New Treatments for Bipolar Disorder: The Role of Atypical Neuroleptic Agents

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Atypical neuroleptic agents are an excellent, safer, and more effective alternative to the widespread practice of maintenance adjunctive treatment with traditional neuroleptic agents in patients with bipolar disorder. Currently, a number of prospective studies are available with clozapine, risperidone, olanzapine, and quetiapine in the treatment of bipolar disorder. Most are short-term studies, although longer-term data are becoming available. Four double-blind studies of acute mania have been conducted with risperidone and olanzapine, leading to recent Food and Drug Administration approval for olanzapine in the indication of acute mania. Given the limited longer-term data, and the evidence for mostly adjunctive benefits with these agents, it seems unlikely that these agents will prove to be primary mood stabilizers in their own right. Nonetheless, they serve an important role as adjunctive treatments along with standard mood stabilizers in the rational polypharmacy of bipolar disorder. To date, differences in efficacy have not been established. However, differences in the side effect of weight gain may be even more relevant in bipolar disorder than in schizophrenia due to the need to use standard mood stabilizers that often potentiate such weight gain.

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Bipolar disorder is a notoriously complicated illness to treat. Mood stabilizers are few in number and often not sufficiently effective, resulting in common use of adjunctive agents, particularly antidepressants and neuroleptics, even though these classes are not indicated for, and in fact can be harmful in, bipolar disorder. Atypical neuroleptic agents may provide a safe, effective way to adjunctively treat bipolar disorder.

Problems With the Use of Standard Antidepressants in Bipolar Disorder

While it is beyond the scope of this article to fully address the risks of antidepressants in bipolar disorder (see Glick and Ghaemi, this issue[1]), it is important to note that antidepressants possess 2 risks: causing acute mania and long-term rapid cycling, which can lead to a gradual worsening of the course of the illness. Although attributing these risks to antidepressants is still controversial and definitive data are not yet available, a number of double-blind studies have found that antidepressants do not appear to be more effective than lithium alone in the prevention of depression.[2–4] Even for acute depression, whether tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs) like paroxetine are examined, controlled studies failed to find any more benefit with antidepressants added to lithium than with lithium alone (or 2 mood stabilizers). Additionally, in the long run, antidepressants have been reported to cause rapid cycling in 24% to 51% of patients.[5–7] This is quite disconcerting given the evidence that bipolar disorder is frequently (perhaps 40% of the time) misdiagnosed as unipolar depression and treated with antidepressants aggressively.[8]

Problems With the Use of Typical Neuroleptics in Bipolar Disorder

Although classical ("typical") neuroleptics speed the response of acute manic symptoms,[9] empirical data have not established their efficacy in maintenance treatment of bipolar disorder. In one longitudinal study of 434 bipolar patients over periods averaging 17 years, the long-term use of neuroleptic agents was associated with a shortening of episode duration and thus a worsening of the course of the illness.[6] In a 2-year double-blind, crossover study that compared the neuroleptic flupenthixol plus lithium to lithium alone,[10] patients receiving flupenthixol experienced more episodes of depression than lithium-treated patients, while the frequency of manic episodes was not significantly different. In a smaller double-blind, crossover study (N = 11), Esparon and colleagues[11] also found that patients given supplemental flupenthixol had more depressive

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symptoms on the Affective Morbidity Index[12] than patients receiving lithium alone ($p < .05$). Whether neuroleptics possess any special advantage over other adjuncts has also not been established. In a comparison with clonazepam, Sachs and colleagues[13] found that 6 of 17 patients previously refractory to lithium plus neuroleptic responded to being openly switched to a regimen of lithium and clonazepam such that they no longer needed neuroleptic treatment.

Despite this lack of evidence for neuroleptic efficacy in maintenance treatment, recent data show that manic inpatients treated with neuroleptics ostensibly for acute mania usually are not tapered off their neuroleptics after the acute manic episode resolves. Sernyak and associates[14] found that 38 of 40 bipolar patients remained on neuroleptic treatment at 1-year follow-up and continued to receive high doses of neuroleptic drugs (mean dose = 634 mg/day chlorpromazine equivalents). Another report also found a high long-term treatment rate of 68% (N = 52).[15]

In summary, there is evidence that neuroleptics and antidepressants are not particularly effective in bipolar disorder beyond perhaps the early stages of acute mania or depression. They are both also unidirectional in effect and can cause long-term worsening of bipolar illness: antidepressants by inducing mania and rapid cycling and typical neuroleptics by causing depression. Do atypical neuroleptic agents provide a more effective and safer alternative?

