Use of Atypical Antipsychotics in Refractory Depression and Anxiety

Charles B. Nemeroff, M.D., Ph.D.

Treatment options for bipolar depression and treatment-resistant unipolar depression include augmentation of antidepressant therapy with a nonantidepressant drug, including atypical antipsychotics. Risperidone is effective in combination with fluvoxamine, paroxetine, or citalopram in treatment-resistant unipolar depression, with reported remission rates of 61% to 76%. Olanzapine in combination with fluoxetine is safe and effective in patients with bipolar depression and those with fluoxetine-resistant unipolar depression. Ziprasidone and aripiprazole augmentation of various selective serotonin reuptake inhibitors has been reported to be effective in refractory unipolar depression in open-label studies. Data on use of quetiapine or clozapine as augmentation therapy for depression or anxiety are not yet available. Further double-blind, placebo-controlled studies of augmentation of antidepressants with atypical antipsychotics in refractory depression and anxiety are justified based on the available literature. *(J Clin Psychiatry 2005;66[suppl 8]:13–21)*

Bipolar depression and treatment-resistant unipolar depression present treatment challenges for the clinician. Although acute manic episodes are often more disabling and dangerous than bipolar depression,[1] patients with bipolar disorder spend more time ill with depression than with mania.[2] Further, subsyndromal depressive symptoms occurring between acute episodes of illness tend to be chronic[3] and associated with ongoing functional impairment.[4]

The true incidence of treatment-refractory unipolar depression is difficult to determine, partly because of the absence of a standardized, validated definition of treatment-resistant depression.[5] Although the U.S. Food and Drug Administration has traditionally used a 50% or greater reduction in symptom severity as the definition of treatment response, many so-called responders exhibit persistent depressive morbidity. This realization coupled with the observation that persistent depressive symptoms are associated with poor prognosis has made remission the gold standard of therapeutic efficacy in the treatment of depression. Remission is defined as a Hamilton Rating Scale for Depression (HAM-D)[6] score of 7 or less[7] or a Montgomery-Asberg Depression Rating Scale (MADRS)[8] score of 10 or less, equivalent to premorbid depressive symptom severity. In acute depression trials of 8 weeks, remission rates with antidepressant monotherapy are at best 45%,[7] indicating the need for treatment regimens that address the more than half of patients with major depression unsuccessfully treated with antidepressant monotherapy.

The options for managing bipolar depression and treatment-resistant unipolar depression are relatively limited and are supported by few published data. Psychopharmacologic strategies for treating patients with unipolar depression unresponsive to a trial of monotherapy with an antidepressant include optimizing the antidepressant dose, switching to an alternative antidepressant of the same or a different class, combining 2 antidepressants, or augmenting the antidepressant with thyroid hormone, lithium, or other agents. However, some patients remain unresponsive to many of these strategies.[5,9,10] In bipolar depression, one obstacle to the use of certain antidepressants is their potential for inducing mania or rapid cycling in some patients.[11–13] This is more likely to occur with tricyclic antidepressants and monoamine oxidase inhibitors and less likely with bupropion or selective serotonin reuptake inhibitors (SSRIs). Also, lamotrigine is an effective agent for treating bipolar depression and is not associated with induction of mania.[14] Clearly, alternative therapeutic strategies are needed for difficult-to-treat bipolar and unipolar depression.

Augmentation refers to using a drug other than an antidepressant in combination with an antidepressant. Both lithium and thyroid hormone have been reported to be

From the Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Ga.

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Corresponding author and reprints: Charles B. Nemeroff, M.D., Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, 101 Woodruff Circle, Suite 4000, Atlanta, GA 30322 (e-mail: cnemero@emory.edu).

