Antipsychotic Drug Side Effect Issues in Bipolar Manic Patients

Carlos A. Zarate, Jr., M.D.

While the efficacy of antipsychotics as a maintenance treatment for bipolar patients has not been systematically studied, these drugs are commonly used in the long-term treatment of bipolar patients, and it is not unusual for a bipolar patient to be taking 3 to 4 medications, including antipsychotics. Conventional antipsychotics may be comparable to lithium for acute mania, but have limitations when used in the long-term treatment of bipolar disorder. Their adverse effects, which include extrapyramidal side effects, tardive dyskinesia, weight gain, sedation, and sexual dysfunction, often lead to noncompliance; their use may have a negative impact on the overall course of illness; and they may not be as effective as lithium in treating the core manic symptoms over the long term. Atypical antipsychotics may prove useful for bipolar patients who require antipsychotic treatment because of their favorable side effect profile, thymoleptic properties, and positive effect on overall functioning.

(J Clin Psychiatry 2000;61[suppl 8]:52–61)

Antipsychotic agents have been used in the treatment of bipolar disorder for close to 40 years. Prior to the lithium era, somatic strategies for bipolar disorder primarily included neuroleptics, antidepressants, barbiturates, and electroconvulsive therapy (ECT). More recently, antipsychotics are increasingly used for those bipolar patients who fail to respond to or are unable to tolerate the traditional mood stabilizers. While conventional antipsychotics may offer some advantages in terms of rapidity of action and availability in the depot form, the use of this class of drugs is frequently associated with troublesome side effects that may make managing the illness much more difficult. Atypical antipsychotics, which have a more favorable side effect profile than traditional neuroleptics, are increasingly being used for refractory patients with bipolar disorder, primarily to augment the effects of mood stabilizers. Increased study of their efficacy and safety in the different phases of bipolar disorder for both the short- and long-term treatment is occurring at a rapid pace.

From the Bipolar and Psychotic Disorders Program, University of Massachusetts Medical School, Worcester.

Presented at the planning roundtable "Side Effects of Antipsychotic Medications: Physicians' Choice of Medication and Patient Compliance," held January 22, 1999, in Dallas, Texas, and sponsored by an unrestricted educational grant from Janssen Pharmaceutica, L.P.

Reprint requests to: Carlos A. Zarate, Jr., M.D., Bipolar and Psychotic Disorders Program, Department of Psychiatry, University of Massachusetts Medical School, 361 Plantation St., Worcester, MA 01655 (e-mail: carlos.zarate@umassmed.edu).

TRADITIONAL ROLE OF ANTIPSYCHOTICS IN BIPOLAR DISORDER

Bipolar disorder is a chronic recurring illness that affects between 0.4% and 1.6% of the population.[1,2] Many patients with bipolar disorder fail to respond to mood stabilizers, and bipolar patients are perhaps more likely than patients with schizophrenia to require a combination of medications. Many data are available on the short- and long-term efficacy and safety of lithium, carbamazepine, and divalproex sodium when used in monotherapy, but very few data exist on how well they "mix" when used in combination for long periods of time. Even more remarkable is the fact that the majority of bipolar patients are more likely to receive combination therapy than monotherapy. While the efficacy of antipsychotics as a maintenance treatment for bipolar patients has not been systematically studied, these drugs have been reported to be commonly prescribed in the long-term treatment of bipolar patients.[3,4] Combination treatment can increase the number and severity of side effects. For this reason, careful consideration should be given each time a new drug is added to the ongoing medication regimen as a synergy in side effects may occur.

Psychotic symptoms are common in bipolar disorder. Goodwin and Jamison[5] reported that 58% of patients with bipolar disorder have at least 1 psychotic symptom, and, by self-report, 90% of patients have at least 1 psychotic symptom (Keck PE Jr. Stanley Foundation Bipolar Network. Unpublished data, 1998). All forms of psychosis may occur in affective psychosis including mood-incongruent, bizarre, and Schneiderian first-rank symptoms.[6,7] Psychotic

symptoms occurring in manic patients may present as either disturbances in the content of thought, formal thought disorder, or both. Delusions have been reported to be 3 times more common than hallucinations in adult manic patients. The frequency of these psychotic symptoms in manic patients are delusions, 45%; Schneiderian first-rank symptoms, 18%; and hallucinations, 15%.

Despite the widely held Schneiderian view that formal thought disorder is diagnostic for schizophrenia, McElroy et al.[8] reported comparable rates of thought disorder in mania and schizophrenia. Qualitative comparisons between manic and schizophrenic thought disorder have been less consistent, but suggest that mania may be more associated with positive thought disorder, such as pressured speech, derailment, loss of goal, and tangentiality, while schizophrenia may be more associated with negative thought disorder, such as poverty of speech content, neologisms, private use of words, disorganized or confused speech, and underinclusive thinking. Andreasen[9] estimated the frequency of types of thought disorder in patients with mania and reported in order of frequency: pressured speech, 72%; derailment, 56%; loss of goal, 44%; tangentiality, 34%; illogicality, 25%; poverty of content, 19%; and incoherence, 16%. In summary, disturbances in thought content and process are common in manic patients. The cross-sectional assessment of the type and severity of psychotic symptoms will not help to differentiate in a consistent manner whether the patient has schizophrenia or mania. The longitudinal course of illness, family history, and other characteristics are more reliable methods for ascertaining an accurate diagnosis of mania.

The presence of psychotic symptoms, particularly mood-incongruent symptoms in bipolar illness, has been suggested to have some prognostic value in that the presence of these features appears to predict a worse course of illness. Tohen et al.[10] conducted a survival analysis in 75 patients for 48 months after recovery from an episode of mania. Patients whose index episode had psychotic features were more likely than those without psychotic features to have a subsequent episode of mania or major depression. By 4 years, only 26% of patients with psychotic features at the index episode remained well as opposed to 52% of those without psychotic features. The risk of having an affective episode is even greater when these patients who presented with psychotic features during their index episode are subtyped by the congruence of their psychotic features. Patients who had mood-congruent psychotic features were more likely to "survive" (less likely to relapse) than patients with mood-incongruent psychotic symptoms. The presence of mood incongruent symptoms at index hospitalization predicted a shorter time in remission at 4 years.[11] Thus, in the presence of a patient with a manic episode, it is important to determine whether the patient has or does not have psychosis and if the patient has psychosis, to determine whether these symptoms are or are not mood congruent.

