Typical and Atypical Antipsychotics in Bipolar Depression

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Background: Symptomatic bipolar patients experience more depressive than manic symptoms, but fewer studies have been designed for bipolar depression than for bipolar mania. Since the antipsychotic agents have been shown to diminish depressive symptoms during the treatment of mania, atypical agents are now being studied for use in bipolar depression.

Data Sources: English-language articles published from 1980 through July 2004 and cited in MEDLINE were searched using the keywords *antipsychotics*, *typical antipsychotics*, *atypical antipsychotics*, *bipolar depression*, *bipolar disorder*, *manic-depressive illness*, *placebo*, and *clinical trial*. The generic and brand names of individual antipsychotics were also entered as keywords. Peer-reviewed abstracts of placebo-controlled studies assessing acute or long-term efficacy in bipolar depression presented at major scientific meetings were also reviewed.

Study Selection: Use of a depression rating scale was required for inclusion of studies of the atypical antipsychotic agents in our analysis.

Data Synthesis: Twenty-one randomized trials and 13 nonrandomized prospective trials were identified. In the only 2 acute, double-blind, placebo-controlled studies of antipsychotics in bipolar depression, the effect size of olanzapine was small (0.32) compared with the effect sizes of quetiapine (0.91–1.09, depending on dose). The effect size in acute mania of olanzapine at week 4 and quetiapine at week 3 was 0.50 and 0.39, respectively. Both olanzapine and quetiapine have been shown to be superior to placebo in the acute treatment of bipolar I depression. In addition, olanzapine has been shown to be more effective than placebo in delaying relapse into bipolar depression. With the exception of a 6-month perphenazine study, there are no other randomized studies of typical antipsychotics that support the conclusion that this class of medication worsens bipolar depression.

Conclusion: Emerging data suggest that the atypical antipsychotic agents have a role in the acute and long-term treatment of bipolar depression. No convincing data support the impression that the typical antipsychotic agents worsen bipolar depression.

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Among psychiatric illnesses, bipolar disorder is second only to unipolar depression as a cause of global disability.[1] Symptomatic patients with bipolar I disorder experience depressive symptoms 3 to 4 times more frequently than manic symptoms,[2,3] and symptomatic patients with bipolar II disorder experience approximately 39 times more depressive symptoms than hypomanic symptoms.[4] Recently, the impact of depressive versus manic symptoms in 593 subjects screening positive for bipolar disorder was assessed. Work, social life, and family life ranged from being moderately impaired to extremely impaired, significantly more from depressive than manic symptoms.[5] Significant psychosocial impairment during illness-free intervals has been reported,[6] and this impairment is more strongly predicted by the number of past depressive episodes than past manic episodes.[7] A review of 29 studies involving 9389 patients concluded that the weighted-mean lifetime rate of suicide in bipolar disorder was 18.9%.[8] Harris and Barraclough[9] reported on 14 published articles from 7 countries involving a population of 3700 patients with bipolar disorder between 1900 and 1985 and noted 15-fold increased risk of suicide compared to the expected rate of suicide in the general population. In a consecutive series of 129 hospitalized bipolar patients, Dilsaver et al.[10] reported that the relative risk of suicidality among patients with bipolar depression and among patients with pure mania was 79.3% and 2.3%, respectively.

It is evident that bipolar depression causes more morbidity and mortality than mania. However, the options for the treatment of bipolar depression are much more limited compared with those for mania. Although lithium and la-

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motrigine have been recommended as initial treatments for bipolar I depression,[11,12] a substantial proportion of bipolar patients either do not respond to lithium completely or cannot tolerate its side effects.[13,14] The efficacy of lamotrigine in the acute or maintenance treatment of bipolar depression has been demonstrated by randomized, double-blind, placebo-controlled studies,[15–19] but some patients eventually relapsed into mania or depression. Therefore, the treatment of bipolar depression presents a major unmet medical need.

The efficacy of typical and atypical antipsychotics in the acute treatment of mania has been well established.[20–34] It was also found that secondary symptoms of depression during mania were reduced by both classes of antipsychotics.[27,35–44] Because of these findings, investigators have begun to systematically evaluate the role of the atypical antipsychotics in the acute and long-term treatment of depressive episodes in bipolar I disorder.[45–48] In addition, the typical antipsychotics continue to be used in the acute and long-term management of mania, and as a result, their impact on depressive symptoms remains a relevant consideration.[49,50] With the increased interest in antipsychotics in the treatment of different phases of bipolar disorder, there exists a need for a review article that summarizes and critically evaluates the role of the antipsychotic agents in bipolar depression.

