A Roadmap to Key Pharmacologic Principles in Using Antipsychotics in the Treatment of Bipolar Disorder

The case examples and discussions in this ACADEMIC HIGHLIGHTS section were developed by Roy H. Perlis, M.D., M.Sc., to illustrate clinical issues in the use of antipsychotics in the treatment of bipolar disorder. The recommendations in this article are based in part on those previously published in a 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. Perlis acknowledges the authors of that supplement and 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.; and 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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On the basis of the National Comorbidity Survey Replication (NCS-R),[2] it is estimated that bipolar I and II disorders may affect nearly 3% of the population (i.e., 5.7 million Americans), with the prevalence of subthreshold but still impairing bipolar presentations estimated to be even higher.[3] Bipolar disorder is associated with significant functional impairment and elevated health care costs. Although unipolar depression appears to be over 6 times as prevalent as bipolar disorder, NCS-R data found that the costs of bipolar disorder to the U.S. workplace, estimated at $14.1 billion annually, were almost *half* the cost of lost productivity associated with unipolar depression.[4]

Treatment of bipolar disorder has changed significantly in recent years due to advances in both pharmacologic and psychosocial interventions. One development has been the recognition that second generation "atypical" antipsychotics (SGAs) have antimanic efficacy, and that some of these agents also have efficacy for depression and preventing recurrence. Table 1 shows antipsychotics that are commonly used in the United States and the disorders for which they have U.S. Food and Drug Administration (FDA) labeling. Management of bipolar disorder can be complex given the many treatment options and the frequent need for combinations of medications, including lithium, anticonvulsants, and conventional and second generation antipsychotics, to adequately control symptoms or prevent recurrence. Management is further complicated by the relative paucity of studies examining combination therapies or comparing treatments head-to-head. This article summarizes recommendations from a recent supplement, *Translating the Psychopharmacology of Antipsychotics to Individualized Treatment for Severe Mental Illness: A Roadmap*,[1] as a quick guide for clinicians on the use of antipsychotics in the treatment of bipolar disorder.

In 2003, the President's New Freedom Commission on Mental Health[5] stressed the importance of incorporating the latest scientific information into mainstream health care as rapidly as possible. In keeping with this goal, the Roadmap drew on clinical trial data, information on antipsychotic pharmacology, practice guidelines,[6–9] consensus statements,[10] and expert opinion to develop recommendations for achieving best outcomes for individual patients. Expert opinion was sampled using an initial survey and roundtable meeting of 10 experts and a follow-up survey of 27 experts, who reached a high level of consensus on many key questions not adequately addressed by the literature. Survey respondents understood that the survey would be used not to create guidelines but to supplement evidence-based recommendations. For a description of the survey methodology and respondents, readers are referred to the Roadmap supplement.[1] The goal of the Roadmap project was to generate recommendations to help clinicians make informed decisions about medication choice, dosing, and switching strategies based on pharmacodynamic and pharmacokinetic properties of antipsychotics; diagnosis, prominent symptoms, and treatment history; demographic characteristics; and medical conditions, including those related to antipsychotic treatment.

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.

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)

- Absorption
- Distribution
- Metabolism
- Elimination

- Genetics
- Age
- Disease
- Environment

[a]Reprinted with permission from Preskorn.[11]

Overview of Pharmacologic Principles

The equation in Figure 1 shows the 3 major variables that determine a drug's effect, both positive and negative, in a specific patient.[11] The Roadmap survey asked the experts how the factors in this equation can help guide medication choices over and above data from clinical trials. Questions such as these are particularly pertinent for antipsychotics, which differ considerably in their pharmacologic properties. Such differences can be important in predicting side effects and avoiding withdrawal or additive effects when drugs are titrated, tapered, or combined. Because patients with bipolar disorder are frequently treated with multiple medications, clinicians also need to be alert for potential drug-drug interactions (DDIs). The following sections briefly describe the variables in the equation as background for the case discussions that follow. For a more detailed review of these issues, readers are referred to the Roadmap supplement[1] and other publications on the pharmacology of psychiatric drugs.[12–16]

Determinants of Clinical Response

Pharmacodynamics. A drug's effects are a function of the site(s) of action to which it binds, how many sites it occupies and for how long, and its actions at these site(s) (e.g., agonism, antagonism) (as well as actions of any active metabolites). *Agonists* act like the endogenous neurotransmitter, binding to and activating a receptor. *Antagonists* produce no activation and prevent the receptor from binding to other ligands. Drugs can also fall between these points (e.g., a partial agonist may produce some activation of a receptor, while preventing full activation). 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. (Binding affinity does not indicate the effect—e.g., agonism or antagonism—a drug has on its target; for example, a drug may bind tightly to its receptor without activating it.)