Table 1. Typical Antipsychotics as Maintenance Treatment in Bipolar Disorder

Study	Year	Patients (N)	Maintenance Antipsychotics (%)
Sachs[15]	1990	215	37
Sernyak et al[16]	1994	40	95
Verdoux et al[17]	1996	222	67
Keck et al[4]	1996	77	68
Sernyak et al[3]	1997	49	67
Zarate and Tohen[18]	2000	129	24

While many somatic therapies have been used in bipolar disorder, only the mood stabilizers lithium, valproate, and carbamazepine have been well studied. Combinations of anticonvulsants, lithium, adrenergic-blocking agents, hormones, calcium-channel blockers, cholinergic agents, antidepressants, phototherapy, ECT, and both conventional and atypical antipsychotic agents have all been tried but are less well studied. Conventional antipsychotics have been used for over 40 years and were originally used to treat highly agitated patients. Many of these patients had a high risk of mortality resulting from dehydration and exhaustion, referred to as *lethal catatonia.* Historically, the use of these agents was also instrumental in discharging many chronically ill patients who had been institutionalized. In later years, the conventional antipsychotic drugs were demonstrated to be useful in the initial control of psychotic symptoms and increased psychomotor activity in manic patients. While this class of drugs were found to have a more rapid onset of action than lithium (in controlling hyperactivity), the neuroleptics were found to be less effective than the mood stabilizers lithium, valproate, and carbamazepine for the prophylaxis of bipolar disorder.[12] Clinical guidelines suggest that conventional antipsychotics should be used sparingly and only during the acute phase of illness because of the risk of adverse events and negative impact on the course of illness they may cause when used long term.[13,14]

However, contrary to the recommendations of experts, many bipolar patients take conventional antipsychotics both intermittently and as adjunctive treatment for long periods of time. A series of studies[3,4,15–18] reviewing the use of typical antipsychotics as maintenance treatment in bipolar disorder found that between 24% and 95% of outpatients were taking conventional antipsychotics on a long-term basis (Table 1). Keck et al.[4] identified several factors significantly associated with maintenance antipsychotic treatment in bipolar patients; these included male gender, medication noncompliance in the month prior to the index hospitalization, severity of manic symptoms, and antipsychotic medication prescribed at discharge.

Limitations of Conventional Antipsychotic Drugs

Conventional antipsychotics may be comparable to lithium for treating hyperactivity or extreme agitation in acute mania, but have many limitations when used in the

long-term treatment of bipolar disorder. Major disadvantages of the conventional antipsychotic drugs include adverse effects. These adverse effects include extrapyramidal side effects (EPS), tardive dyskinesia, weight gain, sedation, and impaired sexual function. These side effects resulting from treatment with conventional antipsychotic drugs may lead to noncompliance and all the consequences associated with noncompliance. Consequences of noncompliance include relapse or recurrence, rehospitalization, impaired interpersonal relationships, family conflicts or dysfunction, occupational difficulties, financial crises, marital difficulties, suicide, violence, and increased costs to society. Prolonged use of traditional neuroleptics as adjunct to lithium or another mood stabilizer may also have a negative impact on the overall course of illness by causing dysphoria (neuroleptic dysphoria) or increasing the frequency of depressive episodes. The patient's response to a mood stabilizer may be obscured when the initial regimen includes both a mood stabilizer and an antipsychotic rather than a mood stabilizer alone, and therefore, determination of the optimal long-term mood-stabilizer regimen for a particular patient may be delayed. Finally, when conventional antipsychotics are used as maintenance treatment, they may not be as effective as lithium in treating core manic symptoms.

It has been suggested that patients with bipolar disorder may have increased vulnerability to EPS and tardive dyskinesia compared with patients who have schizophrenia. Data involving relatively young adult schizophrenics suggest a cumulative incidence of tardive dyskinesia of 4% per year of neuroleptic exposure.[19] In a study of 135 schizophrenic and 46 manic neuroleptic-treated patients, Nasrallah et al.[20] reported that a significantly higher proportion of manic patients (26.1%) than schizophrenic patients (5.9%) developed acute dystonia. The risk of EPS may be increased in patients who are being treated with a combination of lithium and a conventional antipsychotic rather than an antipsychotic alone.[21] Spina et al.[22] recommend the use of prophylactic anticholinergics in young men to prevent dystonic reactions. Since bipolar patients may be exquisitely sensitive to EPS,[23] the long-term use of conventional neuroleptics should in general be avoided in these patients. However, there may be a group of bipolar patients who require prolonged neuroleptic treatment as in the case of noncompliance (depot preparation) or refractoriness to traditional agents.

Other side effects that may limit the use of antipsychotics in bipolar disorder are weight gain, sedation, and sexual dysfunction. When the first neuroleptic chlorpromazine was introduced, a large majority of patients gained considerable amounts of weight, and similar problems have occurred to varying degrees with other antipsychotics. Excessive weight has long-term consequences in terms of medical morbidity. Many patients with bipolar disorder are reluctant to take any medication that will cause weight gain. Traditional neuroleptics are also sedating, particularly at high doses, and this side effect can be troublesome during extended treatment. Sedation may seem beneficial, at least initially, in highly agitated patients with acute mania but may impair the ability to function adequately over the long term. While the true incidence and negative impact of antipsychotics on sexual function are unknown because of reporting difficulties, ejaculatory dysfunction, breast tenderness and swelling, and menstrual cycle irregularities have been linked to increased prolactin levels. Patients with bipolar disorder tend to be noncompliant with treatment, and weight gain, sedation, and sexual dysfunction are frequently cited by bipolar patients as reasons for treatment discontinuation.