METHOD

English-language articles published from 1980 through July 2004 and cited in MEDLINE were searched using the keyword combination of *antipsychotics*, *typical antipsychotics*, *atypical antipsychotics*, *bipolar depression*, *bipolar disorder*, *manic-depressive illness*, *placebo*, and *clinical trial*. The following generic and brand names of antipsychotics were also entered as keywords: *fluphenazine* (*Prolixin*), *haloperidol* (*Haldol*), *perphenazine* (*Trilafon*), *pimozide*, *thiothixene* (*Navane*), *trifluoperazine* (*Stelazine*), *loxapine* (*Loxitane*), *molindone* (*Moban*), *chlorpromazine* (*Thorazine*), *mesoridazine*, *thioridazine* (*Mellaril*), *fluspirilene*, *penfluridol*, *pipothiazine*, *flupenthixol*, *clozapine* (*Clozaril*), *olanzapine* (*Zyprexa*), *risperidone* (*Risperdal*), *quetiapine* (*Seroquel*), *ziprasidone* (*Geodon*), and *aripiprazole* (*Abilify*). Clinical trials of atypical antipsychotic agents that used a depression rating scale (the Hamilton Rating Scale for Depression [HAM-D] or the Montgomery-Asberg Depression Rating Scale [MADRS]) were selected for our analysis. Peer-reviewed abstracts of placebo-controlled studies assessing acute or long-term efficacy in bipolar depression presented at major scientific meetings were also reviewed. Owing to limitations of space, case reports and retrospective studies were excluded, as well as studies enrolling children and adolescents.

RESULTS

This search uncovered 21 randomized studies* and 13 nonrandomized studies of antipsychotics in bipolar disorder [35,37–42,59–64] (Tables 1–3). Only 2 acute, double-blind, placebo-controlled studies have been conducted in bipolar depression.[45,46]

Atypical Antipsychotic Agents

Randomized acute studies. In order to meet an unmet need, 2 large-scale studies with atypical antipsychotic agents have been conducted in bipolar depression.[45,46] The first study was published by Tohen and colleagues in 2003[45] and compared the efficacy of olanzapine and the olanzapine-fluoxetine combination (OFC) with placebo in the treatment of bipolar I depression. A total of 833 patients with moderately severe bipolar I depression were randomly assigned to receive placebo (N = 377), olanzapine (N = 370), or OFC (N = 86) for 8 weeks. In a mixed-effects model repeated-measures (MMRM) analysis, olanzapine monotherapy and OFC exhibited significant improvement in MADRS scores compared with placebo as early as at the end of week 1. The OFC arm was significantly more efficacious than placebo as well as olanzapine monotherapy. MADRS individual item analyses indicated that both olanzapine monotherapy and OFC exhibited significant improvement in vegetative symptoms such as reduced sleep and appetite, but only OFC improved the core mood items, such as apparent sadness, reported sadness, lassitude, inability to feel, and pessimistic thoughts. Neither arm separated from placebo on the suicide item. The response rates (≥ 50% improvement from baseline) and the remission rates (≤ 12 on the MADRS) were also supportive of the superiority of OFC over olanzapine and placebo. The effect size of olanzapine monotherapy for depression was small (0.32). However, the effect size in acute mania (0.5)[27] and that of OFC for depression (0.68) were moderate.[65] In the post hoc analysis of a subgroup of patients with rapid cycling (N = 315),[66] olanzapine was superior to placebo only at the end of week 1. OFC, however, was superior to placebo during the entire 8-week study period.

Several aspects of this study's design were innovative: (1) this study was the first to limit enrollment to a prospectively defined cohort of patients with bipolar I depression; (2) the efficacy analysis employed in the study was MMRM analyses, which has been described as being more suitable for acute studies encumbered by premature study discontinuations[67]; (3) this acute study of bipolar I depression was the first to include patients with a recent history of rapid cycling. The study also had 2 limitations: (1) the rates of premature discontinuation were high (rates for olanzapine, OFC, and placebo were 51.6%, 36%, and

*References 26–29, 33, 34, 36, 43–48, 51–58.

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Table 1. Randomized, Double-Blind, Placebo-Controlled Trials of Antipsychotics Related to Bipolar Depression

