an example, aripiprazole, the first partial agonist approved by the U.S. Food and Drug Administration, has 30% of dopamine's intrinsic activity at the D_2 receptor. Therefore, when it fully occupies 100% of D_2 receptors, it exerts 30% of the expected effect, resulting in a maximum 70% reduction (antagonism) of D_2 receptor activity. This profile is confirmed by studies that show that doses of aripiprazole that produce 95% occupancy of D_2 receptors in the striatum are not associated with an increased risk of EPS.[9]

Some effects of partial agonists *are* dose related, however. For example; the "activation" sometimes reported when patients start taking aripiprazole is more likely at higher doses that produce relatively more dopamine agonism. Since aripiprazole appears to have a "flat" dose-response curve between 15 and 30 mg/day in terms of antipsychotic efficacy in populations of patients, such early activation can often be minimized by aiming for a target dose at the lower end of that range.[16] (Note that flat dose-response curves in populations of patients do not mean that an individual patient may not benefit from a higher or lower dose. Activation occurring shortly after starting a nonsedating antipsychotic can also be due to withdrawal from a more sedating antipsychotic.)

Drugs That Bind to Multiple Receptors

Tables 3 and 4, taken together, provide guidance about side effects that may occur with different doses of different antipsychotics. For example, quetiapine binds most potently to the histamine-1 (H_1) and the alpha-1 norepinephrine (α_1) receptors. To achieve D_2 occupancy, the dose and hence concentration of quetiapine must typically 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 for many patients but 400 to 600 mg is usually needed for antipsychotic effect. With risperidone, the affinity for 5-HT_2 and D_2 receptors is closer, which is consistent with the increased incidence of EPS at doses above 6 mg/day. Ziprasidone's affinity for the 5-HT_{2A} receptor is 10 times more potent than for the D_2 receptor; thus, ziprasidone blocks 5-HT_{2A} receptors at low doses (e.g., 20 mg) but has little effect on D_2 receptors until doses reach 120 to 160 mg/day, at which point the concentration of ziprasidone is typically sufficient to achieve at least 50% D_2 antagonism and antipsychotic efficacy for most patients. Differences in the relative engagement of serotonin and dopamine receptors may explain why early "activation" (thought to be mediated by serotonin mechanisms) with ziprasidone is associated with lower doses and abates at higher doses (e.g., 120 mg/day) when that effect is mitigated by D_2 receptors.[16]

How the Brain Adapts to Receptor Effects of Antipsychotic Medications

The brain adapts to the presence of many psychiatric medications as a result of compensatory mechanisms (e.g., up-regulation of receptors in response to a drug that antagonizes that receptor; down-regulation in response to agonism of that receptor). If such adaptation is not considered when changing drugs, withdrawal effects may occur. Chronic treatment with a D_2 antagonist can lead to up-regulation of D_2 receptors so that patients may develop distressing withdrawal dyskinesia when D_2 receptor blockade is reduced (e.g., by stopping the D_2 blocker, switching to a drug with lower D_2 occupancy [e.g., low-dose ziprasidone], or switching from a full D_2 antagonist to a partial D_2 agonist [e.g., aripiprazole]). Switching abruptly from an antipsychotic with potent antihistaminic properties to one that does not block histamine receptors (e.g., aripiprazole, ziprasidone) may also cause "activation." Such withdrawal effects may be erroneously attributed to the new antipsychotic, so that the patient loses the opportunity for an adequate trial of the new medication.

Drug-Drug Interactions

Drugs are an important cause of acquired biological variance (Figure 1) that can change a patient's response to concomitantly prescribed drugs.[3] Drugs can interact with one another pharmacodynamically (e.g., EPS due to additive effects of 2 D_2 receptor blockers) and/or pharmacokinetically (e.g., effects on metabolism and/or clearance and thus accumulation of another drug). The most common clinically important pharmacokinetic drug-drug interactions involve effects on phase one (oxidative) metabolism via the cytochrome P450 (CYP) enzyme system that is responsible for the clearance of most drugs.[3] For example, coadministration of a substantial CYP2D6 inhibitor (bupropion, fluoxetine, or paroxetine) can increase risk of acute EPS in patients treated with risperidone, by making genetically normal metabolizers functionally deficient in CYP2D6.[17] Thus, it is important to consider other medications a patient is taking in adding, changing, or adjusting the dose of psychiatric medications.[3] For information on drug-drug interactions involving psychiatric drugs, see *Guide to Psychiatric Drug Interactions*.[2]