Not only are conventional antipsychotic drugs associated with adverse effects, but they may have a negative impact on the course of illness. Continued use of conventional antipsychotics may provide protection against recurrent mood elevation and psychotic symptoms, but may neither alter underlying cyclicity nor protect against recurrence of depression.[5] Routine use of conventional antipsychotics to control manic symptoms may precipitate major depressive episodes that often follow manic episodes[24,25] and induce rapid cycling in some patients.[24] Ahlfors et al.[26] found that patients taking the neuroleptic flupenthixol were more likely than those taking lithium to have recurrent depression. Conventional antipsychotics are probably best viewed as antimanic agents that lack antidepressant or mood-stabilizing properties and thus fail to protect against the recurrence of depression. Furthermore, continuous use of the conventional neuroleptics in patients with bipolar disorder has been reported to interfere with long-term functioning.[10]

Although they are effective for the acute treatment of mania, conventional antipsychotics may be less effective than lithium, and possibly other mood stabilizers, for maintenance treatment of the core manic symptoms.[5] In a meta-analysis of 4 controlled, double-blind studies comparing lithium with conventional antipsychotics in patients with mania,[27] lithium was statistically significantly more effective than antipsychotics; 89% of patients treated with lithium responded compared with 54% of those treated with antipsychotics.

Nevertheless, in spite of the limitations with conventional antipsychotic drugs described above, they are an important part of the armamentarium for treating bipolar disorder. Even when acute psychotic mania is treated with mood stabilizers and adjunctive benzodiazepines, adjunctive antipsychotics are sometimes necessary. In addition, some patients are resistant to, intolerant of, or noncompliant with mood stabilizers. However, because conventional antipsychotics probably are not mood stabilizing and may be more likely to induce tardive dyskinesia in bipolar patients than in schizophrenic patients, the risks and benefits of these agents must be carefully evaluated regularly to

determine whether the antipsychotic dose can be decreased or the agent itself discontinued. The newer atypical antipsychotics, which have a more favorable side effect profile than the older conventional agents and appear to have thymoleptic properties, should be considered as potential alternatives to conventional antipsychotics in the acute and long-term treatment of bipolar disorder.

ATYPICAL ANTIPSYCHOTICS IN BIPOLAR DISORDER

Clinical experience accumulated over the last 2 decades indicates that about 40% of patients in the acute phase of bipolar disorder and close to 80% of patients with the mixed manic-depressive and rapid cycling forms of bipolar disorder are resistant to lithium.[28–30] Furthermore, a substantial proportion of bipolar patients are unable to tolerate the side effects of lithium. The introduction of anticonvulsants for the treatment of bipolar disorder has been a significant advance, as they are effective not only in classic mania, but also in the rapid cycling and mixed forms of the illness in which lithium is less effective. In spite of these newer mood stabilizers, some bipolar patients remain nonresponsive to mood-stabilizing compounds and require antipsychotic treatment. Atypical antipsychotics may prove useful for these patients due to their favorable side effect profile and positive effect on overall functioning compared with conventional agents.

There are open-label reports of clozapine and both open-label and controlled studies of risperidone and olanzapine in bipolar disorder. Data are emerging for quetiapine in affective illness. These preliminary reports indicate that the atypical agents clozapine, risperidone, and olanzapine may have an important role in the treatment of bipolar illness.

Clozapine

A growing number of open-label studies performed over the past decade have shown the efficacy of clozapine in some patients with schizoaffective and bipolar disorder who responded inadequately to or were unable to tolerate mood stabilizers or conventional antipsychotic medications. My colleagues and I[31] conducted a meta-analysis involving primarily retrospective and open-label studies of clozapine conducted from 1973 to 1995. Patients in manic or psychotic phases of schizoaffective or bipolar disorder were significantly more likely to respond to clozapine than patients with schizophrenia (71.2% of 315 affective patients vs. 61.3% of 692 schizophrenic patients; $p = .0006$). Patients in the manic and mixed-psychotic state of illness were also more likely to respond to clozapine than patients with major depressive syndromes (72.2% of 79 manic and mixed patients vs. 51.7% of 58 depressed patients; $p = .001$).

Four other open studies suggest that clozapine may be useful in the maintenance treatment of bipolar disorder. In the first, Suppes et al.[32] used clozapine for 7 patients who had dysphoric mania, and all 7 continued to do well over a mean of 4 years of follow-up. The second study[33] found that 11 (65%) of 17 patients with a diagnosis of bipolar or schizoaffective disorder were successfully maintained on clozapine monotherapy for a mean of 16 months with no rehospitalizations. Third, Calabrese et al.[34] reported that 22 patients (11 bipolar and 11 schizoaffective) continued to take clozapine for a mean of 15 months. Finally, an open-label randomized 1-year trial[35] of clozapine for refractory bipolar patients reported a significant improvement in psychotic and manic symptoms by 6 months that was sustained over the next 6 months. All these studies suggest that clozapine is generally well tolerated. In a long-term follow-up study of patients with refractory affective disorders treated with clozapine (mean length of treatment = 19 months), approximately 30% (20/65) discontinued clozapine because of side effects. The most common side effects in the patients still taking clozapine at follow-up were sedation, 24%; hypersalivation, 11%; weight gain, 15%; GI distress, 2%; seizures, 2%; leukopenia, 1%; and hypotension, 1%.[36] It is of special note that in spite of these side effects—generally clozapine is viewed as a difficult drug to use because of its side effects—more patients with bipolar disorder had higher satisfaction ratings when taking clozapine compared with patients who had other diagnoses.

However, because clozapine is associated with the risk of agranulocytosis and potentially death, for the first 6 months of treatment, white blood cell (WBC) counts must be measured weekly. If the WBC count remains within a normal range, the WBC counts may be measured every 2 weeks after 6 months. Many patients are reluctant to comply with the demands for regular blood draws; this reluctance reserves clozapine for treatment-refractory bipolar disorder.

Risperidone

Because risperidone has a more favorable side effect profile compared with clozapine and the conventional antipsychotics, several investigators examined its tolerability and efficacy in the treatment of psychotic mania. Singh and Catalan[37] reported on 4 patients with psychotic mania owing to HIV infection whose Young Mania Rating Scale scores were reduced by a mean of 77% during 10 days of risperidone therapy (mean dose = 1–4 mg/day). Some investigators[38–41] have suggested that risperidone may possess antidepressant activity and induce mania in some patients with the bipolar type of schizoaffective disorder who are not receiving a concomitant mood stabilizer.