A Biochemical Rationale

Why would it be useful to think of atypical neuroleptics as being any better than typical neuroleptics or antidepressants in bipolar disorder? Let us begin by defining the term *mood stabilizer*. While the term has been liberally defined as meaning to treat at least 1 phase of bipolar illness (mania or depression) without worsening it or causing switch into the other phase,[16,17] I would suggest a more strict definition that better captures the clinical use of these agents: a mood stabilizer is an agent with efficacy in *at least 2* phases of bipolar illness (acute mania, acute depression, or prophylaxis of mania or depression). Use of this definition would mean that mood stabilizers would need to have antidepressant *and* antimanic properties to some degree, a bimodal effect previously suggested by Calabrese and Rapport.[18] These opposing properties would prevent the induction of either mania or depression and lead to euthymia. The biochemical profile of atypical neuroleptic agents would suggest that this may be the case: dopamine blockade would lead to antimanic effect, and serotonin-2 ($5\text{-}HT_2$) receptor blockade (as with certain antidepressants like nefazodone and mirtazapine) could produce some antidepressant effects. This is, of course, speculative. Is there clinical evidence for antimanic and antidepressant, i.e., mood-stabilizing, effects with these agents? Elsewhere in this issue, Glick and I[1] have reviewed the data on antidepressant effects of atypical neuroleptics, concluding that they possess such effects to a modest degree. This article will focus on the data on antimanic effects and/or long-term prophylactic mood-stabilizing effects.

Table 1. Summary of Reports on the Effectiveness of Clozapine in Bipolar and Schizoaffective Disorders[a]

Study	N	Response Criterion	Results (% Improved)	Monotherapy or Adjunct
Zarate et al[19]	17	CGI-I	65%	Monotherapy
Calabrese et al[20]	25	YMRS, BPRS	72%	Monotherapy
Suppes et al[21]	38	YMRS, BPRS, HAM-D	82%	Adjunct
Total	80		63%[b]	

[a]Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-I = Clinical Global Impressions-Improvement scale, HAM-D = Hamilton Rating Scale for Depression, YMRS = Young Mania Rating Scale.
[b]Weighted average.

METHOD

To identify studies for this review of the literature, a MEDLINE search was conducted with bibliographic cross-referencing, augmented by a review of abstracts presented at numerous professional meetings since the introduction of the first atypical neuroleptic, clozapine, in 1989. The following inclusion criteria were used: studies of atypical neuroleptic agents were included if they were prospective, contained a sample of equal to or greater than 5 patients (to minimize the biasing effect of case reports and small case series), utilized a rating scale for treatment response (such as the Clinical Global Impressions scale [CGI], or the Young Mania Rating Scale [YMRS]), and clearly identified whether the atypical neuroleptic agent was used as an adjunct to other mood-stabilizing agents or as monotherapy.

RESULTS

The Use of Clozapine

As shown in Table 1, 3 articles met inclusion criteria for this review. In 1 report,[20] 25 treatment-refractory outpatients (10 with bipolar disorder and 15 with schizoaffective disorder) were treated with clozapine during a manic episode. The entire sample had been intolerant of or unresponsive to lithium, an anticonvulsant, and at least 2 neuroleptic drugs, although it was unclear whether these agents had been used sequentially or in combination. Nonetheless, 72% (18/25) responded openly to clozapine alone with a greater than 50% decrease in YMRS scores. In another study, Zarate and colleagues[19] reported a 65% response rate to clozapine monotherapy using the CGI in 17 patients with bipolar disorder, 14 of whom had failed previous treatment with 2 mood stabilizers and at least 1 neuroleptic agent, and 3 of whom had failed treatment

with or been intolerant of 2 or fewer mood stabilizers; again, sequential or combinational use of these agents could not be determined).

In the only randomized study so far,[21] clozapine added to standard treatment (N = 19) was studied in 1-year prospective randomized outcome compared with treatment as usual (N = 19) in severe bipolar or schizoaffective illness. Overall improvement on psychiatric rating scales, such as the Brief Psychiatric Rating Scale (BPRS), was statistically better with clozapine than with treatment as usual, based on a pattern-mixture random-regression model. When assessing categorical response based on 30% improvement on BPRS scores, somewhat more response was seen with clozapine (65% at 3 months, 82% at 6 months) than with treatment as usual (48% at 3 months, 57% at 6 months). Dropouts were greater in the treatment-as-usual group (N = 9) than the clozapine group (N = 3). This study was not double-blind or placebo-controlled, and the use of treatment as usual as a comparator raises the variability of treatments, making the control group difficult to standardize. Nonetheless, the results are encouraging and have the advantage of being longer-term findings, providing evidence for a mood-stabilizing effect. Since clozapine was mainly used as an adjunct to mood stabilizers, and not in monotherapy, definitive evidence for activity as a stand-alone mood stabilizer is still lacking.

A few other reports also document effectiveness of clozapine in bipolar disorder but are not included in the summary table due to failure to meet inclusion criteria for this review.[22–25] These reports were generally retrospective or failed to use a specific rating scale for treatment response. Often, they also failed to distinguish between monotherapy and adjunctive therapy.