The relationship between receptor binding profiles and adverse effects is better understood than the effect of receptor binding profiles on efficacy. All currently 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 (Table 2) explain some differences in the clinical profiles of these drugs, such as their propensity to cause extrapyramidal symptoms (EPS) (Table 3).[16]

The pharmacology and clinical profile of antipsychotics that affect *multiple* receptors change as the dose increases and the drug sequentially engages different target receptors in a dose-dependent, concentration-dependent manner.[14] For example, quetiapine binds most potently to the histamine-1 (H_1) and the alpha-1 norepinephrine (α_1) receptors and only affects other receptors as its dose and hence concentration increases. To achieve D_2 occupancy, the dose and hence concentration of quetiapine must typically be increased to a level 10

Table 2. 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,[14] with permission, based on Richelson,[17] Abilify package insert,[18] Arnt and Skarsfeldt,[19] Bymaster et al.,[20] and Seeger et al.[21]
[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.

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.[16]
Abbreviations: α_1 = alpha-1 norepinephrine, M_1 = muscarinic acetylcholine-1.

times higher than is needed to affect the H_1 and α_1 receptors.[1,16] Thus, while lower doses may be effective for sedation, randomized controlled trials suggest that higher doses (e.g., 300 mg for bipolar depression and 400–800 mg for bipolar mania) are usually needed for efficacy in treating bipolar disorder.[22] Risperidone's affinity for the 5-HT_2 and D_2 receptors is fairly close, explaining the increased incidence of EPS at doses above 6 mg/day.[1] 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.[1,21] Differences in the relative engagement of serotonin and dopamine receptors may explain why early "activation" and insomnia sometimes seen with ziprasidone (thought to be mediated by serotonin mechanisms) are associated with lower doses and abate at higher doses (e.g., 120 mg/day) when that effect is mitigated by effects on D_2 receptors.[23] In contrast, early activation and insomnia sometimes seen with aripiprazole are believed to be associated with dopamine agonism and are more common at higher doses.[1,23] Since aripiprazole appears to have a flat dose-response curve between 15 and 30 mg/day, aiming for a target dose at the lower end of that range can help minimize problems with activation with this agent.[23]

Because of their effects on the D_2 receptor, antipsychotics can cause EPS. Generally, D_2 blockade greater than 80% is associated with markedly increased risk of acute EPS,[24,25] so that unopposed D_2 antagonism is associated with a relatively narrow window between efficacy and risk of acute EPS. It has been postulated that SGAs have a lower risk of EPS because of the mediating effects of other receptors they affect. There is also a lower risk of EPS with the new class of D_2 partial agonists. For example, aripiprazole has 30% of dopamine's intrinsic activity at the D_2 receptor and hence cannot exceed the equivalent of 70% blockade (antagonism) of D_2 receptors even if it occupies 100% of those receptors.[1,18] This profile is confirmed by studies showing that doses of aripiprazole that produce 95% occupancy of D_2 receptors in the striatum are not associated with increased risk of EPS.[18]

Pharmacokinetics refer to the ways in which drugs enter and leave the body and 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 later cleared from the body. Differences in how antipsychotics are metabolized and cleared are relevant to questions about use of long-acting antipsychotics, effects of coprescribed medications, 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. This variation is partly due to factors such as age, gender, and individual genetic variability in receptor activity or metabolic pathways. Other medications the person is taking may also affect response due to pharmacodynamic or pharmacokinetic DDIs. Some variations in response cannot be predicted given our current level of knowledge (e.g., clinically important but currently unknown genetic differences), although tests for some variations in drug-metabolizing enzymes have become available.[26]

Drug-Drug Interactions

Drugs are an important cause of acquired biological variance that can change response to concomitantly prescribed drugs.[13] Drugs can interact 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 DDIs involve effects on phase one (oxidative) metabolism via the cytochrome P450 (CYP) enzyme system responsible for the clearance of most drugs.[13] 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.[27] Thus, it is important to consider other medications a patient is taking in adding,

changing, or adjusting the dose of psychiatric medications.[13] For information on DDIs involving psychiatric drugs, see Preskorn and Flockhart.[12]

Diagnostic Issues

Before discussing specific cases that illustrate how to apply the Roadmap principles, it is important to review 2 diagnostic issues that frequently arise in the treatment of patients with bipolar disorder.