Study	Mood State	Study Design	Treatment Arms	Duration, wk	Outcome[a]
Olanzapine					
Tohen et al[45]	Bipolar I depression	Acute monotherapy or OFC	Olan 9.7 mg/d (N = 370), Olan 7.4 + Flu 39.3 mg/d (N = 86), PBO (N = 377)	8	Olan or OFC vs PBO, p < .001; Olan vs OFC, p < .01
Tohen et al[47]	Bipolar I mania, remission on Olan	Acute open, then maintenance monotherapy	Olan 12.5 mg/d (N = 225), PBO (N = 136)	6–12, plus 48	Olan vs PBO, p < .001, longer time to relapse into any mood, mania, or depression; fewer patients relapsed into any mood or mania; p = .046, fewer patients relapsed into syndromic depression
Tohen et al[48]	Bipolar I mania	Acute open, then maintenance add-on to MS	Olan 8.6 mg/d (N = 51), PBO (N = 48)	6, plus 78	Olan vs PBO, p = .023, longer time to symptomatic relapse into any mood; p = NS for time to syndromic relapse into mania or depression and for rates of relapse into mania or depression
Tohen et al[26]	Bipolar I mania	Acute monotherapy	Olan 14.9 mg/d (N = 70), PBO (N = 69)	3	Olan vs PBO, p = NS
Tohen et al[27]	Bipolar I mania	Acute monotherapy	Olan 16.4 mg/d (N = 55), PBO (N = 60)	4	Olan vs PBO, p = NS; Sub: Olan vs PBO, p < .05
Tohen et al[43]	Bipolar I mania, inadequate response to MS for > 2 weeks	Acute, add-on	Olan 10.4 mg/d (N = 229), PBO (N = 115), Li (N = 115), Val (N = 218)	6	Olan vs PBO, p < .001; patients in mixed state had greater reduction
Baker et al[36]	Bipolar I mania	Post hoc analysis, monotherapy	Olan 5–20 mg/d (N = 124), PBO (N = 122)	3	Dysphoric group: Olan vs PBO, p = .038
Sanger et al[54]	Bipolar I mania, rapid cycling	Second analysis, monotherapy	Olan 5–20 mg/d (N = 19), PBO (N = 26)	3	Olan vs PBO, p = NS
Quetiapine					
Calabrese et al[46]	Bipolar I depression, bipolar II depression	Acute monotherapy	Quet 600 mg/d (N = 180), Quet 300 mg/d (N = 181), PBO (N = 181)	8	Quet vs PBO, p < .001
Sachs et al[34]	Bipolar I mania, Val or Li at least 7 d	Acute, add-on to MS	Quet 504 mg/d (N = 81), PBO (N = 89), Li (N = 77), Val (N = 113)	3	Quet vs PBO, p = NS
Flupenthixol					
Esparon et al[52]	Manic-depressive, frequent relapses on Li	Maintenance, crossover, add-on to Li	Flup 20 mg IM q 4 wk (N = 11), PBO (N = 11)	52 and 52	Flup vs PBO, p = NS for time spent in hospital; p < .05, PBO better on AMI
Perphenazine					
Zarate and Tohen[53]	Bipolar I mania	Acute open, then maintenance add-on to MS	Per 4–64 mg/d (N = 19), PBO (N = 18)	10, plus 26	Per vs PBO, p < .03, shorter time to relapse into depression, shorter time to discontinuation
Risperidone					
Yatham et al[29]	Bipolar I mania	Acute, add-on to MS	Risp 4.0 mg/d (N = 75), PBO (N = 15), Li (N = 86), Val (N = 38), Car (N = 26)	3	Risp vs PBO, p = NS; Risp or PBO vs BA, p = NS
Hirschfeld et al[33]	Bipolar I mania	Acute monotherapy	Risp 4.1 mg/d (N = 127), PBO (N = 119)	3	Wk 1 only: Risp vs PBO, p < .01

[a]Outcome measured with Hamilton Rating Scale for Depression (HAM-D) or Montgomery-Asberg Depression Rating Scale (MADRS).
Abbreviations: AMI = Affective Morbidity Index, BA = baseline, Car = carbamazepine, Flu = fluoxetine, Flup = flupenthixol, IM = intramuscularly, Li = lithium, MS = mood stabilizer; NS = not significant, Olan = olanzapine, OFC = olanzapine-fluoxetine combination, PBO = placebo, Per = perphenazine, Quet = quetiapine, Risp = risperidone, Sub = subgroup, Val = valproate or divalproex.

Table 2. Randomized, Non–Placebo-Controlled Trials of Antipsychotics Related to Bipolar Depression