Maximizing Efficacy While Minimizing Side Effects

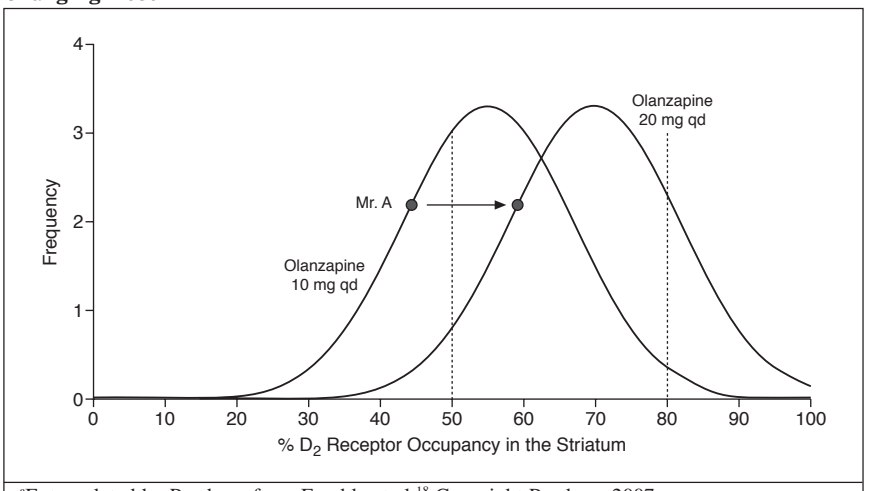
None of the currently available antipsychotics are free of side effects; thus, achieving best outcomes for patients being treated with these agents involves balancing risks and benefits, and tradeoffs often have to be made. The following cases illustrate how a better understanding of pharmacologic principles can help maximize efficacy while minimizing side effects.

Mr. A: Effect of a Dose Increase

Mr. A, a patient with schizophrenia, had not achieved a satisfactory response with 10 mg of olanzapine. When the dose was raised to 20 mg, his response improved markedly with no occurrence of EPS.

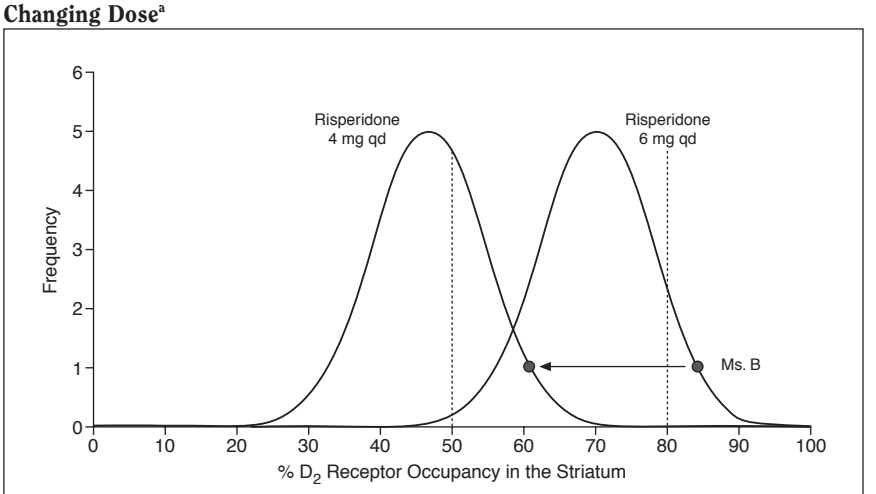
This case illustrates how a dose increase resulted in an improved response without development of problematic side effects. A majority of patients on 10 mg/day of olanzapine are in the correct range to achieve antipsychotic efficacy without EPS, but a sizable percentage fall below the minimum threshold of 50% blockade for antipsychotic efficacy and need a higher dose to achieve satisfactory antipsychotic response. Figure 3 illustrates what might have been happening in terms of receptor occupancy for this patient. Mr. A fell below the 50% threshold on 10 mg/day but achieved approximately 60% D_2 receptor blockade and experienced a good response on 20 mg/day.

Figure 3. Predicted Change in Distribution Curves for Olanzapine as a Result of Changing Dose[a]



[a]Extrapolated by Preskorn from Frankle et al.[18] Copyright Preskorn 2007.