Misdiagnosis of Bipolar Depression

The Roadmap stresses the importance of obtaining as much information as possible about diagnosis and treatment history before making treatment decisions.[1] A major issue, especially early in the course of illness, is the frequency with which the diagnosis of bipolar disorder, especially bipolar II, is missed. Because many individuals with bipolar disorder spend a greater percentage of their time in depressive than manic or hypomanic episodes[28,29] and are more likely to present for care for depression, bipolar depression is often misdiagnosed as unipolar depression. Bipolar II disorder, characterized by prominent depressive episodes and hypomanic but never manic episodes, is particularly challenging to diagnose correctly, since hypomanic symptoms are often not recognized as a problem or reported by patients and families. Based on a review of the literature, Muzina et al.[30] reported that as many as 1 in 5 depressed outpatients may have unidentified bipolar disorder.

Misdiagnosis of bipolar disorder can lead to inappropriate treatment, worsened symptoms, and increased hospitalization and emergency room visits.[31] Patients with bipolar disorder misdiagnosed with unipolar depression are often prescribed antidepressants alone without appropriate mood-stabilizing agents, which can induce a switch into a manic or mixed episode (see case of Mr. A below) and result in more severe rapid cycling.[32,33] In a naturalistic 1-year study, Ghaemi et al.[32] found that 37% of patients with affective disorders in a psychiatric clinic were misdiagnosed with unipolar depression and treated with antidepressant monotherapy and that 55% of these patients developed a manic or hypomanic episode and 23% developed new or accelerated rapid cycling. Therefore, mood-stabilizing medications (e.g., lithium, divalproex, an SGA) are recommended for all phases of bipolar illness.[7,32,33] Perhaps most importantly, untreated bipolar illness is associated with a high risk of suicide, reported to be 15% to 19%.[34] Accurate diagnosis is particularly important because suicidal behavior is more prevalent in patients with bipolar disorder than unipolar depression, with suicidal acts more likely during the first year of illness.[35] Studies have found that *appropriate* treatment of all types of mood disorders can significantly reduce the incidence of suicide over the course of illness,[36] highlighting the importance of correctly identifying and appropriately treating bipolar disorder as early as possible.

Thus, before prescribing for patients with depressive symptoms, it is important to rule out a bipolar disorder. Clinicians should be alert for clues that suggest bipolarity, including early (prepubertal or adolescent) or postpartum onset of depression; family history of bipolar disorder; multiple comorbid disorders, especially substance use disorders; greater recurrence; higher number of previous depressive episodes; "treatment-resistant" unipolar depression (i.e., failure to respond to multiple trials of antidepressant monotherapy); and a recurring pattern of disrupted employment and interpersonal relationships.[33,37,38] However, only careful history-taking and symptom assessment can establish the diagnosis, and a provisional diagnosis and longitudinal follow-up may be needed before the diagnosis is established. While screening tools, such as the Mood Disorder Questionnaire,[39] can be helpful in starting a conversation with a patient about bipolar disorder, no instrument has been shown to substitute for, or be superior to, a careful diagnostic assessment.

Substance Abuse

Patients with bipolar disorder have higher rates of substance abuse than the general population,[40] and it is estimated that over half will meet criteria for substance abuse at some point in their lives.[41] Bipolar disorder with comorbid substance abuse is associated with significantly reduced adherence to treatment and poorer outcomes, as well as higher rates of suicidality.[42–44] It is important that patients with bipolar disorder who do not have an adequate treatment response or who have persistent relapses be evaluated for substance abuse. Treatment guidelines for serious mental illness recommend that substance abuse problems be targeted in integrated treatment programs.[45] Studies[46,47] suggest that divalproex is helpful for patients with bipolar disorder and co-occurring substance or alcohol dependence. A recent placebo-controlled study[48] found that quetiapine was associated with a statistically significant decrease in depressive symptoms, but not alcohol use, in patients with bipolar disorder and alcohol abuse or dependence. The experts in the Roadmap survey also recommended considering use of a long-acting injectable antipsychotic (preferably an SGA) when lack of response to antipsychotic medication occurs in the context of consistent substance abuse, probably reflecting concern that patients are less likely to take their medications as prescribed when intoxicated.[1]