Study	Mood State	Study Design	Treatment Arms	Duration, wk	Outcome[a]
Flupenthixol					
Ahlfors et al[51]	Group I: bipolar or unipolar recurrent manic-depressive, any index state	Open-label, Flup vs Li	Flup 10–40 mg IM q 2–4 wk (N = 19), Li 0.8–1.0 mmol/L (N = 14)	78	No effect on depression
	Group II: bipolar or unipolar recurrent manic-depressive, intolerant or unresponsive to Li; any index state	Open-label, nonrandomized monotherapy maintenance	Flup 10–40 mg IM q 2–4 wk (N = 93)	78	Prior (2 years) vs post Flup (2 years): During Flup treatment: $p < .01$, less frequent in mania; $p < .05$, less time spent in mania; $p < .05$, more frequent in depression; $p < .05$, more time spent in depression Subgroup analysis: no previous Li exposure group: p = NS, frequency in depression, time spent in depression. Previous Li exposure group: $p < .05$, more frequent in depression; $p < .01$, more time spent in depression
Clozapine					
Suppes et al[55]	Schizoaffective (N = 12), bipolar I (N = 26); history of mania TR to MS, any index state	Open-label, add-on vs TAU	Cloz 355 (range, 50–900) mg/d (N = 19), TAU (N = 19)	52 1/7	Cloz vs TAU, p = .06
Olanzapine					
Tohen et al[28]	Bipolar I mania	Double-blind, Olan vs Val	Olan 17.4 mg/d (N = 125), Val 1401.2 mg/d (N = 123)	3	Olan vs Val, p = NS
Zajecka et al[56]	Bipolar I mania	Double-blind, Olan vs Val	Olan 14.7 mg/d (N = 57), Val 2115 mg/d (N = 63)	12	Olan vs Val, p = NS
Tohen et al[57]	Bipolar I mania	Double-blind, Olan vs Val	Olan 16.2 mg/d (N = 125), Val 1584.7 mg/d (N = 126)	47	Olan vs Val, p = NS
Tohen et al[44]	Bipolar I mania	Double-blind, Olan vs Hal	Olan 5–20 mg/d (N = 234), Hal 3–15 mg/d (N = 234)	12	Olan vs Hal, p = NS
Quetiapine					
Altamura et al[58]	Bipolar I, II disorder, partial or full remission	Open-label, Quet vs MS	Quet 157 mg/d (N = 14), Val 496 mg/d (N = 8), Li 675 mg/d (N = 4), Gaba 300 mg/d (N = 1)	52	Quet vs MS, p = NS

[a]Outcome measured with Hamilton Rating Scale for Depression (HAM-D) or Montgomery-Asberg Depression Rating Scale (MADRS).
Abbreviations: Cloz = clozapine, Flup = flupenthixol, Gaba = gabapentin, Hal = haloperidol, IM = intramuscularly, Li = lithium, MS = mood stabilizer, NS = not significant, Olan = olanzapine, Quet = quetiapine, TAU = treatment as usual, TR = treatment-resistant, Val = valproate or divalproex.

61.5%, respectively); and (2) there was no fluoxetine monotherapy comparison arm because of concerns regarding possible induction of mania.

Recently, Calabrese et al.[46] carried out a study of quetiapine monotherapy for the treatment of bipolar depression. In this study, 542 outpatients with bipolar I (N = 360) or II (N = 182) disorder experiencing a major depressive episode were randomly assigned to receive 8 weeks' quetiapine monotherapy (300 or 600 mg/day) or placebo. The completion rates for the quetiapine 600 mg/day, quetiapine 300 mg/day, and placebo groups were 54%, 68%, and 59%, respectively, with no significant difference among them. In the intent-to-treat and last-observation-carried-forward or MMRM analysis, quetiapine 600 mg/day or 300 mg/day demonstrated significantly greater improvement in MADRS scores compared with placebo as early as at the end of week 1; these improvements were similar to those seen with olanzapine and OFC. There was no significant difference between the 2 active arms in the total MADRS score changes during the entire study period. Apparent sadness and reported sadness were among the significantly improved MADRS items in addition to suicidal thoughts. Comparable response (58%) and remission (53%) rates for both active arms were observed, which were significantly higher than the rates with placebo. The effect size was large for the quetiapine 600 mg/day arm (0.81) and moderate in size for the 300 mg/day arm (0.67). In the subgroup analysis, the effect sizes reported in the bipolar I subgroup continued to be large for quetiapine 600 mg/day (1.09) and became large for quetiapine 300 mg/day (0.91). However, the effect sizes were much smaller in the bipolar II subgroup, 0.39 for quetiapine 600 mg/day and 0.28 for quetiapine 300 mg/day. In contrast to the limited efficacy of olanzapine in the subgroup of patients with rapid cycling described above, quetiapine was efficacious in both patients with and patients without rapid cycling.

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Table 3. Nonrandomized, Prospective Trials of Antipsychotics Related to Bipolar Depression