Clozapine lacks double-blind data, but the recent randomized study, combined with previous experience, supports its likely effectiveness in bipolar disorder. Its main drawbacks are the risk of agranulocytosis, a substantial risk of seizures, drug interactions (such as possible increased risk of agranulocytosis with carbamazepine), and high cost.

The Use of Risperidone

As shown in Table 2, 4 of 6 reports published to date support risperidone's effectiveness. In one,[26] 8 of 13 outpatients with bipolar disorder had a partial or complete response, using prospective CGI ratings during open treatment with adjunctive risperidone added to mood stabilizers. In another,[27] risperidone was used with mood-stabilizer medications in open treatment of acute psychotic mania in 13 inpatients, 8 of whom had at least 50% improvement in BPRS scores after 3 weeks of treatment ($\chi^2 = 16.4$, p = .0025), and all of whom had at least 25% improvement in BPRS scores. In a third study,[28] among a group of 14 risperidone-treated outpatients with bipolar disorder (5 mixed, 4 pure manic, 2 depressed, 1 each with rapid cycling, hypomania, and psychosis), 9 were rated much improved on CGI scores, and their Global Assessment of Functioning scores improved from 48.2 ± 4.9 to 58.8 ± 7.3 (t = 4.49, p = .0006, paired t test). Mean ± SD duation of treatment was 6.4 ± 2.7 weeks, and mean ± SD continuation dose used was 2.75 ± 1.8 mg/day. Eleven (79%) were receiving concomitant mood-stabilizing treatment. Improvement was found in 6 (55%) of 11 patients taking concurrent mood stabilizers and in all 3 patients taking no concurrent mood stabilizers. Nine patients were taking other medications as well (clonazepam, lorazepam, levothyroxine), with only 1 taking an antidepressant (paroxetine). Treatment was well tolerated, and no patient experienced worsening of mood symptoms while receiving risperidone. Nine patients (64%) had also either not tolerated or not responded to typical neuroleptic agents. In a recent report,[30] 6-month follow-up was obtained on 12 outpatients treated with adjunctive risperidone for breakthrough symptoms of mood instability, hypomania, or mixed or depressive symptoms, with mild-to-moderate improvement in 4 patients (33%) and 1 depressive relapse during follow-up. There were no cases of a manic episode with risperidone.

Two of these studies[26,28] found risperidone to be effective in bipolar patients with nonpsychotic mood episodes; in each study, only 1 patient experienced psychosis, suggesting that risperidone may be beneficial for affective symptoms per se in bipolar disorder, whether or not psychotic symptoms are present. The other study included patients with psychotic mood disorders exclusively.[27]

A few other case reports and abstracts support risperidone use in bipolar disorder, and a few do not, none of

Table 2. Summary of Reports on the Effectiveness of Risperidone in Bipolar and Schizoaffective Disorders[a]

Study	N	Response Criterion	% Improved[b]	Monotherapy or Adjunct	Mania Induction
Jacobsen[26]	13	CGI	62%	Mainly adjunct	None
Tohen et al[27]	13	BPRS	62%	Adjunct	None
Ghaemi et al[28]	14	CGI, GAF	64%	Mainly adjunct	None
Dwight et al[29]	8	YMRS, HAM-D	50%	Monotherapy	50% (N = 4)
Ghaemi and Sachs[30]	12	CGI	33%	Adjunct	None
Sajatovic et al[31]	5	CGI, YMRS, BPRS	0%	Monotherapy	40% (N = 2)
Segal et al[32]	45	MRS, BPRS	...[c]	Monotherapy	None
Vieta et al[33]	305	YMRS, HAM-D	...[c]	Adjunct	None
Sachs et al[34]	158	YMRS	57%	Adjunct	None
Total	573		55%[d]		3%[d]

[a]Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions scale, GAF = Global Assessment of Functioning, HAM-D = Hamilton Rating Scale for Depression, MRS = Mania Rating Scale, YMRS = Young Mania Rating Scale.
[b]If monotherapy studies are excluded, there are no reports of mania.
[c]Categorical response not provided.
[d]Weighted response based on available data.

which were included in this review for failing to meet inclusion criteria.

In addition to these open studies, 2 double-blind studies of risperidone in acute mania have been published.[32,34] In 1 study,[32] 45 inpatients with acute mania were randomly assigned to monotherapy with risperidone, 6 mg/day; haloperidol, 10 mg/day; or lithium, 800 to 1200 mg/day for 1 month. All 3 groups showed clinically significant improvement on the Mania Rating Scale (10.2–15.7 points), with no statistically significant differences between them. This study lacked a placebo-control group, and its small sample size increases the possibility of false negative error. However, there was significant clinical improvement in all groups, 2 of which received widely accepted and proven treatments for acute mania (haloperidol and lithium). This would argue for the presumption of similar efficacy with risperidone. In a second, larger placebo-controlled double-blind study,[34] preliminary data analyses indicate that risperidone (57% response) was as effective as haloperidol (58%) and more effective than placebo (38%; p = .05) as add-on treatment to standard mood stabilizers (divalproex or lithium) in the 3-week treatment of acute mania (N = 158). YMRS scores improved equally with risperidone (13.5-point improvement) and haloperidol (11.3 points) compared with placebo (7.5 points), with the difference statistically significant beginning at 1 week ($p < .05$). Risperidone also exhibited fewer extrapyramidal side effects than haloperidol (13% vs. 28%, p = .10). Risperidone showed no greater worsening of mania or new episodes of mania than were associated with placebo.