Applying the Roadmap Principles in Treatment of Bipolar Disorder

Mr. A: Mania With Psychotic Symptoms

Mr. A, a 26-year-old man, is brought to the emergency room (ER) by ambulance after being arrested for running on the field during a professional baseball game. He is observed in the ER wearing a baseball hat and shirt and carrying a baseball glove he refuses to relinquish. When asked

about the incident at the baseball stadium, he declaims in a loud voice that he is the "greatest baseball player who ever lived" and jumped on the field because "the team needs me if they are ever going to get to the World Series." He says he hears voices telling him he is "the athlete the world has been waiting for" and "to take action before it is too late." When a nurse asks Mr. A to put the glove down so that he can take his blood pressure, Mr. A becomes belligerent and begins cursing in a loud and menacing voice. The ER physician diagnoses acute mania. Because the patient refuses to take oral medication and is judged to be out of control and potentially dangerous, the ER physician elects to give him an injection of olanzapine 10 mg IM. Over the next hour, Mr. A becomes much calmer and is admitted to the inpatient psychiatry service, where oral olanzapine treatment is continued.

If you were the inpatient psychiatrist, what information and assessments would you want to obtain?

Before deciding on a treatment recommendation, the inpatient psychiatrist will want to obtain as complete a medical history as possible, including information from the family and significant others if the patient agrees to such contact, as well as vital signs, routine laboratory tests, a toxicology screen, and a physical examination if possible. The purpose of these assessments is to rule out other possible causes of the patient's symptoms (e.g., delirium, intoxication, and withdrawal must always be considered in the differential diagnosis of the manic patient).[49]

The toxicology screen shows no evidence of substance abuse, and the laboratory results and physical examination do not reveal any conditions that might be responsible for the patient's symptoms. With the patient's permission, the inpatient psychiatrist speaks with Mr. A's wife, from whom he learns that his primary care physician had prescribed sertraline 50 mg/day 10 days earlier because of Mr. A's complaints of depression. What medication options would you consider at this point?

As discussed above, it appears that Mr. A was initially misdiagnosed with unipolar depression and prescribed antidepressant monotherapy, which led to a switch into acute mania. Guidelines on the treatment of bipolar mania with psychotic symptoms recommend use of a mood stabilizer (e.g., lithium, divalproex) combined with an antipsychotic.[7,9] Lithium is the only medication that has been shown to reduce suicide rates among patients with bipolar disorder.[50] Thus, unless there is a medical contraindication (e.g., kidney disease) for use of lithium or the patient appears unable to adhere to necessary blood level monitoring, lithium is generally a good initial treatment option for monotherapy for a patient such as Mr. A who presents with classic manic symptoms. The inpatient psychiatrist discontinues sertraline treatment and begins the patient on lithium treatment, while continuing treatment with oral olanzapine, with a plan to taper and discontinue it once the patient is stabilized. A common error in this situation is discontinuing the atypical antipsychotic too early: it is generally recommended that clinicians wait approximately 8 weeks after the patient achieves remission before beginning to taper the antipsychotic.[9]

Mr. A improves with a combination of lithium and olanzapine and is discharged with referral for follow-up in the outpatient clinic. When first seen for follow-up, he continues to be symptomatic but is improving. However, Mr. A, who participates in a number of sports, complains about some weight gain (2–3 lb) and wants to discontinue both medications. If you were the outpatient psychiatrist, what would you suggest?

The outpatient psychiatrist discusses the risk of relapse associated with discontinuing medication at this point and encourages Mr. A to continue both medications for at least 4 more weeks to reduce risk of relapse. The patient agrees to continue both medications until his 8-week follow-up. The psychiatrist orders a lipid panel, which shows normal levels.

When seen for his 8-week follow-up, Mr. A's symptoms appear to be in remission, but he complains about continued weight gain despite exercise and trying to watch his diet. He says he is doing fine and really wants to stop the medications. What would you suggest?

The outpatient psychiatrist suggests that Mr. A taper and discontinue one of the medications to see if this will help with the weight problem, since he believes the combination of the agents may be having an additive effect on the patient's weight. He suggests continuing lithium treatment because of its possible benefit in suicide prevention and slowly tapering the olanzapine.

Mr. A does well symptomatically with lithium monotherapy; however, he continues to complain of weight gain and also about a tremor in his hands that interferes with his ability to participate in the sports he enjoys. He says he wants to stop the lithium. What would you advise?