Figure 4. Predicted Change in Distribution Curves for Risperidone as a Result of Changing Dose[a]



[a]Extrapolated by Preskorn from Frankle et al.[18] Copyright Preskorn 2007.

Ms. B: Effect of a Dose Reduction

Ms. B, 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 and the EPS resolved.

This case illustrates how a dose reduction resulted in an improvement in side effects without loss of efficacy. Figure 4 illustrates what might have been happening in terms of receptor occupancy for this patient. At 6 mg/day, Ms. B was above the 80% threshold for EPS; when the dose was lowered, receptor blockade went down to approximately 60%—above the threshold for efficacy but below that for EPS.

While these 2 cases illustrate the general principle in Figure 2, not all patients experience a good response just because they achieve 60% to 80% D_2 receptor blockade. Some may need treatment that involves additional mechanisms besides D_2 blockade. Moreover, it is sometimes not possible to resolve efficacy and side effect problems with a dosage adjustment, as illustrated in the case of Mr. C, who presented to a PCP after a year and a half of psychiatric treatment.

Mr. C: A Stable Patient With Significant Weight Gain and Elevated Lipid Levels

Mr. C is 24-year-old man who was diagnosed with schizophrenia during college. During his sophomore year, his grades began to go down, and in

the spring of that year, Mr. C's roommate called his parents and told them he was acting "out of control" and asked that they come get him. When they arrived, Mr. C accused his parents of being strangers who had taken the place of his real parents. He became very agitated and refused to go with them. This was the occasion of his first admission for psychiatric care. Mr. C initially responded to risperidone but only at a dose of 8 mg/day, which caused distressing EPS. His psychiatrist switched the patient to olanzapine, on which he has done well at a dose of 15 mg/day. The patient has been able to resume taking 1 or 2 classes a term at the local community college. After Mr. C has been on olanzapine for approximately 1 year, his mother brings him in to see the family doctor. She is very concerned because Mr. C has gained 35 lb and gets no exercise.

Unlike Ms. B above, Mr. C was unable to retain his response to risperidone at a dose that did not cause distressing EPS. When switched to olanzapine, the patient responded well but gained a significant amount of weight, which led to the PCP's becoming involved.

What assessments would you do? Before deciding on a treatment recommendation, the PCP should calculate the patient's body mass index (BMI) (calculator available on the National Institutes of Health's Heart, Lung, and Blood Institute Web site[19]), measure abdominal girth, obtain lipid and blood glucose levels, and do a quick assessment for other cardiovascular risk factors such as smoking, hypertension, and family history of cardiovascular disease. Before intervening, it is also important to assess other factors that may have a bearing on the patient's overall clinical situation, including other prescription and over-the-counter medications being taken, current or history of drug or alcohol abuse, and HIV risk factors (see U.S. Preventive Services Task Force Web site[20] for expert recommendations for clinical preventive services).

Table 5. Second Generation Antipsychotics and Metabolic Abnormalities[a]

Antipsychotic	Weight Gain	Risk for Diabetes	Worsening Lipid Profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole[b]	+/–	–	–
Ziprasidone[b]	+/–	–	–

[a]Reprinted with permission from the American Diabetes Association.[23]
[b]Newer drugs with limited long-term data.
Symbols: + = increase effect, – = no effect, D = discrepant results.

Based on the patient's weight, his BMI has increased from 26 to 29. The lab report shows a triglyceride level of 350 mg/dL and a total cholesterol level of 332 with an HDL of 38 and an LDL of 224. A repeat fasting lipid profile demonstrates only a slight reduction in triglycerides. The patient smokes cigarettes. You suggest to the patient and his mother that it would be helpful to send a report with recommendations to the patient's psychiatrist. What information can inform your recommendation to the psychiatrist?