My colleagues and I[42] conducted a 6-week open-label study of risperidone (mean dose = 3 mg/day) and concurrent mood-stabilizing drugs in the treatment of DSM-III-R acute psychotic mania. By week 6, all of the completers ($N = 8$) had a 50% improvement as assessed by the Young Mania Rating Scale. One controlled study[43] compared the

efficacy and safety of risperidone versus lithium and haloperidol in mania. Patients with DSM-IV mania (N = 45) were assigned to take 6 mg/day of risperidone (monotherapy), 10 mg/day of haloperidol, or 800 to 1000 mg/day of lithium. Patients in all 3 groups showed a similar improvement on Brief Psychiatric Rating Scale and Young Mania Rating Scale scores. The EPS of risperidone and haloperidol were not significantly different. Importantly, mania did not worsen in any of the risperidone-treated patients. Other possible side effects that may occur with risperidone therapy include insomnia, dizziness, agitation, and nausea. A recent multisite double-blind, parallel-group study[44] investigated adding risperidone, haloperidol, or placebo to a mood stabilizer (lithium or valproate) in 158 inpatients with acute mania. The haloperidol arm of the study was included as an internal reference. After completing the 3-week, double-blind phase of the study, patients were offered open-label risperidone therapy for an additional 10 weeks of follow-up. Compared with placebo, risperidone was associated with significantly greater improvement on the Young Mania Rating Scale and the Clinical Global Impressions-Improvement scale at 3 weeks. The investigator concluded that risperidone is a safe and effective addition to lithium or valproate for the treatment of bipolar mania.

While there have been cases of patients becoming manic on risperidone, without a denominator (total number of patients at risk or treated with risperidone) and a numerator (total number of cases "manic" on risperidone), it remains impossible to determine whether this event is more or less common than with other treatments. Nevertheless, until more information becomes available, it is recommended that when risperidone is used in bipolar disorder, it be used adjunctively with a mood stabilizer.

Long-term use of adjunctive risperidone for breakthrough episodes of mania or depression has been reported useful in a small open study.[45] A group of outpatients (N = 12) with bipolar disorder, type I who experienced breakthrough episodes despite adequate maintenance medication were treated with a mean dose of 2.75 mg/day of risperidone. Scores on the Global Assessment of Functioning scale improved from 10 to 25 points in 4 of the 8 patients who completed 6 months of treatment. No patient experienced a worsening of mania.

Olanzapine

Increasing data are becoming available for olanzapine in the treatment of bipolar disorder. Two studies[46,47] suggest olanzapine may be useful for depressive symptoms in schizoaffective disorder and schizophrenia. Other researchers have reported a switch to mania in patients treated with olanzapine.[48–50] McElroy et al.[51] evaluated response to olanzapine in 14 treatment-refractory bipolar patients. In this study, the authors concluded that olanzapine was well tolerated, and the most common side effects were sedation, tremor, dry mouth, and appetite stimulation with weight gain. Recently, Tohen et al.[52] reported their findings of the largest study conducted to date with an atypical antipsychotic drug in acute mania. This was a 3-week, double-blind study of patients in the acute phase of a DSM-IV bipolar manic or mixed episode comparing olanzapine (N = 70) with placebo (N = 69). Forty-nine percent of the patients responded to olanzapine compared with 24% who responded to placebo. The most common side effects in the olanzapine-treated patients compared with placebo were somnolence, dizziness, dry mouth, and weight gain. The mean weight gain in olanzapine-treated patients in this 3-week study was substantial, averaging 1.65 kg (3.63 lb) or roughly 1 lb per week of treatment with olanzapine. More long-term studies are warranted with olanzapine in bipolar patients to determine the nature and extent of this side effect. As reviewed in other sections of this supplement,[53] considerable weight gain may lead to an increased risk of morbidity and mortality.

Quetiapine

Preliminary evidence suggests that quetiapine may be an alternative antipsychotic drug for the treatment of bipolar disorder. Ghaemi and Katzow[54] first reported the efficacy of quetiapine as an adjunctive to other mood stabilizers in 6 treatment-refractory bipolar I disorder patients. The main side effect noted in their case series was sedation. In a recent study, my colleagues and I[55] assessed (by chart review) the response and factors associated with response to quetiapine in 145 consecutive patients with affective and nonaffective psychotic disorders who were newly treated with quetiapine at a psychiatric hospital. Patients displaying a moderate-to-marked response to quetiapine were more likely to receive a diagnosis of major depression with psychotic features, to be either in the manic or depressive phase of bipolar and schizoaffective disorder, and to have a shorter duration of illness than the other patients. In addition, we found quetiapine was well tolerated, and no patient discontinued it because of intolerable side effects. Eighty percent of subjects taking quetiapine were taking concomitant psychotropic medications. The most common side effects in this study were sedation, 15%; dizziness, 6%; hypotension, 4%; dyspepsia, 4%; headache, 3%; tremor, 1%; and akathisia, less than 1%. Quetiapine may be a useful alternative or adjunctive treatment for patients with psychotic mood and schizoaffective disorders. More studies are needed to determine the extent of its effectiveness and safety in patients with bipolar disorder.

Augmentation With Atypical Antipsychotics

Bipolar patients are frequently treated with combinations of antipsychotics and mood stabilizers. Freeman and Stoll[56] conducted a review of the published literature on the efficacy and safety of combination treatment with mood stabilizers. They established a safety score (5 = safe

Table 2. Management of Side Effects of Antipsychotic Drugs in Patients With Bipolar Disorder[a]