Five SGAs—aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone—are approved by the U.S. FDA as monotherapy for acute manic and (except for quetiapine, which was studied only in "pure" mania) mixed episodes, but only 3 of the SGAs, aripiprazole, olanzapine, and quetiapine, have so far been approved for the maintenance treatment of bipolar disorder.[51–53] The Roadmap experts concluded that dose reductions of antipsychotics are unlikely to help with weight or metabolic problems and suggested switching to an agent with lower weight gain liability and metabolic risk (Table 4) if these problems do not respond to changes in diet or lifestyle.[1] For a review of metabolic effects of SGAs, see Newcomer.[54] For recommendations on monitoring weight and metabolic problems in patients treated with antipsychotics, see the 2004 Consensus Development Conference statement from the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the

Table 4. 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.[10]
[b]Newer drugs with limited long-term data.
Symbols: + = increase effect, – = no effect, D = discrepant results.

North American Association for the Study of Obesity.[10]

The outpatient psychiatrist discusses options with Mr. A, including switching to a different medication such as divalproex or one of the atypical antipsychotics. Mr. A expresses reluctance to try divalproex because of concern about weight gain. Given that Mr. A's weight has not responded to diet or exercise, the outpatient psychiatrist recommends adding aripiprazole and gradually discontinuing lithium. He advises Mr. A and his wife about the need for close monitoring for emergence of depressive symptoms, since there is no evidence that aripiprazole is effective in preventing depressive recurrences in bipolar disorder. Mr. A does well on aripiprazole monotherapy and, at 6-month follow-up, reports that he has returned to his previous weight and the hand tremor has vanished.

Ms. B: Breakthrough Manic Symptoms

Ms. B, a 32-year-old woman with a well-documented history of bipolar disorder, has been treated with lithium 1200 mg daily (blood level 0.8 ng/mL). While she has had fewer recurrences than prior to treatment and has tolerated the lithium well, she has had repeated manic episodes and is now admitted for the third time for manic symptoms. On admission, the patient is agitated and hyperactive and speaks rapidly with marked flight of ideas and clanging associations, but no evidence of psychotic thinking. In the week before admission, she was sleeping only 2 to 3 hours per night, charged several thousand dollars of clothing she did not need, and drew up an elaborate plan to reorganize the company for which she works even though no one has asked her to do so. Because the patient's mania has not responded to lithium monotherapy, the inpatient clinician considers whether to switch to or add another mood stabilizer.

What factors would influence your decision?

Treatment guidelines for bipolar disorder stress the importance of optimizing lithium treatment before making other changes in regimen.[7,9] Although there is disagreement about optimum lithium levels, a recent literature review reported 0.4 ng/mL as the minimum efficacious serum lithium level in long-term bipolar treatment, with optimal response seen at levels of 0.6 to 0.75 ng/mL, while levels > 0.75 ng/mL may improve control of interepisode manic symptoms.[55] Ms. B's blood level indicated that lithium levels had been optimized, so the clinician was faced with the decision of whether to switch to or add a different mood stabilizer to try to achieve better control of the mania.

If a patient such as Ms. B has had a partial response to mood stabilizer monotherapy, the Expert Consensus Guidelines recommend adding an atypical antipsychotic.[9] Although only 1 head-to-head comparison of SGAs in bipolar mania has been published,[56] 2 recent meta-analyses[57,58] suggest that all 5 SGAs have similar antimanic efficacy comparable to (but not greater than) that of lithium, divalproex, or haloperidol; that combinations of antipsychotics and mood stabilizers are modestly but significantly more effective than mood stabilizer monotherapy for acute mania; and that the main differences among the SGAs and between SGAs and other mood stabilizers involve their side effects. Thus, choice of specific agent as monotherapy or adjunctive therapy for bipolar mania is generally guided by considerations of safety, tolerability, and cost.

With traditional mood stabilizers, clinicians must consider potential for renal and thyroid toxicity, safety concerns about lithium overdose,[59] potential for myelotoxicity with divalproex,[60] and potential for weight gain and required blood level monitoring with both lithium[59] and divalproex.[60] Side effects of concern with the atypical antipsychotics include metabolic dysfunction (weight gain, type 2 diabetes, dyslipidemia), hyperprolactinemia, and EPS.[51] Safety and tolerability issues also include the potential for pharmacodynamic and/or pharmacokinetic DDIs. No currently available treatment is free of side effects or safety concerns, so that achieving best outcomes involves balancing risks and benefits.[1] As noted in the Roadmap supplement,[1] better understanding of pharmacologic principles and the properties of specific agents and how they are likely to interact with the individual's characteristics can help clinicians maximize efficacy while minimizing side effects. A review of controlled studies of adjunctive therapy for acute mania[61] found that combinations of lithium or divalproex with olanzapine, risperidone, haloperidol, or quetiapine had additional antimanic efficacy over monotherapy similar in magnitude to the differences seen between monotherapy with these agents and placebo, and that the benefits of the combinations enhanced tolerability of adverse effects sufficiently to allow a higher proportion of subjects to complete the studies than those treated with monotherapy.