Study	Mood State	Study Design	Treatment Arms	Duration, wk	Outcome[a]
Olanzapine					
Sanger et al[39]	Bipolar I mania	Open-label following 3 wk double-blind, PBO-controlled phase	Olan 13.9 mg/d (N = 113) + Li 786 mg/d (N = 36) or + Flu 13.5 mg/d (N = 37)	49	BA vs EN, p < .001
Gonzalez-Pinto et al[38]	Bipolar I disorder, rapid cycling, MS for at least 1 year	Open-label, add-on to MS	Olan 16.15 mg/d (N = 13)	4	BA vs EN, p < .001
Janenawasin et al[35]	Bipolar I (N = 14), bipolar II (N = 10), bipolar NOS (N = 1); any index episode	Open-label, add-on to MS or monotherapy	Olan 7.8 mg/d (N = 25): monotherapy (N = 10), cotherapy (N = 15)	9	BA vs EN, p < .01
Quetiapine					
Brown et al[42]	Bipolar I, II; cocaine dependence; any index episode	Open-label, add-on to ongoing treatment	Quet 229.4 mg/d (N = 17)	12	BA vs EN, p = .001
Vieta et al[59]	Bipolar with rapid cycling, any index episode	Open-label, add-on to ongoing treatment	Quet 720 mg/d (N = 14); wk 12 360 mg/d	17 4/7	BA vs average, p = NS
Risperidone					
Vieta et al[37]	Schizoaffective, bipolar I, bipolar II, bipolar NOS	Open-label, monotherapy or add-on to MS	Risp 4.0 mg/d (N = 541); Risp at 6 mo 3.9 mg/d (N = 430)	26	BA vs EN, p < .0001
Vieta et al[41]	Bipolar II hypomania	Open-label, monotherapy or add-on to MS	Risp 2.8 mg/d (N = 44)	26	BA vs EN, p < .0001
Vieta et al[40]	Bipolar I and II mania or hypomania	Open-label, add-on to MS or monotherapy	Risp 4.5–5.1 mg/d (N = 151)	6	BA vs EN, p < .0001
Vieta et al[60]	Bipolar I mania	Open-label, Risp and Top	Risp 2.7–5.6 mg/d (N = 58), Top 236.3 mg/d (N = 58)	52	BA vs wk 2 onward, p < .05
Yatham et al[61]	Bipolar I mania	Open-label, add-on to MS	Risp 0.5–4 mg/d (N = 108)	12	BA vs wk 3 or wk 12, p < .0001
Vieta et al[62]	Bipolar I mania	Open-label, monotherapy	Risp 4.2 mg/d (N = 96)	26	BA vs all study period, p < .0001
Yatham et al[63]	Bipolar I mania	Open-label, add-on to Li or Val	Risp 0.5–6 mg/d (N = 79), Li (N = 33), Val (N = 46)	12	BA vs wk 12, p < .05; Li vs Val, p = NS
Bowden et al[64]	Bipolar I mania	Open-label, add-on to MS following 3-wk double-blind, PBO-controlled phase	Risp 3.1 mg/d (N = 85)	10	BA vs wk 1 or 10, p < .05

[a]Outcome measured with Hamilton Rating Scale for Depression (HAM-D) or Montgomery-Asberg Depression Rating Scale (MADRS).
Abbreviations: BA = baseline, EN = endpoint, Flu = fluoxetine, Li = lithium, MS = mood stabilizer, NOS = not otherwise specified, NS = not significant, Olan = olanzapine, PBO = placebo, Risp = risperidone, Quet = quetiapine, Top = topiramate, Val = valproate or divalproex.

Several aspects of this study's design were innovative: (1) inclusion of bipolar II depressed patients into a large-scale study was novel, enhances the generalizability of the findings, and represents the first time any antipsychotic agent has been concurrently studied in patients with bipolar I or II depression; (2) this study also included health-related quality of life and sleep quality measures; and (3) using effect size determinations gives clinicians useful information that goes beyond the simple reporting of significant differences. The study also had limitations: (1) the number of enrolled patients with bipolar II disorder (N = 182) may not have been sufficient to draw firm conclusions regarding efficacy in this subgroup; (2) the moderate rates of sedation or somnolence in both quetiapine groups might have had the potential of compromising the integrity of the double-blind design; and (3) the doses of quetiapine might have been too high because there were few significant differences in efficacy between the quetiapine 600 mg/day and 300 mg/day groups.

Maintenance studies. The incomplete prophylactic effect of the currently available agents for bipolar disorder has turned investigators' focus onto atypical antipsychotics. Tohen et al.[47] carried out a double-blind, randomized, placebo-controlled, 12-month study of olanzapine maintenance in bipolar disorder. Of the 731 patients entering the open-label olanzapine treatment, 361 (49.4%) met criteria for symptomatic remission of mania (Young Mania Rating Scale [YMRS] score ≤ 12) and entered the double-blind maintenance period, at which time they were randomly assigned to receive either olanzapine (N = 225) or placebo (N = 136). A total of 66 patients completed the entire 48 weeks of double-blind treatment without relapsing, with significantly more olanzapine (23.6%) than placebo (9.6%) patients having their bipolar disorder remain

in remission. The rate of discontinuation due to lack of efficacy was significantly lower in the olanzapine group (28.4%) than in the placebo group (57.4%). Meanwhile, the time to symptomatic relapse (YMRS score ≥ 15, 21-item HAM-D score ≥ 15, or hospitalization for manic, mixed, or depressed episode) and syndromic relapse (defined according to DSM-IV criteria) into any mood was significantly longer in patients treated with olanzapine compared with those treated with placebo. Concomitantly, the rates of symptomatic relapse into any mood, mania, or depression were significantly lower in olanzapine-treated patients. However, olanzapine prevented patients from relapse into mania more than into depression.