Does Risperidone Cause Mania?

Two reports[29,31] conflict with the evidence above and have led to a perception that risperidone actually may exacerbate mania.

Dwight and colleagues[29] reported a case series of 8 inpatients with schizoaffective disorder in whom open treatment with risperidone alone, without concomitant mood stabilizers, led to increases in YMRS[35] and decreases in Hamilton Rating Scale for Depression (HAM-D)[36] scores. A closer look at the methodology of this study may explain some of the findings. The YMRS and the HAM-D were used every other day in 8 risperidone-treated patients with schizoaffective disorder, and the investigators reported elevations beyond baseline in peak YMRS scores and declines in peak HAM-D scores. The HAM-D was designed for use on a weekly basis,[36] and in his original report, Young[35] used his scale to assess acute symptoms after a 2-week time frame; neither scale was designed for use on an every-other-day basis. Also, peaks and valleys in daily feeling states, with increased mania on some days and increased depressive symptoms on other days, are typical of the natural history of a pure manic episode.[37] Most rating scales have instructions for use on a weekly basis, rather than every other day as in Dwight and colleagues' report,[29] partly to smooth out daily noise and obtain a clearer picture of the course of symptoms. Evaluation of brief periods of time might result in misleading impressions of the mood state. In a recent symposium, Keck,[38] one of the authors in the original study, makes reference to this fluctuation in the course of these patients. He reports that the above patients only "had a slight worsening of manic symptoms,"[38(p25)] and he adds that "the qualitative worsening of manic symptoms was not substantial. Essentially there was a hypomanic blip that lasted for a week or two, but four of the six patients who had worsening manic symptoms were able to be maintained on risperidone."[38(p27)]

In the report by Sajatovic and colleagues,[31] of 6 acutely manic patients treated with risperidone alone, 2 could not tolerate it and 2 had worsening of manic symptoms. However, again, none were taking concomitant mood stabilizers, which had been discontinued before initiating the trial. Thus, this study is subject to the confounding factor of the well-established increased risk of early relapse with sudden discontinuation of lithium treatment. Specifically, Suppes and colleagues[39] found that about 50% of patients suffer a manic relapse within 1 month of lithium discontinuation, the same relapse rate observed in the above study.

It should also be noted that the patients in 2 of the reports finding risperidone effective in bipolar disorder[26,28] received lower doses of risperidone (2–3 mg/day) than in the above reports that failed to find risperidone to be effective in mania (mean ± SD = 7 ± 1 mg/day).[29,31] If, as one of the authors of the latter study suggests, "these atypical drugs may have some application, especially by dint of the 5-HT$_2$ blockade, in patients with psychotic symptoms and affective symptoms,"[38(p27)] then lower rather than higher doses may be more likely to bring out that unique pharmacologic profile.[40] In fact, in one of the few in vivo human positron emission tomography studies of receptor binding and dose,[41] the classic atypical neuroleptic profiles of risperidone and olanzapine (with 40%–60% D_2 receptor blockade and 90% 5-HT$_2$ receptor blockade) are achieved at low doses (1–3 mg/day of risperidone, 5–10 mg/day of olanzapine). As the doses are increased further, both drugs (unlike clozapine) achieve a profile similar to typical neuroleptic agents (with over 80% D_2 blockade and no further 5-HT$_2$ blockade).

These scattered cases of mania reported with atypical neuroleptics (including olanzapine as well as risperidone) also tend to occur when these agents are used alone, without other standard mood stabilizers (like lithium or divalproex sodium).[78] It may be that the atypical neuroleptics have more mood-stabilizing benefit as adjuncts to standard mood stabilizers than when used in monotherapy.