- The Roadmap expert panel[1] indicated that, in most cases, weight gain is not a dose-related side effect and that a dose reduction does not appear to help much with weight and metabolic problems, such as Mr. C is experiencing. This opinion is supported by findings in clinical trials.[21,22]
- The patient has only been tried on 1 previous antipsychotic and has never tried either aripiprazole or ziprasidone, the 2 SGAs associated with the least weight gain. Relative risks of weight gain and metabolic abnormalities with different SGAs are shown in Table 5.
- The patient has multiple risk factors for cardiovascular disease.
- In such a situation, the Roadmap experts recommended trying to switch to an antipsychotic with less liability to cause weight gain and lipid problems.[1]
- A change of antipsychotic will only be effective for weight gain that is related to antipsychotic medication.
- In switching from one antipsychotic to another, it is best to cross-taper the medications to maintain adequate antipsychotic coverage and minimize withdrawal side effects.
- Additive side effects can occur when 2 antipsychotics are combined during a switching crossover. It is important not to attribute these effects to the new drug and discontinue treatment before the patient has had a chance to have an adequate trial of the new agent.
- After being switched to a new antipsychotic, the patient should return for follow-up lipid testing in 4 to 6 weeks to evaluate levels and consider whether a lipid lowering medication should be started. Table 6 presents consensus recommendations from the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity for monitoring weight and metabolic status in patients taking SGAs.[23]

What counseling would you provide to Mr. C and his mother? The PCP asked Mr. C and his mother what they knew about his illness. Although they appeared to be reasonably well informed about schizophrenia, the PCP encouraged them to continue learning more about the illness. He provided them with a pamphlet concerning the National Alliance on Mental Illness (NAMI, http://www.nami.org), which included information on how to contact the local chapter, and encouraged them

Table 6. Monitoring Protocol for Patients on Second Generation Antipsychotics[a,b]

	Baseline	4 Weeks	8 Weeks	12 Weeks	Quarterly	Annually	Every 5 Years
Personal/family history	✓					✓	
Weight (body mass index)	✓	✓	✓	✓	✓		
Waist circumference	✓					✓	
Blood pressure	✓			✓		✓	
Fasting plasma glucose	✓			✓		✓	
Fasting lipid profile	✓			✓		✓[c]	✓

[a]Reprinted with permission from the American Diabetes Association.[23]
[b]More frequent assessments may be warranted based on clinical status.
[c]Revised to reflect current consensus on annual monitoring.

to look into the peer support and family education offered by NAMI.[24]

The PCP told Mr. C and his mother that he was concerned about the effect on Mr. C's health of his smoking, weight, and lack of exercise. He also stressed that it is not a good idea to try to target more than one problem at a time. After further discussion, Mr. C said he would be willing to consider trying to stop smoking. Mr. C began smoking at age 14 and currently smokes 30 cigarettes a day. He has considered quitting in the past, and has made several unsuccessful attempts, but he has never obtained professional help in quitting. Therefore, the PCP prioritized smoking cessation as the first item to focus on after Mr. C had been stabilized on a new antipsychotic with less weight gain liability.

Mr. C was successfully switched to a different antipsychotic and, after 4 months, had been able to lose 15 lb. At that time, the PCP scheduled a counseling session to discuss setting a quit-smoking date and to instruct Mr. C in the use of a nicotine patch. Mr. C agreed to follow up in 1 week with the nurse practitioner in the office. Weight and exercise were identified as additional goals they might want to pursue, and plans were made to discuss food choices and ways to increase exercise at a follow-up visit.

Mr. D: A Stable Patient on Clozapine With Weight Gain and Lipid Abnormalities

Mr. D is a 33-year-old man who was diagnosed with schizophrenia at age 25. The patient is currently taking clozapine 500 mg/day. He is referred to the family practice clinic for evaluation by his psychiatrist because he has gained 40 lb and a recent laboratory work-up showed elevated triglyceride and blood glucose levels.

Before making any recommendations, what additional information would you want to obtain from the patient's psychiatrist? Clozapine is associated with a significant risk of weight gain and metabolic problems (Table 5). However, patients are generally being treated with clozapine either because they have not responded to adequate trials of several other antipsychotics or because they are believed to be at increased risk for suicide. Clozapine is the antipsychotic that has been shown to be most effective for treatment-resistant schizophrenia[25] and has also been found to be most helpful in reducing suicide risk.[26] Therefore, when a patient on clozapine develops significant weight gain and/or metabolic abnormalities, the risk-benefit equation is more complicated and a potential change of medications must be approached much more cautiously. Before making any recommendations, the PCP therefore requests a treatment history and, in particular, asks why the patient is being treated with clozapine.