Side Effect	Characteristic	Recommended Treatment
EPS	Bradykinesia, shuffling gait, tremor	Dose reduction; anticholinergic agent; consider changing to risperidone, olanzapine, quetiapine
Tardive dyskinesia	Likely less risk with atypical agent than conventional antipsychotic	Determine need for antipsychotic (a combination of mood stabilizers is preferable to mood stabilizers and antipsychotic combinations); reduce dose or stop antipsychotic; use vitamin E; use GABAergic agent such as clozapine
Seizures	Grand mal, myoclonic	Reduce dose; consider other antipsychotic or divalproex
Sedation	Usual at beginning of treatment; useful for inpatients, but not outpatients	Consider eliminating other sedating drugs; change antipsychotic (consider risperidone); monitor thyroid function; consider less sedating mood stabilizer such as lamotrigine; consider caffeine, bupropion, or stimulant
Anticholinergic	Constipation, urinary retention, bowel obstruction; dry mouth	Discontinue other anticholinergic agents; consider changing to risperidone or quetiapine
Blood dyscrasia	Agranulocytosis	Stop antipsychotic drug; consult with hematologist; avoid combination of clozapine and carbamazepine or mirtazapine
Elevated prolactin	Unclear relationship with sexual dysfunction	Determine clinical relevance (eg, high value alone without signs and symptoms); reduce dose; change antipsychotic drug (consider olanzapine or quetiapine); consider bromocriptine
Sexual dysfunction	Galactorrhea, amenorrhea,	Consider eliminating other drugs that may affect sexual function (eg, change SSRI to bupropion, nefazodone); reduce dose; change antipsychotic agent (consider olanzapine or quetiapine); efficacy and safety of buspirone, cyproheptadine, sildenafil, bupropion are unknown
Weight gain	May be major limiting factor in maintenance treatment in order of frequency (greatest to lowest) clozapine > olanzapine > quetiapine > risperidone > haloperidol	Diet, exercise, cognitive behavioral groups; consider risperidone; consider avoiding olanzapine or quetiapine (especially if combined with valproate); consider carbamazepine or lamotrigine; unknown efficacy and safety of sibutramine, topiramate, phentermine, orlistat

[a]Abbreviations: EPS = extrapyramidal side effects; SSRI = selective serotonin reuptake inhibitor.

to 1 = not safe) and an efficacy score (5 = very efficacious to 1 = not beneficial) for combinations of mood stabilizers and antipsychotics.

There are double-blind studies that provide evidence for the efficacy and safety of lithium and conventional antipsychotics used in combination, while mainly retrospective and/or open studies or case reports are available on the efficacy and safety of either lithium or divalproex used in combination with clozapine or risperidone. There is, however, a lack of published data on the efficacy and safety of the combination of lithium or divalproex sodium and olanzapine or quetiapine. For patients with classic acute mania with psychotic features, a conventional antipsychotic and lithium are often administered first, although substantial controversy exists regarding the safety of such combinations. Freeman and Stoll[56] assigned combined treatment with lithium and a conventional antipsychotic an efficacy score of 4 and a safety score of 3. The combination may have synergistic effects, but sporadic reports of neurotoxicity, hypotension, somnambulistic-like events, cardiac and respiratory arrest, and risk of tardive dyskinesia have been linked to its use. While a lithium-clozapine combination—which was given an efficacy score of 4 and a fairly low safety score of 2—has been gaining acceptance as an effective mood stabilizer for treatment-refractory illness, the combination has been reported to cause diabetic ketoacidosis, neuroleptic malignant syndrome, myoclonus, and seizures. Rare cases of delirium and possibly a neuroleptic malignant syndrome have been reported with the use of the combination of risperidone and lithium, which received an efficacy score of 3 and a high safety score of 4. The olanzapine-lithium combination was not given an efficacy or safety score because of lack of published literature, but the authors noted the combination carries the risk of additive side effects including weight gain and sedation.

Substantial data in the form of retrospective and/or open studies or case reports exist for the efficacy of the combination of valproate and conventional antipsychotics, clozapine, risperidone, or olanzapine. Data on the efficacy of a combination of valproate and quetiapine are lacking. A conventional antipsychotic along with valproate is often administered first to patients with mixed or rapid cycling episodes or dysphoric mania with psychotic features. Freeman and Stoll[56] gave this combination an efficacy score of 4 and a safety score of 3 due to reports of encephalopathy resulting from its use. Data concerning the combination of valproate and clozapine are variable, which led to an efficacy score of 3 and a safety score of 4. In one open-label study[57] of 55 patients, the combination was effective for 87% of the patients, and the most common adverse reactions were sedation, enuresis, nausea, excessive salivation, and benign increase in liver function tests. However, another report[58] found that outcome was worse in patients receiving this combination than in those receiving clozapine alone. The combination of risperidone and valproate was given both an efficacy and a safety score of 4. No adverse events have been reported with this combination, which is likely to have less risk of tardive dyskinesia than the combination of conventional antipsy-

chotics and valproate. The olanzapine-valproate combination was not assigned an efficacy or safety score because of lack of published literature, but the authors noted the combination carries the risk of additive side effects including weight gain and drowsiness. Data from 2 large retrospective chart reviews found that both olanzapine[59] and quetiapine[55] were effective and well-tolerated when given in combination with other psychotropic drugs (e.g., mood stabilizers and antidepressants) in patients with affective and nonaffective psychotic disorders.

MANAGEMENT OF SIDE EFFECTS

The management of antipsychotic side effects is similar in both patients with bipolar disorder and in those with schizophrenia, but there are some differences. The main difference is that in patients with schizophrenia, the primary drug for the management of schizophrenia is an antipsychotic drug; in contrast the primary drug(s) for the long-term prophylaxis of bipolar disorder is not the antipsychotic drug but a mood stabilizer (lithium, divalproex, or carbamazepine). The most common side effects that clinicians encounter when treating bipolar patients when using a combination of mood stabilizers and antipsychotics are EPS, sedation, anticholinergic side effects, sexual dysfunction, and weight gain. Practical recommendations for the management of these side effects as well as others are reviewed in Table 2. It is beyond the scope of this article to review the management of all the different side effects that clinicians may encounter, and thus I will focus mainly on side effects that occur with the combination of mood stabilizers and antipsychotic drugs.

EPS and Tardive Dyskinesia

First, it should be determined if there is a need for an antipsychotic drug. If there is no need for an antipsychotic, then the drug should be discontinued. In general, a combination of mood stabilizers (lithium, divalproex, or carbamazepine) is favored over the combination of a mood stabilizer with an antipsychotic drug (better evidence in terms of short- and long-term efficacy and safety). If it is determined that an antipsychotic drug is necessary, consider reducing its dose and/or the addition of an anticholinergic agent. If the patient is already taking a conventional antipsychotic, than a switch to one of the atypical antipsychotic drugs may prove advantageous in terms of offering a lower risk for neurologic side effects. The risk of tardive dyskinesia is likely to be lower when the atypical antipsychotics are used.