Even if these reported cases of mania were attributable to risperidone, overall risperidone response rate in bipolar disorder derived from pooling all available reports meeting inclusion criteria (123/223; 55%) was much higher

Table 3. Summary of Reports on the Effectiveness of Olanzapine in Bipolar and Schizoaffective Disorders[a]

Study	N	Response Criterion	Results	Monotherapy, Adjunct, or Both
McElroy et al[42]	14	CGI-BP	57% response	Adjunct
Tohen et al[43,b]	139	YMRS	49% response in acute mania vs 24% for placebo (p = .004)	Monotherapy
Sanger et al[44,c]	113	YMRS, HAM-D	...	Both
Tohen[45,b]	115	YMRS	65% vs 43% for placebo	Monotherapy
Total	268		50%	

[a]Abbreviations: CGI-BP = Clinical Global Impressions scale for Bipolar Disorder, HAM-D = Hamilton Rating Scale for Depression, YMRS = Young Mania Rating Scale.
[b]Study was double-blind and placebo-controlled.
[c]Categorical response not provided. Sample same as in Tohen et al.[43] study and thus not recounted.

Table 4. Summary of Studies of Quetiapine in Bipolar Disorder[a]

Study	N	Response Criterion	Results	Monotherapy, Adjunct, or Both
Ghaemi and Katzow[48]	6	CGI-I	2/6 responded	Both
Sajatovic et al[49]	16	YMRS, HAM-D	...[b]	Adjunct
Total	22			

[a]Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, HAM-D = Hamilton Rating Scale for Depression, YMRS = Young Mania Rating Scale.
[b]Categorical response not provided.

than the reported incidence of mania after risperidone treatment in patients with bipolar disorder (6/223; 3%) (see Table 2). Finally, and most definitively, the recent double-blind study of risperidone in acute mania found no elevated risk of induced mania compared with placebo.[34]

The Use of Olanzapine

There are fewer naturalistic studies published with olanzapine in bipolar disorder than with risperidone or clozapine, partly a reflection of its being a newer agent (Table 3). One prospective naturalistic study of olanzapine in bipolar disorder has been published to date.[42] In that study, olanzapine as an adjunct to mood-stabilizing agents was effective in 8/14 patients (57%) with treatment-resistant bipolar disorder, based on moderate-to-marked response on the CGI for Bipolar Disorder.[46] The most common side effect was sedation, occurring in 5/14 (36%), and possible extrapyramidal symptoms of tremor and restlessness occurred in 3/14 (21%). While their study was retrospective, Zarate and colleagues[47] have published a large naturalistic sample of 150 patients treated with olanzapine for psychotic mood disorders, with 62% moderate-to-marked response in schizoaffective disorder and 83% response in bipolar disorder, based on systematic chart review.

In contrast to the limited naturalistic experience, there has been more industry-sponsored clinical trial research with olanzapine. Two recent double-blind studies of acute mania found olanzapine to be more effective than placebo.[43,45] In the first study (N = 139),[43] olanzapine led to a greater decline in YMRS scores than placebo over 3 weeks (–10.3 vs. –4.9, p = .19), and there were more responders based on 50% decline in YMRS scores with olanzapine than with placebo (48.6% vs. 24.2%, p = .004). In the second report[45] with identical methods (N = 115), despite a higher placebo response rate (43%), olanzapine monotherapy (65% response) was still statistically superior for acute mania. Based on these 2 studies, olanzapine has recently been approved by the Food and Drug Administration (FDA) for the indication of mania. While these studies support the idea that olanzapine has direct acute antimanic effects, as is likely with clozapine and risperidone, the question remains open whether olanzapine has prophylactic mood-stabilizing properties.

The Use of Quetiapine

Research on quetiapine has lagged behind the other agents (Table 4). No double-blind clinical trials have been presented yet, and so far only 1 open report[48] of a retrospective case series of 6 patients has been published, in which 2 refractory bipolar patients responded to quetiapine. A larger open series[49] followed 16 neuroleptic-dependent bipolar and schizoaffective patients who received add-on quetiapine (154.7 mg/day for 10.8 weeks) with standard mood stabilizers and found improvement in prospectively assessed standard mood rating scales (HAM-D score improved from about 16 to 8, YMRS score improved from approximately 9 to 4; p < .01 for both scales). These data are encouraging, but further experience and controlled research are required.

Long-Term Outcome With Risperidone and Olanzapine

While these studies all support at least antimanic effects with atypical neuroleptic agents, it is important to emphasize that an antimanic agent is not necessarily a mood stabilizer. For instance, haloperidol is a powerful antimanic agent, but it is not a mood stabilizer because it tends to cause depression and has not been proved to prevent mania or depression. Thus, besides assessing their antidepressant efficacy, clinicians should seek to know what long-term preventive effects atypical neuroleptics possess.

Until recently, no data existed on this topic. Now, 2 almost identical studies have been presented at research meetings with risperidone and olanzapine, with strikingly similar results.[33,44] In the study with risperidone, Vieta and

associates[33] openly followed 305 patients with bipolar and schizoaffective disorders for 6 months while they were taking risperidone as add-on treatment to standard mood stabilizers. All patients entered the study manic, hypomanic, or mixed (DSM-IV criteria) with inadequate response to standard mood stabilizers. They were followed prospectively with standardized ratings scales. YMRS scores improved from acutely manic at baseline (24.8) to residual levels (5.2). HAM-D scores improved from subthreshold depressive levels (12.7) to residual symptoms (5.6). All improvements were statistically significant. These results are consistent with long-term *adjunctive* mood-stabilizing effects with risperidone.