The psychiatrist discusses options with Ms. B and her husband and provides information about the side effects associated with each agent so that they can make an informed decision. He explains that the goal is to better control the manic symptoms by adding another medication that has antimanic efficacy

but is unlikely to interact with the lithium (i.e., will not require lithium dose adjustment and does not have a high risk for additive side effects).

Ms. C: Bipolar Depression

Ms. C, a 40-year-old woman with bipolar disorder, has been stable on lithium monotherapy for several years but now presents with increasingly dysphoric mood, anhedonia, increased appetite, and lethargy. She denies suicidal thoughts and does not have psychotic signs or symptoms. Her outpatient psychiatrist diagnoses bipolar depression and orders a lithium level and thyroid function tests. The lithium level is 0.8 ng/mL and thyroid function tests are normal.

What options would you consider for a patient with breakthrough depression during lithium monotherapy, and how would you choose among them?

Although treatment guidelines generally recommend continuing effective, well-tolerated acute phase treatment for long-term maintenance therapy, limited data are available to guide maintenance treatment decisions. Among the SGAs, olanzapine (in fixed-dose combination with fluoxetine) and quetiapine are FDA-approved for treatment of acute bipolar depression, while only aripiprazole, olanzapine, and quetiapine are approved for bipolar maintenance treatment. There are also promising findings concerning quetiapine in maintenance therapy.[62,63] Lamotrigine is also indicated for the maintenance treatment of bipolar disorder, although it does not have an indication for and has not shown significant benefit in placebo-controlled studies for treatment of acute depression. Both olanzapine and quetiapine are associated with weight gain and metabolic abnormalities when taken on a long-term basis, while lamotrigine is associated with a risk of rash. The psychiatrist discusses the options with Ms. C, who expresses concern about the risk of rash with lamotrigine, despite the relatively low risk.

The psychiatrist decides to add quetiapine 50 mg at bedtime to the lithium. The dose of quetiapine is increased to 100 mg at bedtime the next day and then 200 mg at bedtime 1 day later. One week later, Ms. C reports that she is beginning to feel less depressed. The dose is ultimately raised to 300 mg at bedtime, and her depressive episode resolves. However, the patient complains about feeling fatigued and sedated with this dose of quetiapine, but is reluctant to stop the medication because of concern about the depression returning.

The psychiatrist reviews options with Ms. C, which include tapering and discontinuing the quetiapine and going back to monotherapy with lithium or cross-tapering to another agent such as olanzapine or lamotrigine for prevention of recurrence. Given the patient's problem with sedation and the fact that her depressive symptoms have remitted, the psychiatrist suggests a trial of adjunctive lamotrigine as maintenance therapy. The patient is now willing to try lamotrigine and does well with a combination of lithium and lamotrigine 200 mg/day.

Conclusion

The Roadmap recommendations concerning use of antipsychotic medications are based on the principle that best outcomes for individual patients can be achieved by considering risks and benefits of each treatment option in the context of each patient's diagnosis (including both primary psychiatric illness and comorbid psychiatric and medical conditions), current symptomatic presentation, illness and treatment history, age, gender, and psychosocial situation, as well as personal goals and preferences. Achieving best outcomes involves balancing risks and benefits, and trade-offs frequently have to be made.[1,64] Clinicians also need to encourage optimism and educate patients that it may take a number of trials before a treatment regimen that is well suited to their situation is identified. Since no available treatments are free of adverse effects, a better understanding of pharmacologic principles and of the properties of the different agents and how they are likely to interact with the patient's individual characteristics can help clinicians maximize efficacy while minimizing side effects.

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin and others), divalproex (Depakote), fluoxetine (Prozac and others), haloperidol (Haldol and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), olanzapine/fluoxetine combination (Symbyax), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft and others), ziprasidone (Geodon).

Disclosure of off-label usage: Dr. Perlis has determined that, to the best of his knowledge, divalproex is not approved by the U.S. Food and Drug Administration for maintenance treatment in bipolar disorder, and lamotrigine and quetiapine are not approved for the treatment of bipolar depression.

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