The psychiatric clinic sends a report with the following information: *Mr. D has been followed by the psychiatrist at the community mental health center over the past 8 years, during which time he was treated with risperidone, olanzapine, and ziprasidone, with only limited response. A year ago, he made a serious suicide attempt and was hospitalized. During hospitalization, he was started on clozapine, to which he has responded better than to anything else. He currently denies any suicidal ideation.*

Would it be appropriate to recommend a change of antipsychotic medications for this patient? This was the kind of complicated problem the Roadmap expert panel was asked to consider. The panel said they would consider switching a patient who has gained significant weight or developed serious metabolic abnormalities from clozapine to another SGA if the patient had previously had trials of only 1 or 2 of the other SGAs and did not have a history of violence or serious suicidal ideation or behavior. However, in a case such as Mr. C's, the experts would clearly be reluctant to take the patient off clozapine. In a situation in which switching from clozapine is not a good option, the next step is to treat the weight gain and metabolic symptoms (e.g., with lifestyle changes including diet, exercise, smoking cessation, lipid lowering agents, and anti-hyperglycemic medication).

What additional information would it be helpful to obtain before making recommendations for medical management? The PCP would want to know about the patient's current diet, exercise history, and family history of diabetes and cardiovascular disease, as well as any potential interactions between clozapine and agents that might be prescribed to treat the patient's lipid and metabolic problems.

Ms. E: A Stable Patient With Amenorrhea

Ms. E is 22-year-old woman diagnosed 2 years earlier with bipolar disorder. She has a history of manic episodes with psychotic features, alternating with serious, debilitating depressive episodes. She is being followed by a private psychiatrist. Her current treatment regimen is risperidone 5 mg/day plus valproate 3000 mg/day (most recent valproic acid level was 95 μg/mL). The patient comes in to her family doctor because she is concerned that she may have a serious gynecologic problem because her periods have stopped.

What assessments would you do? The PCP would want to exclude a medication side effect by obtaining a prolactin level, exclude pregnancy using a β-HCG pregnancy test, and exclude hypothyroidism or hyperthyroidism by obtaining a thyroid-stimulating hormone level. Chronic renal disease can be ruled out by obtaining blood urea nitrogen and creatinine levels. A pelvic examination may be necessary depending on the nature of additional complaints.

What questions would you ask the patient? It is important to learn more about the patient's lifestyle and perceptions of the problem. For example, the PCP could ask: How do you feel about your periods stopping? Are you sexually active? Are you using a birth control method? What other medications have you taken in the past? Have you had any nipple discharge? Have you had headaches or changes in your vision? Have you experienced any fatigue or weakness? Have you become more sensitive to being cold? Have you had any constipation?

The patient's prolactin level is 65 ng/mL, with 20 ng/mL being the laboratory's upper limit of normal. The pregnancy test is negative. The patient says she is not sexually active at the moment but is dating someone regularly. The history, physical examination, and laboratory tests rule out pregnancy, hypothyroidism, and renal disease, and they are not suggestive of a pituitary adenoma. You suggest to the patient that it would be helpful for you to send a report with recommendations to her psychiatrist. What information can inform your recommendation to the psychiatrist?

- Hyperprolactinemia (elevated prolactin levels) is a major neuroendocrine-related cause of reproductive disturbances. A number of antipsychotics can cause hyperprolactinemia because of their potent effects as dopamine (D_2) blockers.[27] Among the SGAs, risperidone is associated with the most prolactin elevation; aripiprazole, clozapine, and quetiapine are associated with the least; and ziprasidone and olanzapine fall in between.[27,28]
- Prolactin elevation is to some extent a dose-related side effect. Therefore, the Roadmap expert panel,[1] consistent with the recommendations in the American Psychiatric Association *Practice Guideline for the Treatment of Patients With Schizophrenia,*[29] considered it appropriate to try lowering the dose of the antipsychotic if symptomatic prolactin elevation occurs. If dose reduction does not succeed and the symptoms are distressing to the patient, a change to a more prolactin-sparing antipsychotic could be considered. If a dose reduction or change of antipsychotic is not possible, the addition of a dopamine agonist such as bromocriptine or amantadine may reduce prolactin levels.[29]
- If the dose of risperidone is lowered or the patient is switching to a different antipsychotic, she should be cautioned that her periods are likely to resume in a few weeks to months and that she needs to use appropriate birth control if she becomes sexually active.
- Further work-up to rule out other causes of amenorrhea, such as a pituitary tumor (specifically, an MRI to evaluate the hypothalamic-pituitary region), should be considered if prolactin levels do not decrease and menses do not resume after a change of medications. It might also be appropriate to consider a bone scan, since increased prolactin levels can lead to a decrease in bone density.