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Table 1. Studies of Augmentation of an Antidepressant With an Atypical Antipsychotic in Patients With Bipolar Depression

Study	Design	N	Antidepressant	Atypical Antipsychotic	Primary Efficacy Measure and Result	Remission and Response Rate (%)
Tohen et al, 2003[28]	8-wk, double-blind, randomized, placebo-controlled	833	Fluoxetine 25 or 50 mg/d	Olanzapine as monotherapy 5–20 mg/d as combination therapy 6 or 12 mg/d	Decrease in MADRS score from baseline at 8 wk Combination –18.5* Olanzapine –15.0 Placebo –11.9	Remission Combination 48.8** Olanzapine 32.8 Placebo 24.5 Response Combination 56.1*** Olanzapine 39.0 Placebo 30.4
Stahl and Shelton, 2001[27]	12-wk, double-blind, randomized	30	Paroxetine 10–40 mg/d	Risperidone 1–4 mg/d	Decrease in MADRS score; no significant difference between 3 treatment groups; statistical trend toward greater improvement on BDI in combination group	NR

*$p < .001$ vs. placebo; $p = .01$ vs. olanzapine.
**$p < .001$ vs. placebo; $p < .007$ vs. olanzapine.
***$p < .001$ vs. placebo; $p = .006$ vs. olanzapine.
Abbreviations: BDI = Beck Depression Inventory, MADRS = Montgomery-Asberg Depression Rating Scale, NR = not reported.

effective as augmentation therapy,[15–19] although negative controlled studies with the latter have recently been reported (Appelhof et al.[20] and P. T. Ninan, M.D.; C.B.N.; unpublished observations, 2005). In bipolar depression, antidepressants have been combined with anticonvulsants and other mood stabilizers.[21–23] Emerging evidence indicates that atypical antipsychotics at relatively low doses are effective in combination with antidepressants for both unipolar and bipolar depression.[24–30]

Support for investigation of atypical antipsychotics in patients with depression comes partly from preclinical studies suggesting that several atypical antipsychotics are potent 5-HT_{2A} antagonists at low doses[31–33] and may facilitate the action of serotonin at the 5-HT_{1A} receptor, thereby augmenting the efficacy of SSRIs.[24] In addition, certain atypical antipsychotics have other pharmacologic properties that may contribute to antidepressant effects, including α_2 antagonism (risperidone), 5-HT_{1A} agonism (aripiprazole and ziprasidone), and monoamine reuptake blockade (ziprasidone). Further, atypical antipsychotics decrease the mild-to-moderate depressive symptoms seen in patients with schizophrenia[34–38] and other psychotic disorders.[39,40]

This review summarizes the available data on the efficacy of atypical antipsychotics when combined with antidepressants in patients with difficult-to-treat bipolar or unipolar depression. Evidence that these agents also are effective as augmentation therapy in anxiety disorders, including generalized anxiety disorder and obsessive-compulsive disorder (OCD),[41,42] which is often comorbid with depression, is reviewed as well.

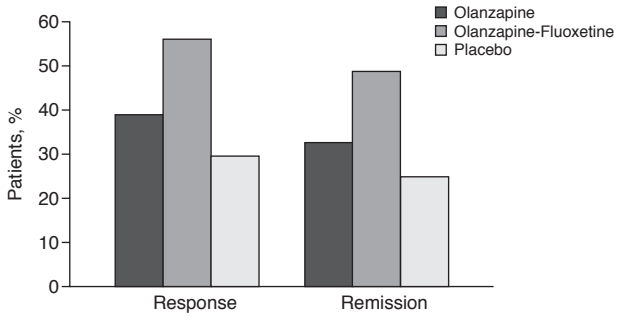
EFFICACY OF ATYPICAL ANTIPSYCHOTICS IN BIPOLAR DEPRESSION

Two double-blind trials[27,28] have investigated the use of an atypical antipsychotic in combination with an antidepressant in the treatment of bipolar depression (Table 1). Tohen et al.[28] conducted a multicenter, double-blind, placebo-controlled trial in which 833 patients with bipolar I depression were randomly assigned to receive olanzapine (5 to 20 mg/day), olanzapine (6 or 12 mg/day) in combination with fluoxetine (25 or 50 mg/day), or placebo for 8 weeks. The primary efficacy measure was the change from baseline in the MADRS score at 8 weeks.