Several aspects of this study's design were innovative: (1) the study was the first to examine not only relapse into mania or depression, but also relapse into mixed episodes; (2) symptomatic relapse was also used as a primary measure of efficacy. The study also had limitations: (1) the completion rate was low; (2) the period that patients were required to remain in remission prior to randomization was relatively short (1 week minimum); and (3) there was no taper period for placebo patients as they entered the double-blind period, which might have placed this group at a disadvantage due to the possibility of withdrawal effects associated with abrupt discontinuation of olanzapine.

In contrast to monotherapy, olanzapine augmentation to mood stabilizer therapy did not yield robust results in the prevention of relapse of bipolar I disorder in an 18-month, double-blind study.[48] In that study, patients who were treated with lithium or valproate at a therapeutic blood level for at least 2 weeks and continued having persistent manic symptoms (YMRS score ≥ 16) received the addition of olanzapine. Those who had achieved syndromic remission with augmentation were randomly assigned to receive an additional 18 months of either combination therapy or mood stabilizer plus placebo. The completion rate with combination therapy (31%) was significantly higher than that with mood stabilizer plus placebo (10%), and patients with combination therapy also stayed in the study significantly longer than those with mood stabilizer plus placebo (111 vs. 82 days). Except for the significant prolongation to symptomatic relapse into any mood in the combination group (163 vs. 42 days), the prolongation of time to syndromic relapse into any mood and to symptomatic relapse into mania or depression was not significant. The decreased rates of neither syndromic nor symptomatic relapse into any mood episode, mania, or depression alone were significant. Interestingly, women and Caucasian patients receiving combination therapy had significantly longer time to symptomatic relapse than did patients receiving mood stabilizer plus placebo.

Not only has olanzapine monotherapy been compared with placebo, but, recently, a maintenance study was conducted that compared this compound with divalproex.[57] This maintenance study was unable to show differences between these 2 compounds in time to relapse and the proportion of patients who relapsed.

In another long-term study of an atypical antipsychotic agent,[55] patients with treatment-refractory bipolar disorder were randomly assigned to either clozapine augmentation or treatment as usual. Compared with patients in the treatment as usual arm, clozapine-treated patients showed significant improvement in symptoms of mania, but not depression. This study was confounded with a small sample size (N = 19 for each group), different patient populations (schizoaffective and bipolar), different index episodes (manic, mixed, depressed), and the absence of a placebo arm (Table 2).

Nonrandomized trials. Most nonrandomized trials were open, prospective, and add-on studies (Table 3). Similar to findings with olanzapine and quetiapine, the efficacy of risperidone in the reduction of secondary depressive symptoms in patients with bipolar disorder was demonstrated.[40,41,60–64]

Typical Antipsychotics

Although there is evidence to support the use of the typical antipsychotic agents in the treatment of mania,[20–23] the efficacy of these agents in the treatment of bipolar depression has not been established. On the contrary, Kukopulos and colleagues[68] proposed that typical antipsychotic agents were "depressogenic" on the basis of their longitudinal observation of bipolar disorder. They found that patients who continued taking neuroleptics after resolution of mania had deeper and longer depression, and when neuroleptics were suspended, the depression was much attenuated or ended. However, the extent to which these agents cause or worsen the symptoms of depression is still unclear.[51–53]

In 1981, Scandinavian investigators[51] evaluated the spectrum of prophylactic efficacy of flupenthixol decanoate administered to a cohort of 93 manic-depressive patients believed to be intolerant or nonresponsive to lithium. These investigators reported significant increases in the frequency of depressive episodes and the percentage of time spent depressed concurrent with decreases in the frequency of manic episodes and the percentage of time spent manic during this 18-month open-label trial. Rather than concluding that flupenthixol was "depressogenic," Ahlfors and colleagues[51] reasoned this untoward consequence was from the withdrawal of treatment of lithium because only patients who took lithium prior to the study presented with more depressive episodes. To further evaluate the putative "depressogenic" properties of flupenthixol, British investigators[52] conducted a small double-blind, randomized, add-on, crossover trial lasting 1 year in 11 patients with bipolar disorder. Partial responders to lithium were randomly assigned to either flupenthixol decanoate augmentation or placebo for 1 year, and then crossed over to the

other arm for another year. With 1 exception, there were no significant differences on measures of clinical outcome. According to an affective morbidity index, patients did significantly better ($p < .05$) during the augmentation with placebo than during the augmentation with flupenthixol. Until recently, these 2 preliminary trials of flupenthixol decanoate and 2 other reports[68,69] represented the extent of the early data that support the impression that the typical antipsychotic agents cause or worsen the symptoms of depression when used in the treatment of bipolar disorder.