Providing Collaborative Care With a Psychiatrist

Ms. F: A Patient With a Bagful of Medications

Ms. F is a 56-year-old woman who comes in for medical evaluation. She is being followed by a psychiatrist for bipolar disorder and is taking risperidone and lamotrigine. She also has a history of hypertension, angina, and insomnia. Her psychiatrist referred her to your family practice clinic for a medical check-up and told Ms. F to bring all her medications with her so that the doctor could decide what she needed to be taking.

Ms. F arrives for her first visit to the PCP with many bottles of medication in a brown paper bag. These include a β-blocker (propranolol), a calcium channel blocker (nifedipine), a statin, estrogen for replacement therapy, alprazolam, and zolpidem. The clinic doctor notices that the patient seems sedated and that her gait is slightly uncoordinated when she walks. The patient confirms that she has been feeling very sleepy lately. She also tells the doctor that she doesn't think her medications are working as well as they once did. The PCP carefully reviews all of the medications the patient is taking. She notes that the combination of antianxiety (alprazolam) and hypnotic (zolpidem) medications with risperidone can cause excessive daytime sedation. Moreover, estrogen, which the patient's gynecologist had

recently prescribed when the patient complained of menopausal symptoms (hot flushes, night sweats), can increase the clearance of lamotrigine, thereby markedly reducing plasma levels of this agent. The PCP recommends that the psychiatrist stop either the alprazolam (with appropriate tapering to avoid withdrawal effects) or the zolpidem. She also recommends discontinuing the estrogen replacement therapy in view of recent studies indicating that the risk of long-term hormone replacement therapy outweighs the benefits.[30] Both of these recommendations are carried out, leading to marked improvements in the patient's symptoms.

Mr. G: A Patient Whose Relapse Is Associated With Alcohol Abuse

Mr. G, a 40-year-old man with schizoaffective disorder, lives in a small rural community where he is seen by the psychiatrist at the community mental health center every 4 months for medication checks and followed by his PCP between appointments. He is currently being treated with ziprasidone 120 mg/day. Mr. G is on disability and does not work; he rents a 1-room apartment in subsidized housing. He has a sister who checks on him regularly and brings him in for his appointments. Mr. G was recently brought to the ER at the nearest hospital (in the town 25 miles away) for evaluation. He was floridly psychotic and was admitted to the psychiatric floor. During a 5-day admission, the patient was stabilized on a slightly higher dose of ziprasidone (160 mg/day). The inpatient psychiatrist contacted Mr. G's PCP to discuss discharge plans and informed the PCP that Mr. G had admitted during his hospitalization that he had been drinking on a regular basis and that, when he was drinking, he "sometimes didn't remember to take his medicine."

What interventions would you undertake when the patient is discharged? In a situation in which a patient's relapse is associated with alcohol abuse and likely nonadherence, the best course is to observe the patient to see if he improves once he becomes sober. If the psychotic symptoms ameliorate, it can be concluded that they were exacerbated by either the direct effects of alcohol or the effect of alcohol abuse on the patient's adherence to antipsychotic medication, or by a combination of the 2.

After release, the patient continues to have breakthrough psychotic symptoms despite negative toxicology screens indicating sobriety. What would you do? If the patient's symptoms do not improve completely after he becomes sober, it may be that the ziprasidone monotherapy is not sufficiently effective, although it is also possible that the patient may not be taking the medication as prescribed. It is also important to ensure that the patient is taking the ziprasidone with food, since taking ziprasidone while fasting can significantly decrease plasma and brain concentrations of this agent and might contribute to poor response.

For patients with adherence or substance abuse problems, the Roadmap panel recommended considering a long-acting injectable antipsychotic (with a long-acting SGA such as long-acting injectable risperidone preferred).[1] If use of a long-acting agent is not possible, patients should be educated as to the importance of continuing to take their antipsychotic medications as prescribed even when they are using alcohol or drugs. Another possibility to consider in this case would be adding a mood stabilizer to the patient's regimen. Lithium would be acceptable *except* that the patient's lack of adherence to medication might also translate into lack of adherence to the necessary precautions to avoid lithium toxicity, such as avoiding dehydration or coming in for measurement of lithium levels. Alternatives to lithium would be divalproex, although this might interact with ziprasidone and lead to sedation and motor impairment, or lamotrigine. Treatment guidelines for patients with serious mental illness complicated by substance abuse problems (dual diagnosis patients) also recommend that the substance abuse be targeted in integrated treatment programs if possible.[31,32]