Seizures

For patients who are at risk for seizures, divalproex, which has mood-stabilizing properties, may offer prophylaxis against recurrent affective episodes and seizures. For this reason, I routinely use divalproex in the patient who is being treated with clozapine in doses above 500 mg/day, especially since there is a higher risk for having seizures in patients who take clozapine at this dose range.

Sedation

Sedation is a very troublesome side effect that is often difficult to manage. In many instances, it may be difficult to differentiate whether the patient is having a depressive syndrome, sedation, or both. Sedation is generally a desired side effect for the highly agitated acute manic patient, but is extremely undesirable and bothersome for the outpatient. Rates of sedation among the antipsychotic drugs vary depending on the study cited, but are probably greatest for clozapine and chlorpromazine. Since there are few long-term (12 months or more) head-to-head studies (none in bipolar disorder) comparing the antipsychotic drugs (none in combination with other drugs), the risk is based mainly on clinical impression and is probably: clozapine > chlorpromazine > olanzapine > quetiapine > risperidone > haloperidol. The first step to manage this side effect is to simplify the medication regimen as much as possible. If at all possible, remove the benzodiazepines or other central nervous system depressants that may be contributing to sedation. For sedating drugs, it is advised (if at all possible) to give the largest dose at bedtime to reduce daytime somnolence. Also consider checking the thyroid function of the patient should sedation continue in spite of the above recommendations. If sedation remains troublesome, consider using agents within the same drug class that tend to be less sedating. For example, consider using risperidone instead of olanzapine or quetiapine. In certain cases (although no research studies exist to prove the efficacy or safety of these options), consider caffeine, bupropion, or a stimulant that might be added in low doses to combat sedation.

Anticholinergic Side Effects

If a patient experiences anticholinergic side effects such as constipation, urinary retention, bowel obstruction, or dry mouth, consider eliminating other drugs that have this side effect or changing the antipsychotic agent to one with a lower anticholinergic profile such as risperidone or quetiapine.

Blood Dyscrasia

The clinician should consider avoiding the combination of clozapine with carbamazepine or mirtazapine because there may be an increased risk for developing a blood dyscrasia when these drugs are used in combination.

Elevated Prolactin

To date, it remains unclear whether there exists a strong association between elevated prolactin levels and sexual dysfunction. Increased prolactin blood levels have been reported to be more common with risperidone than with olan-

zapine or quetiapine. For patients with hyperprolactinemia, consideration should be given to the measured blood levels of prolactin; whether there are other accompanying complications; whether the hyperprolactinemia should be treated with a dopamine agonist; or whether changing to another atypical antipsychotic drug should be considered. In certain cases, bromocriptine may be used to treat hyperprolactinemia. The use of bromocriptine is not without risk. Since this drug is a dopamine agonist, there may be an increased risk for psychosis with its use.

Sexual Dysfunction

It is important to establish whether the sexual dysfunction predated the use of the current medications, i.e., whether it is associated with depressive syndrome. The management of sexual dysfunction is beyond the scope of this review. In general it is important to identify (if at all possible) which of the drugs is contributing to this complication. If more than one drug is responsible, removing the drug less likely to be helping the patient (in terms of response) should be considered. If the patient complains of sexual dysfunction and the patient is concurrently taking an antidepressant, e.g., a selective serotonin reuptake inhibitor (SSRI) with an antipsychotic, it is important first to determine the need for an antidepressant. In general, long-term treatment with an antidepressant is not recommended as this class of drugs may destabilize the bipolar illness (cause a switch into mania or cycling). One may also opt to use an antidepressant that is less likely to cause sexual dysfunction such as bupropion or nefazodone instead of an SSRI. There is very little information on the efficacy and safety of using buspirone, cyproheptadine, bupropion, and sildenafil in managing sexual dysfunction secondary to psychotropic medications in bipolar disorder patients.

Weight Gain

Diet and exercise are of major importance and preventative measures should be viewed as part of the ongoing treatment process rather than implemented after the patient gains weight. Whether or not a good diet and regular exercise will be protective against weight gain remains to be proved, but certainly they will make the process of losing weight much easier. Support groups (e.g., Weight Watchers) should also be considered in the management of this complication. When patients gain excessive weight on valproate or lithium therapy, carbamazepine may be an alternative as it is perhaps less likely to cause weight gain compared with these other drugs. Lamotrigine has also been suggested to have a favorable profile in terms of weight gain. Much interest has been generated with examining the efficacy and safety of topiramate in bipolar patients as this drug has been associated with weight loss when tested in patients with epilepsy. Sibutramine, phentermine, and orlistat have unproved efficacy and safety in promoting weight loss in bipolar patients. Caution is urged when using any of these drugs in mood disorder patients who are obese until more data become available on their short- and long-term efficacy and safety. Weight gain, its associated complications, and its management are thoroughly reviewed in other sections of this supplement.[53]

General guidelines in the treatment of bipolar disorder suggest using a traditional mood stabilizer such as lithium or valproate as first-line treatments. Combinations of mood stabilizers such as lithium and valproate or carbamazepine are recommended after the first-line treatment has failed. A combination of mood stabilizers is recommended before utilizing mood stabilizers with antipsychotic drugs. Also, maintenance treatment with an atypical antipsychotic agent (without a standard mood stabilizer) should generally be avoided until more information becomes available on the safety and efficacy of this approach. In patients who are experiencing a first episode of mania or who are neuroleptic naive, an atypical agent such as risperidone, olanzapine, or quetiapine should be tried before a conventional antipsychotic. For a treatment-responsive patient experiencing an episode of mania, the antipsychotic may be added to a mood stabilizer and should generally not be continued for longer than 3 to 6 months after recovery, before gradual taper and discontinuation. When a patient is considered nonresponsive to a standard mood stabilizer, combinations of mood stabilizers should be tried before the mood-stabilizer combination is augmented with either risperidone or olanzapine. At present, it appears that acute manic inpatients will require full doses of olanzapine ranging as high as 15 to 20 mg/day (in some cases even higher). For risperidone, a vast majority of inpatient manic patients will respond to doses ranging from 4 to 6 mg/day. For the outpatient, dosages for olanzapine and risperidone have not been established, but are probably within the range of 10 to 20 mg/day for olanzapine and 2 to 3 mg/day for risperidone. There has been anecdotal experience that some bipolar disorder outpatients may do well with very low doses of olanzapine (1.25 to 5 mg/day) or risperidone (0.5 to 2 mg/day) when given in combination with other mood stabilizers. Clinical experience indicates that risperidone may be a better choice for depressive syndromes and olanzapine for manic syndromes, but this is speculative and has not been based on controlled data as of yet. Until such data become available, the selection of an atypical agent for the treatment-refractory patient should be individualized and based on either taking advantage of or avoiding certain side effects. For example, if a patient is having sexual dysfunction or prolactin-related adverse events on risperidone treatment, olanzapine or quetiapine may prove better alternatives. On the other hand, if a patient is having severe problems with weight gain or sedation, risperidone may offer certain advantages over olanzapine. Patients should be informed about the common side effects for each of the treatment choices and engaged in the decision-making process.