The MADRS scores (mean ± SD) at baseline ranged from 30.8 ± 6.1 to 32.6 ± 6.2. The mean decrease in MADRS scores from baseline at week 8 were –15.0, –18.5, and –11.9 in the olanzapine, olanzapine-fluoxetine, and placebo groups, respectively ($p < .001$, olanzapine-fluoxetine vs. placebo); treatment versus placebo differences were significant as early as week 1. Response (defined as a 50% or greater decrease in MADRS scores from baseline to endpoint) and remission (defined as a MADRS score of 12 or less [usually defined as 10 or less] at endpoint and completion of 4 or more weeks of treatment) occurred in a significantly higher percentage of patients in either active treatment group compared with the placebo group ($p = .02$ and $p < .001$, olanzapine and olanzapine-fluoxetine, respectively, both criteria) (Figure 1). Response and remission rates were significantly higher in the olanzapine-fluoxetine group than in the olanzapine group alone ($p < .01$). Patients in the olanzapine group and the olanzapine-fluoxetine group also had significantly greater improvement in scores on the Young Mania Rating Scale (YMRS),[43] Clinical Global Impressions scale (CGI) Bipolar Version–Severity of Depression (CGI-BP-S),[44] and the Hamilton Rating Scale for Anxiety (HAM-A)[45] than did patients in the placebo group ($p < .01$). Improvement on the CGI-BP-S was greater in the olanzapine-fluoxetine group than in the olanzapine group ($p = .01$).

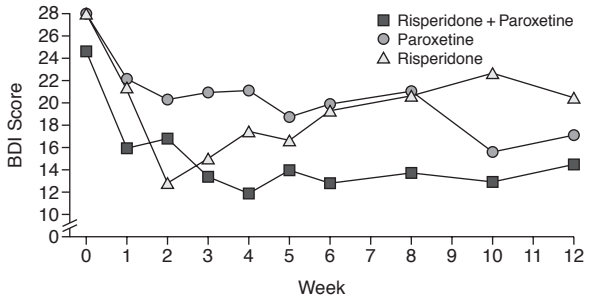
Treatment-emergent mania, defined as a YMRS score of less than 15 at baseline and 15 or greater at any time

Figure 1. Response and Remission Rates in Patients With Bipolar I Depression After 8 Weeks of Treatment With Olanzapine (N = 351), Olanzapine Plus Fluoxetine (N = 82), or Placebo (N = 355)[a,b]



[a]Data from Tohen et al.[28]
[b]p = .02 for both comparisons olanzapine vs. placebo; p < .001 for both comparisons olanzapine-fluoxetine vs. placebo; p < .01 for both comparisons between active treatment groups.

Figure 2. Scores on the Beck Depression Inventory (BDI) in Patients With Bipolar Depression Treated With Risperidone, Paroxetine, or Risperidone and Paroxetine Combined[a,b]



[a]Adapted with permission from Stahl and Shelton.[27]
[b]No significant differences between treatment groups at endpoint were observed.

thereafter, occurred in approximately 6% of patients in each treatment group. Although olanzapine clearance decreases when the drug is given concomitantly with fluoxetine,[46] little difference was seen in the adverse event profiles of the olanzapine and olanzapine-fluoxetine groups, other than a significantly higher incidence of nausea (12%) and diarrhea (19%) in the combined treatment group.

In a post hoc analysis of data from the Tohen et al. study,[28] Corya et al.[47] reported on the efficacy of olanzapine and olanzapine-fluoxetine in a subset of patients with bipolar depression and comorbid anxiety. In the 359 patients studied, those treated with olanzapine-fluoxetine (N = 31) or olanzapine (N = 168) had significantly greater decreases in MADRS scores compared with those given placebo (N = 160) ($p < .001$ and $p < .002$, respectively). Decreases in scores on the HAM-A also were significantly greater with olanzapine-fluoxetine and olanzapine alone compared with placebo ($p < .001$ and $p = .044$, respectively).

Stahl and Shelton[27] presented data from a small double-blind controlled trial of risperidone and paroxetine in the treatment of bipolar depression. Thirty patients with *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV) bipolar disorder, depressive subtype who had been treated with a mood stabilizer at stable doses for 3 weeks were randomly assigned to receive risperidone (1 to 4 mg/day plus placebo), paroxetine (10 to 40 mg/day plus placebo), or risperidone at the same dose plus paroxetine at a 30% lower dose for 12 weeks. Patients with current psychotic symptoms or mixed features were excluded.