Mr. H: Deciding When a Patient Needs a Referral for Specialized Care

Mr. H is a 22-year-old man whose psychotic symptoms began less than 2 years ago and who has been diagnosed with schizophrenia, paranoid subtype. His last hospitalization was almost a year ago. Mr. H lives in a very rural area, and the nearest psychiatrist is a 3-hour drive from his home. He is currently being followed by his PCP. Mr. H's current medications are quetiapine 300 mg b.i.d. and risperidone 4 mg q.d. On this regimen, he has been free of positive symptoms since his last hospital discharge.

Mr. H is seen by his PCP for a routine, monthly evaluation. The PCP asks him how he has been feeling, and he says, "I don't feel anything." He denies hallucinations and delusions, and the PCP considers him free of psychotic symptoms. However, the PCP notes that Mr. H is unusually sullen and responds to questions with 1- or 2-word answers delivered in a monotone. Mr. H tells the PCP that he has not been "doing much of anything" since his last visit a month ago. The PCP is able to learn only that the patient has not been sleeping or eating much and that he has mainly spent his time watching television and smoking cigarettes. The PCP believes there has been clinical deterioration, but is not sure what to make of Mr. H at this point.

What are the clinical considerations in this case? There are at least 3 possible explanations for Mr. H's apparent lack of motivation and restricted affect. One is that he is suffering from akinesia,[15] an extrapyramidal symptom caused by some antipsychotic medications. A second is that Mr. H may be experiencing a worsening of the nega-

tive symptoms of schizophrenia. Negative symptoms tend to be relatively refractory to antipsychotic medication compared with positive symptoms. Finally, Mr. H may have developed a new episode of major depression. Depression is common in patients with schizophrenia, and patients with schizophrenia have a very high rate of attempted and completed suicides, particularly early in the course of the illness.

What does the PCP do in this case? The PCP asks Mr. H about suicidal ideation and receives only a vague answer. He is not comfortable making a full assessment of suicidality and calls for a local ambulance to transport the patient to the nearest psychiatric emergency room.

The concern that a patient may be suicidal is one of the clearest indications for referral to a psychiatrist. In this case, because of the relatively rapid onset of new symptoms (over the period of 1 month) and the fact that Mr. H's medications had not been changed for almost a year, the most likely diagnosis is depression. Given the fact that patients with schizophrenia are prone to suicide attempts, the PCP correctly insisted that the patient be evaluated on an emergency basis by a psychiatrist.

Conclusion

The care of patients with bipolar disorder or schizophrenia is complex, usually involving multiple psychiatric medications and nonpharmacologic interventions to maintain patients in their communities. Such patients frequently also have chronic medical illnesses or are at increased risk for developing them due to either the psychiatric disease process itself or the psychiatric medications used. Fortunately, the atypical antipsychotics have improved the care and outcomes for such patients, including the likelihood that they will be able to live in the community rather than being institutionalized. Consequently, primary care physicians increasingly are engaged in the care of these patients. Their involvement can help improve psychiatric outcomes while also reducing morbidity from the chronic medical illnesses that often affect these patients. Collaboration between primary care and psychiatric care, especially when it includes primary care physicians knowledgeable about key characteristics of antipsychotic medications, can maximize the benefits to be derived from these new medications.

Drug names: alprazolam (Xanax, Niravam, and others), amantadine (Symmetrel and others), aripiprazole (Abilify), bromocriptine (Parlodel and others), bupropion (Wellbutrin and others), clozapine (FazaClo, Clozaril, and others), divalproex (Depakote), fluoxetine (Prozac and others), haloperidol (Haldol and others), lamotrigine (Lamictal and others), nifedipine (Adalat, Procardia, and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), propranolol (Innopran, Inderal, and others), quetiapine (Seroquel), risperidone (Risperdal), valproate (Depacon and others), valproic acid (Depakene and others), ziprasidone (Geodon), zolpidem (Ambien and others).

Disclosure of off-label usage: Dr. Culpepper has determined that, to the best of his knowledge, alprazolam is not approved by the U.S. Food and Drug Administration for the treatment of anxiety accompanying bipolar disorder.

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