In the study with olanzapine, Sanger and associates[44] reported the 49-week open extension of a previous 3-week double-blind study of olanzapine in acute mania. One hundred thirteen patients received olanzapine (13.8 mg/day) with prospective assessment of response for a mean duration of 201 days (6.6 months). YMRS scores improved from 25.5 at baseline to 7.5 at endpoint, and HAM-D scores improved from 12.2 to 6.4. Both improvements were statistically significant. Most patients receive adjunctive lithium or fluoxetine, however, thus making these results, like those of the risperidone study, reflective mostly of the long-term *adjunctive* mood-stabilizing effects of the atypical neuroleptic agent.

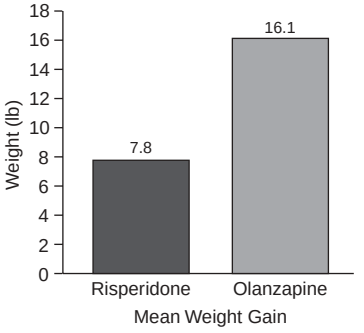
In summary, these 2 studies find almost identical results for risperidone and olanzapine, suggesting that they have adjunctive mood-stabilizing effects in the long run, but not providing evidence that either of these agents are primary mood stabilizers by themselves. While open, these studies were prospective and had appreciable sample sizes.

It is notable that in many of the studies reviewed, doses of risperidone and olanzapine used tend to be about half those used in schizophrenia (1–3 mg/day for risperidone, 5–10 mg/day for olanzapine).

A Comparison of Atypical Neuroleptic Agents in Bipolar Disorder

These studies allow some comparison of the atypical neuroleptic agents. However, clinicians cannot definitively conclude that one agent is different from another until head-to-head comparisons are made in the same sample. Recently, such a comparison was made at the Massachusetts General Hospital Bipolar Clinic, Boston.[50] In that study, prospective assessments of treatment response were made in 50 consecutive treatment trials in 42 patients with bipolar disorder type I who received clozapine (N = 5 trials), risperidone (N = 25 trials), or olanzapine (N = 20 trials) as add-on treatments to standard mood stabilizers. Patients had not responded to those mood stabilizers for manic, mixed, hypomanic, or rapid-cycling symptoms. Efficacy was not statistically significantly different between the groups, nor were most side effects, including extrapyramidal symptom rates. The only difference was in weight gain, which was greater with olanzapine (16.1 ± 13.7 lbs [7.2 ± 6.2 kg]) than with risperidone (7.8 ± 11.2 lb [3.5 ± 5.0 kg], $p < .03$; Figure 1). The greatest weight gain was associated with the divalproex-olanzapine combination. Since this study was naturalistic, uncontrolled, and limited in sample size, these results must be interpreted with caution. The lack of difference in efficacy between groups may represent a false negative error. However, the marked weight gain differences were striking and suggest that a bigger difference for weight gain exists between these agents than for efficacy or extrapyramidal symptoms.

Figure 1. Weight Gain With Risperidone vs. Olanzapine in Bipolar Disorder[a]



[a]Data from Guille et al.[50]

New-onset diabetes mellitus and diabetic ketoacidosis have also been reported in patients treated with olanzapine (N = 7). Both patients who developed diabetic ketoacidosis had gained weight while taking olanzapine, but only 4 of the 7 who developed diabetes mellitus had gained weight on olanzapine treatment.[51]

DISCUSSION

These clinical studies provide evidence for short-term acute antimanic effects and possibly longer-term adjunctive mood-stabilizing effects with atypical neuroleptic agents. Combined with some evidence for modest antidepressant effects (see Glick and Ghaemi, this issue[1]), these data suggest that atypical neuroleptics are probably effective as adjunctive mood-stabilizing agents.

If efficacy is accepted, and it appears roughly equal among atypical neuroleptics, the main question involves safety. What are the risks with these agents? The most common risks of concern for patients with bipolar and schizoaffective disorders often are extrapyramidal symptoms (EPS), tardive dyskinesia, and weight gain.

Risks

Extrapyramidal symptoms. A specific concern that might be raised is that the risks of the new atypical neuro-

leptic agents are less well known than those of the classical agents, in particular, risks of EPS and tardive dyskinesia. However, recent data are beginning to clarify the real risks involved.

While clinical trial data for clozapine and risperidone suggested that they both would have fewer EPS than typical neuroleptic agents,[52–56] preliminary reports from clinical practice after FDA approval have suggested that the prevalence of EPS may be greater than previously expected. In the Guille et al. study,[50] EPS were noted in 12 (28.6%) of 42 patients treated with an atypical antipsychotic. Another study[57] showed that, while EPS were noted in atypical-treated patients, the rate of EPS was higher in patients treated with typical antipsychotics. For example, the prevalence of akathisia was 10.5% with clozapine, 11.1% with risperidone, and 22.7% with typical neuroleptic agents.