More recently, Zarate and Tohen[53] have evaluated the extent to which the typical antipsychotic agents cause or worsen the symptoms of depression in bipolar disorder in a study of perphenazine. This double-blind study compared the continued use of perphenazine versus its discontinuation in recently manic patients. Thirty-seven patients were randomly assigned to 6 months of double-blind treatment of mood stabilizer plus perphenazine continuation treatment versus mood stabilizer plus placebo (perphenazine discontinuation group) following remission of mania. Patients given placebo were significantly more likely than those given perphenazine to complete the study and to have longer times to discontinuation (163 vs. 130 days). Patients given perphenazine were significantly more likely to discontinue the study due to relapse into depression, to have shorter times to relapse into depression, and to discontinue the study for any reason. This study was well designed, but was confounded with a small sample size (N = 19 for perphenazine, N = 18 for placebo) (Table 1).

Besides these long-term studies of the impact of typical antipsychotics in bipolar disorder, a 12-week head-to-head comparison of olanzapine versus haloperidol has been carried out.[44] In that study, both agents were equally effective in the acute treatment of manic and depressive symptoms. However, a subset of patients (N = 34) who were not clinically depressed at study entry became depressed at some points during the study. In this subgroup, haloperidol-treated patients (22/131) switched to depression significantly earlier than olanzapine-treated patients (12/128), but the incidence of switch was not significantly different between the 2 groups. Without a placebo arm, it is difficult to determine whether the switch to depression was due to "depressogenic" properties of antipsychotics or insufficient prevention of depressive relapse.

DISCUSSION

To our knowledge, the present article represents the first systematic review of the efficacy data regarding the role of the typical and atypical antipsychotic agents in the treatment of bipolar depression. In an attempt to inform the medical management of the depressed phase of bipolar disorder, we have integrated the available data from MEDLINE and major scientific meetings.

The 2 double-blind, randomized, placebo-controlled studies designed for the acute treatment of bipolar depression provide reasonable evidence that olanzapine and quetiapine are effective in the acute treatment of bipolar I depression.[45,46] Data from the olanzapine maintenance studies[47,48] and other open-label, prospective long-term studies[37,58,60,62] suggest that atypical antipsychotic agents may also have a role in the maintenance treatment of bipolar depression. Good-quality data for typical antipsychotics in bipolar depression are limited.

Investigators are now commonly using effect size determinations (improvement over placebo divided by pooled standard deviation) to gauge the magnitude of a drug's acute clinical effect. This statistical construct gives clinicians an appreciation for the degree to which significant separation from placebo is clinically relevant. Effect sizes of 0.2 to 0.49 are viewed as being small, 0.5 to 0.79 as moderate, and ≥ 0.8 as large.[65]

Olanzapine monotherapy had different effect sizes in depression and mania, small (0.32) for depression versus moderate (0.5) for mania.[27,45] The cause for this difference is unclear. One possibility is the dose differences: a relatively low dose (mean modal dose 9.7 mg/day) in the depression study compared with that in a study of acute mania (mean modal dose 14.9 mg/day).[26] It would be interesting to know whether a higher dose of olanzapine can increase the effect size, or whether olanzapine must be used with fluoxetine to yield a larger effect size in depression. Unlike with olanzapine, the effect size of quetiapine in the treatment of acute depression was larger than its effect size in the acute treatment of mania. At a comparable drug dose (≈ 600 mg/day), the effect size of quetiapine was large (1.09) for depression at the end of week 8 and small (0.49) for mania at the end of week 12.[46,70]

Compared with the effect size of olanzapine in bipolar I depression, that of quetiapine was much larger, 1.09 for quetiapine 600 mg/day and 0.91 for quetiapine 300 mg/day. However, quetiapine had much smaller effect sizes in bipolar II patients, suggesting that quetiapine is less effective for treating bipolar II depression. It is unclear whether the difference between olanzapine and quetiapine in bipolar I depression is due to their pharmacologic differences or due to study designs. The baseline MADRS scores in both studies were similar, but the olanzapine study included inpatients and also had more patients with rapid cycling than the quetiapine study. In contrast to a large difference in effect size in depression between olanzapine and quetiapine, the difference in the effect sizes for both agents in mania was relatively small (0.5 for olanzapine at the end of week 4 versus 0.39 for quetiapine at the end of week 3).[27,70] The importance of this differentiation is unclear.