CONCLUSION

Few controlled studies have examined the use of combinations of antipsychotic drugs and mood stabilizers, which are used frequently in the treatment of bipolar disorder. These combinations, in general, are often useful and appear to be well tolerated. Some situations where atypical antipsychotics may be considered include the following: (1) initially in first-episode manic patients as an adjunctive treatment; (2) as an adjunctive treatment during maintenance treatment in patients who are unresponsive or intolerant to the combination of standard mood stabilizers; and (3) in patients who experience significant and distressing side effects on conventional antipsychotic drugs (e.g., EPS, tardive dyskinesia, neuroleptic dysphoria).

Drug names: bromocriptine (Parlodel), bupropion (Wellbutrin), buspirone (BuSpar), carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clozapine (Clozaril and others), cyproheptadine (Periactin), divalproex (Depakote), haloperidol (Haldol and others), lamotrigine (Lamictal), mirtazapine (Remeron), nefazodone (Serzone), olanzapine (Zyprexa), orlistat (Xenical), phentermine (Fastin and others), quetiapine (Seroquel), risperidone (Risperdal), sibutramine (Meredia), sildenafil (Viagra), topiramate (Topamax), trazodone (Desyrel and others).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, these agents are not approved by the U.S. Food and Drug Administration for the following indications: carbamazepine, clozapine, lamotrigine, risperidone, and topiramate for bipolar disorder; bromocriptine for prolactin increases; bupropion for weight loss; quetiapine for extrapyramidal side effects; and bupropion, buspirone, and cyproheptadine for sexual dysfunction.

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
2. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8–19
3. Sernyak MJ, Godleski LS, Griffin RA, et al. Chronic neuroleptic exposure in bipolar outpatients. J Clin Psychiatry 1997;58:193–195
4. Keck PE Jr, McElroy SL, Strakowski SM, et al. Factors associated with maintenance antipsychotic treatment of patients with bipolar disorder. J Clin Psychiatry 1996;57:147–151
5. Goodwin FK, Jamison KR. Manic-Depressive Illness. New York, NY: Oxford University Press; 1990
6. Pope HG Jr, Lipinski JF. Diagnosis in schizophrenia and manic-depressive illness: a reassessment of the specificity of schizophrenic symptoms in the light of current research. Arch Gen Psychiatry 1978;35:811–828
7. Schatzberg AF, Rothschild AJ. Psychotic (delusional) major depression: should it be included as a distinct syndrome in DSM-IV? Am J Psychiatry 1992;149:733–745
8. McElroy SL, Keck PE Jr, Strakowski SM. Mania, psychosis, and antipsychotics. J Clin Psychiatry 1996;57:14–26
9. Andreasen NC. Thought, language, and communication disorders, I: clinical assessment, definition of terms, and evaluation of their reliability. Arch Gen Psychiatry 1979;36:1315–1321
10. Tohen M, Waternaux CM, Tsuang MT. Outcome in mania: a 4-year prospective follow-up of 75 patients utilizing survival analysis. Arch Gen Psychiatry 1990;47:1106–1111
11. Tohen M, Tsuang MT, Goodwin DC. Prediction of outcome in mania by mood-congruent or mood-incongruent features. Am J Psychiatry 1992; 149:1580–1584
12. Licht RW. Drug treatment of mania: a critical review. Acta Psychiatr Scand 1998;97:387–397
13. Hirschfeld RMF, Clayton PJ, Cohen I, et al. Practice guidelines for the treatment of patients with bipolar disorder. Am J Psychiatry 1994;151 (suppl):1–31
14. Frances A, Docherty JP, Kahn DA. The Expert Consensus Guidelines Series: treatment of bipolar disorder. J Clin Psychiatry 1996;57(suppl 12A): 1–88
15. Sachs GS. Use of clonazepam for bipolar affective disorder. J Clin Psychiatry 1990;51(5, suppl):31–34
16. Sernyak MJ, Griffin RA, Johnson RM, et al. Neuroleptic exposure following inpatient treatment of acute mania with lithium and neuroleptic. Am J Psychiatry 1994;151:133–135
17. Verdoux H, Gonzales B, Takei N, et al. A survey of prescribing practice of antipsychotic maintenance treatment for manic-depressive outpatients. J Affect Disord 1996;38:81–87
18. Zarate CA Jr, Tohen M. Antipsychotic drug treatment in first-episode mania: a 6-month longitudinal study. J Clin Psychiatry 2000;61:33–38
19. Kane JM, Smith JM. Tardive dyskinesia: prevalence and risk factors, 1959 to 1979. Arch Gen Psychiatry 1982;39:473–481
20. Nasrallah HA, Churchill CM, Hamdan-Allan GA. Higher frequency of neuroleptic-induced dystonia in mania than in schizophrenia. Am J Psychiatry 1988;145:1455–1466
21. Addonizio G. Rapid induction of extrapyramidal side effects with combined use of lithium and neuroleptics. J Clin Psychopharmacol 1985;5: 296–298
22. Spina E, Sturiale V, Valvo S, et al. Prevalence of acute dystonic reactions associated with neuroleptic treatment with and without anticholinergic prophylaxis. Int Clin Psychopharmacol 1993;8:21–24
23. Kane JM. The role of neuroleptics in manic-depressive illness. J Clin Psychiatry 1988;49(11, suppl):12–13
24. Kukopulos A, Reginaldi D, Laddomada P, et al. Course of the manic-depressive cycle and changes caused by treatment. Pharmakopsychiatrie-Neuropsychopharakol 1980;13:156–167
25. McKeon P, Manley P, Swanwick G. Manic-depressive illness, II: treatment outcome in bipolar disorder subtypes. J Psychol Med 1992;9:9–12
26. Ahlfors UG, Baastrup C, Dencker SJ, et al. Flupenthixol decanoate in recurrent manic-depressive illness. Acta Psychiatr Scand 1981;64:226–237
27. Janicak PG, Newman RH, Davis JM. Advances in the treatment of manic and related disorders: a reappraisal. Psychiatr Ann 1992;22:92–103
28. McElroy SL, Keck PE Jr, Pope HG Jr, et al. Clinical and research implications of the diagnosis of dysphoric or mixed mania or hypomania. Am J Psychiatry 1992;149:1633–1644
29. Calabrese JR, Delucchi GA. Spectrum of efficacy of valproate in 55 patients with rapid-cycling bipolar disorder. Am J Psychiatry 1990;147: 431–434
30. McElroy SL, Keck PE Jr, Pope HG Jr, et al. Valproate in the treatment of rapid-cycling bipolar disorder. J Clin Psychopharmacol 1988;8:275–279
31. Zarate CA Jr, Tohen M, Baldessarini RJ. Clozapine in severe mood disorders. J Clin Psychiatry 1995;56:411–417
32. Suppes T, McElroy SL, Gilbert J, et al. Clozapine in the treatment of dysphoric mania. Biol Psychiatry 1992;32:270–280
33. Zarate CA Jr, Tohen M, Banov MD, et al. Is clozapine a mood stabilizer? J Clin Psychiatry 1995;56:108–112
34. Calabrese JR, Kimmel SE, Woyshville MJ, et al. Clozapine for treatment-refractory mania. Am J Psychiatry 1996;153:759–764
35. Suppes T, Rush AJ, Webb A, et al. One year randomized trial of clozapine vs usual care in bipolar I patients. Biol Psychiatry 1996;39:531
36. Banov MD, Zarate CA Jr, Tohen M, et al. Clozapine in refractory affective disorders: polarity predicts response in long-term follow-up. J Clin Psychiatry 1994;55:295–300
37. Singh AN, Catalan J. Risperidone in HIV-related manic psychosis. Lancet 1994;344:1029–1030
38. Dwight MM, Keck PE Jr, Stanton SP, et al. Antidepressant activity and mania associated with risperidone treatment of schizoaffective disorder. Lancet 1994;344:554–555
39. O'Croinin F, Zibin T, Holt L. Hypomania associated with risperidone [letter]. Can J Psychiatry 1995;40:51
40. Diaz SF. Mania associated with risperidone use [letter]. J Clin Psychiatry 1996;57:41–42
41. Koek RJ, Kessler CC. Probable induction of mania by risperidone [letter]. J Clin Psychiatry 1996;57:174–175
42. Tohen M, Zarate CA Jr, Centorrino F, et al. Risperidone in the treatment of mania. J Clin Psychiatry 1996;57:249–253