A study with a blinded review using the Extrapyramidal Rating Scale found akathisia of comparable severity to be present in 39% of clozapine-treated patients (N = 23) compared with 45% of patients treated with typical neuroleptic agents (N = 29).[58] Similar findings were reported in another blinded review of 151 patients with schizophrenia participating in a multicenter study, in which akathisia was as common with clozapine as with chlorpromazine while parkinsonism was less common with clozapine.[59] A conflicting report on 14 patients with schizophrenia who received stable clozapine doses for 4 or more months found that akathisia was present in only 2 patients.[60] A drawback of the latter study, besides its smaller size, is that the requirement that patients be treated with clozapine for at least 4 months may have excluded those who developed akathisia early in treatment and dropped out.

These studies suggest that EPS are still a problem with atypical neuroleptic agents, particularly akathisia, which occurs in about 20% or more of patients with any type of atypical neuroleptic agent, probably in a dose-dependent fashion.

Tardive dyskinesia. Concerning tardive dyskinesia, it is important to recognize the baseline risks. First, it is reported that the spontaneous incidence of tardive dyskinesia in schizophrenia is 1% per year.[61] Second, a prospective study[62] of tardive dyskinesia conducted with typical neuroleptic treatment of schizophrenia found that the highest incidence occurred early in treatment, with about 20% of patients developing tardive dyskinesia in the first 3 years of treatment. After that high-risk period, however, the incidence of tardive dyskinesia fell to about 1% per year or less, near the spontaneous rate. Thus, in contrast to the commonly believed proposition that the risk of tardive dyskinesia increases with time, the highest incidence risk for tardive dyskinesia occurs early in treatment and may actually decrease with time. Keeping these factors in mind, the evidence regarding atypical neuroleptic agents and tardive dyskinesia is not unimpressive. For risperidone, preliminary data on its use in the first year of treatment in clinical trial conditions (N = 4000) indicate a tardive dyskinesia incidence of 0.3%.[63] With olanzapine, the tardive dyskinesia incidence defined as 2 or more successive abnormal ratings on the Abnormal Involuntary Movement Scale was 1% (N = 400) compared with 4.5% for haloperidol, again a tardive dyskinesia rate near the spontaneous baseline rate.[64] Despite scattered case reports of the occurrence or decrease of tardive dyskinesia during treatment with all atypical neuroleptic agents,[65–72] the comparisons of these clinical trial data with the expected tardive dyskinesia rate during treatment with classic neuroleptic agents suggest a minimal risk of tardive dyskinesia with the atypical neuroleptic agents.

Weight gain. Patients with bipolar disorder are at particular risk for weight gain due to the use of primary mood stabilizers, like lithium and divalproex, which promote weight gain. Unfortunately, it appears that all available atypical neuroleptic agents cause weight gain, although some more than others. A recent study[73] found that weight gain was associated with antihistaminic effects, with clozapine causing more than olanzapine, which demonstrated more weight gain than quetiapine, followed by risperidone. The antiserotonin effects of the atypical class by itself may also promote weight gain, however.[74] As noted above,[50] we found that olanzapine use produced much more weight gain than risperidone use in bipolar patients treated with standard mood stabilizers.

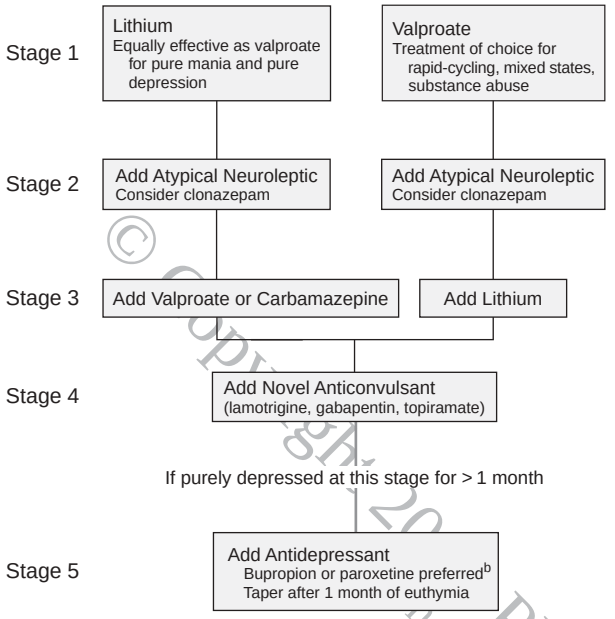
Practical Aspects of the Acute Management of Mania

In the treatment of acute mania, rapid response is imperative. Manic patients are impulsive and sometimes dangerous, and usually they require hospitalization. Control of mania, which often is associated with agitation and/or psychosis, needs to occur quickly. Untreated mania tends to resolve within 1 to 3 months, but during that time, manic patients are at high risk of causing irreparable damage to their own lives and perhaps those of others.