Like atypical antipsychotics, typical agents may also have an acute antidepressant effect on secondary depressive symptoms in mania.[44] This acute effect of both

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classes is more likely dependent on the severity of the baseline depressive symptoms. For example, in a whole sample analysis, olanzapine had no significant effect on depressive symptoms of patients with mania, but olanzapine significantly reduced depressive symptoms in a subgroup of patients with mixed features.[27] It is suggested that antipsychotics are effective in reducing both manic and depressive symptoms of patients in a mixed manic (dysphoric) state. Similar to olanzapine and quetiapine, risperidone could reduce secondary depressive symptoms in dysphoric mania, suggesting it may also be effective in the acute treatment of bipolar depression.

So far, the good-quality maintenance data for atypical antipsychotics are limited to olanzapine.[47,48] Similar to the acute treatment of mania and depression, olanzapine was more than twice as effective in the prevention of relapse into mania as it was in the prevention of relapse into depression, suggesting that olanzapine works more like lithium than lamotrigine in the treatment of bipolar disorder.[18,19] The results from the open-label, prospective, long-term studies of risperidone and quetiapine in the prevention of relapse appear promising, but randomized, double-blind, placebo-controlled trials are warranted. Olanzapine did not show significant advantage in treating acute mania or preventing relapse over divalproex.[28,56,57] Serious consideration of the short- and long-term safety and tolerability of atypical antipsychotics and mood stabilizers should be taken into account. Comparing the results of olanzapine and clozapine augmentation to mood stabilizer treatment[48,55] with olanzapine monotherapy[47] suggests that patients whose illness is resistant to treatment with a mood stabilizer alone are also less responsive to antipsychotic augmentation treatment.

In contrast to the evidence of the efficacy of atypical antipsychotics in the acute treatment of bipolar depression and prevention of relapse, the role of typical antipsychotics in these 2 phases of bipolar disorder is still unclear. The available evidence regarding the use of the typical antipsychotics in the treatment of bipolar disorder does not support the conclusion that this class of medication is "depressogenic." A randomized, placebo-controlled trial in bipolar depression that compares the safety and efficacy of atypical versus typical antipsychotic agents is needed for this controversial matter.

A detailed discussion of the mechanism of antidepressant effect of antipsychotics is beyond the scope of this review. However, a brief discussion may help explain the efficacy differences among the antipsychotic agents. There is evidence that dopamine and dopamine D_2 blockade have opposite roles in the treatment of bipolar disorder. Pramipexole, a dopamine agonist, and bupropion, a weak dopamine reuptake inhibitor, could improve depressive symptoms in patients with bipolar disorder.[71–73] However, the antimanic effect of antipsychotic agents was believed to be through the blockade of dopamine receptors, especially D_2 receptors.[20,74] Although the exact mechanism of dopamine in mania and depression is unclear, it is logical to think that dopamine plays an important role in the improvement in depressive symptoms of bipolar patients and that its release caused by antipsychotic agents[75–78] may, at least in part, be responsible. The efficacy of each antipsychotic agent in the treatment of bipolar mania or depression may depend on the balance of neurotransmitters released, including dopamine, and receptor blockade, including D_2 receptors, in the different parts of the brain.

Limitations

This review is limited by the parameters of the computer search, which included English-language articles published from 1980 to July 2004 reporting clinical trials that utilized the HAM-D or the MADRS and primarily featured randomized controlled trials. Another factor that complicates our interpretation of the acute bipolar depression trial data revolves around the use of therapeutic effect size determinations across differently designed studies. Although one can use the construct of effect size in an attempt to quantify the magnitude of the acute clinical effect between different studies, this type of analysis does not take into account different designs (e.g., inclusion and exclusion criteria, sample sizes) and different methods of efficacy analyses (last observation carried forward, MMRM).

CONCLUSION

Emerging data suggest that the class of atypical antipsychotic agents has a role in the acute and long-term treatment of bipolar depression. However, the relative efficacy of individual agents may be different. There are no acute data in the published literature to support the impression that the typical antipsychotics worsen symptom severity in bipolar depression; however, their long-term use should be carefully monitored for side effects associated with D_2 receptor blockade.

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin and others), chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril, FazaClo, and others), divalproex sodium (Depakote), fluoxetine (Prozac and others), fluphenazine (Prolixin and others), haloperidol (Haldol and others), lamotrigine (Lamictal), lithium (Lithobid, Eskalith, and others), loxapine (Loxitane and others), molindone (Moban), olanzapine (Zyprexa), olanzapine-fluoxetine combination (Symbyax), perphenazine (Trilafon and others), pimozide (Orap), pramipexole (Mirapex), quetiapine (Seroquel), risperidone (Risperdal), thiothixene (Navane and others), trifluoperazine (Stelazine and others), ziprasidone (Geodon).

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