43. Segal J, Berk M, Brook S. Risperidone compared with both lithium and haloperidol in mania: a double-blind randomized controlled trial. Clin Neuropharmacol 1998;21:176–180
44. Ghaemi SN, Sachs GS. Long-term risperidone treatment in bipolar disorder: 6-month follow up. Int Clin Psychopharmacol 1997;12:333–338
45. Sachs G. Safety and efficacy of risperidone vs placebo as add-on therapy to mood stabilizers in the treatment of manic phase of bipolar disorder. Presented at the American College of Neuropsychopharmacology Annual Meeting; Dec 12–16, 1999; Acapulco, Mexico
46. Baker R, Ames D, Umbricht D, et al. Olanzapine's impact on depressive and obsessive-compulsive symptoms in schizophrenia. Psychopharmacol Bull 1995;31:549
47. Tollefson GD, Beasley CM Jr, Tran PV, et al. Olanzapine versus haloperidol: results of the multicenter, international trial. Schizophr Res 1996;18:130–131
48. Reeves RR, McBride WA, Brannon GE. Olanzapine-induced mania. J Am Osteopath Assoc 1998;98:549–550
49. Lindenmayer J-P, Klebanov R. Olanzapine-induced manic-like syndrome [letter]. J Clin Psychiatry 1998;59:318–319
50. London JA. Mania associated with olanzapine [letter]. J Am Acad Child Adolesc Psychiatry 1998;37:135–136
51. McElroy SL, Frye M, Denicoff K, et al. Olanzapine in treatment-resistant bipolar disorder. J Affect Disord 1998;49:119–122
52. Tohen M, Sanger TM, McElroy SL, et al. Olanzapine versus placebo in acute mania. Am J Psychiatry 1999;156:702–709
53. Blackburn GL. Weight gain and antipsychotic medication. J Clin Psychiatry 2000;61(suppl 8):36–41
54. Ghaemi SN, Katzow JJ. The use of quetiapine for treatment-resistant bipolar disorder: a case series. Ann Clin Psychiatry 1999;11(3):137–140
55. Zarate CA Jr, Rothschild A, Fletcher KE, et al. Clinical predictors of acute response with quetiapine in psychotic mood disorders. J Clin Psychiatry 2000;61:185–189
56. Freeman MP, Stoll AL. Mood stabilizer combinations: a review of safety and efficacy. Am J Psychiatry 1998;155:12–21
57. Kando JC, Tohen M, Castillo J, et al. Concurrent use of clozapine and valproate in affective and psychotic disorders. J Clin Psychiatry 1994;55:255–257
58. Wilson W. Do anticonvulsants hinder clozapine treatment? Biol Psychiatry 1995;37:132–133
59. Zarate CA Jr, Narendran R, Tohen M, et al. Clinical predictors of acute response with olanzapine in psychotic mood disorders. J Clin Psychiatry 1998;59:24–28