Traditionally, since lithium tends to have a slow onset of action on the order of weeks, typical neuroleptic agents were frequently used to control acute mania. Even before the advent of atypical neuroleptic agents, however, clinicians were aware that high-dose typical neuroleptic treatment caused many side effects. Thus, clinicians were often advised to utilize benzodiazepines liberally, to control the agitation of mania, and typical neuroleptics in low-to-moderate doses to speed up the antimanic response of lithium. This is still sage advice today. Even though atypical neuroleptic agents are less toxic than typical neuroleptics, they still can cause many side effects as reviewed previously, especially at high doses. Thus, benzodiazepines remain an important part of the acute management of mania. Atypical neuroleptics for mania should still be used, as discussed above, at about half the dose used in schizophrenia.

The availability of divalproex sodium, with its much more rapid onset of action for mania compared with lith-

Figure 2. An Algorithm for the Treatment of Bipolar Disorder[a]



[a]Stages 2 and 3 can be reversed in order depending on the clinical setting.
[b]Bupropion and paroxetine are preferred because they are the only 2 antidepressants with established decreased risk of acute mania based on double-blind, tricyclic-controlled studies (based on data from Sachs et al.[75] and Young et al.[76]).

ium, also limits the need to use high-dose neuroleptic agents. Sometimes, loading doses of divalproex sodium (20–30 mg/kg/d) can obviate the need for neuroleptic treatment altogether.[77] Generally, divalproex loading seems most helpful in the nonpsychotic patient who is not markedly agitated. Otherwise, atypical neuroleptics are likely to be helpful adjunctive treatments.

Today, one is hard pressed to find much advantage to typical neuroleptic use in the treatment of acute mania. While drug costs are low, the medical benefits to patients appear negligible compared with the safer and at least equally effective atypical neuroleptic alternatives.

Rational Polypharmacy

I propose an algorithm of treatment for bipolar disorder that incorporates this experience with atypical neuroleptic agents, using them as first-line adjunctive treatments after the initiation of a primary mood stabilizer (Figure 2). It is sometimes intimated that practitioners often overtreat bipolar illness, adding multiple agents in a haphazard manner, unlike unipolar depression and schizophrenia, where fewer classes of agents tend to be used. As noted at the beginning of this article, haphazard polypharmacy reflects the frustration of clinicians and patients. While today polypharmacy is still inevitable in the treatment of bipolar illness due to the limitations of available mood stabilizers, I believe that this algorithm provides a reasoned way to proceed, based on clinical data. The main caveat to note is that, obviously, the extent of combination treatments may be limited by patients' ability to tolerate side effects, with weight gain as a major problem.

SUMMARY

The current state of the literature is clearly not ideal. Even with the minimal inclusion criteria for this review, a number of studies on atypical neuroleptic agents had to be excluded because they were retrospective or anecdotal. Compared to 2 decades ago, it is surprising how difficult it appears to be to implement well-controlled studies of neuroleptic agents in bipolar disorder. While most research work has focused on schizophrenia, the literature on the use of atypical neuroleptic agents in bipolar and schizoaffective disorders has been remarkably sparse. Given these caveats, the limited literature available appears to generally support the effectiveness of this class of medications in bipolar and schizoaffective disorders. Individual differences between the agents are more difficult to assess, but may be more related to side effects, especially weight gain, than to efficacy. Randomized naturalistic studies may also be useful in assessing response in representative clinical samples and may be more feasible than double-blind studies. A few double-blind controlled studies are under way nevertheless. In the meantime, clinicians currently might be best served by recognizing the probable effectiveness and safety of atypical neuroleptic agents in bipolar disorder while awaiting more definitive data.

Drug names: bupropion (Wellbutrin), carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clonazepam (Klonopin and others), clozapine (Clozaril and others), divalproex sodium (Depakote), fluoxetine (Prozac), gabapentin (Neurontin), haloperidol (Haldol and others), lamotrigine (Lamictal), levothyroxine (Synthroid), lorazepam (Ativan and others), mirtazapine (Remeron), nefazodone (Serzone), olanzapine (Zyprexa), paroxetine (Paxil), quetiapine (Seroquel), risperidone (Risperdal), topiramate (Topamax).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, the following agents mentioned in this article are not approved by the U.S. Food and Drug Administration for the following indications: bupropion, fluoxetine, and paroxetine for the treatment of bipolar depression; carbamazepine, clozapine, gabapentin, lamotrigine, quetiapine, risperidone, and topiramate for the treatment of bipolar disorder; and chlorpromazine, clonazepam, and haloperidol for the treatment of mania.

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