At weeks 6 and 12, no significant differences were seen in treatment response as indicated by the primary efficacy measure (MADRS) or secondary efficacy measures (HAM-D, YMRS, and CGI-Improvement scale[48]) across the 3 treatment groups. On the Beck Depression Inventory,[49] trends favoring the combination treatment group were identified (Figure 2).

The combination of risperidone and paroxetine was safe and well tolerated. There were no significant between-group differences in scores at endpoint on the Barnes Akathisia Scale[50] or the Abnormal Involuntary Movement Scale (AIMS)[51]; however, mean ± SD scores on the Simpson-Angus Scale in the combination treatment group (1.22 ± .30) were higher than scores in either the risperidone plus placebo group (0.57 ± 0.5) or the paroxetine plus placebo group (0) at 8 weeks (last observation carried forward; $p < .04$, risperidone + paroxetine vs. risperidone + placebo). Hypomania occurred in 3 patients in the group treated with paroxetine alone and in 1 patient in each of the other 2 groups. Although paroxetine[52] and carbamazepine[53] have been reported to alter plasma levels of risperidone and 9-hydroxyrisperidone via inhibition and induction of CYP2D6, respectively, there were no apparent clinical consequences of such interactions in this study. Studies with adequate statistical power are clearly needed.

Quetiapine has been studied as monotherapy for bipolar depression. In an 8-week, randomized, double-blind, placebo-controlled trial, patients with bipolar depression taking quetiapine (300 or 600 mg/day) had significantly greater improvement in mean MADRS scores compared with those given placebo ($p < .001$).[54]

EFFICACY OF ATYPICAL ANTIPSYCHOTICS IN TREATMENT-RESISTANT UNIPOLAR DEPRESSION

Several studies have sought to determine whether an atypical antipsychotic in combination with an antidepressant in patients with treatment-resistant unipolar depression is an effective augmentation strategy (Table 2). In a case series, Ostroff and Nelson[24] studied 8 patients with

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Table 2. Studies of Augmentation of an Antidepressant With an Atypical Antipsychotic in Patients With Treatment-Resistant Unipolar Depression

Study	Design	N	Antidepressant	Atypical Antipsychotic	Primary Efficacy Measure and Result	Remission and Response Rate (%)
Ostroff and Nelson, 1999[24]	Case series	8	Paroxetine 10–30 mg/d or fluoxetine 20–40 mg/d	Risperidone 0.5 or 1 mg/d	Baseline and endpoint HAM-D scores, 20.5 and 3.7, respectively; maintained for ≥ 3 mo	100
Hirose and Ashby, 2002[25]	6-wk open-label	36	Fluvoxamine 150 mg/d for patients ≤ 60 y; 100 mg/d for patients > 60 y	Risperidone 1 mg/d for patients ≤ 60 y; 0.5 mg/d for patients > 60 y	Decrease in HAM-D scores from baseline; NR	Remission 76 Response 17
Rapaport et al, 2004[56]	4-wk open-label; 6-mo double-blind	119	Citalopram 20–60 mg/d	Risperidone 0.25–2.00 mg/d depending on age	Decrease in MADRS scores from baseline at 4 wk	Remission Combined 61 Citalopram 10 Response Combined 58 Citalopram 9
Shelton et al, 2001[26]	8-wk double-blind with 8-wk open-label extension	34	Fluoxetine 20–60 mg/d	Olanzapine 5–20 mg/d	Overall decrease in MADRS scores from baseline Combined –13.6* Olanzapine –2.8 Fluoxetine –1.2	Remission NR Response Combined 60** Olanzapine 0 Fluoxetine 10
Dube et al, 2002[29]	Meta-analysis; one 8-wk and one 12-wk double-blind parallel-group	797	Fluoxetine; dose NR	Olanzapine; dose NR	Decrease in MADRS scores from baseline Week 1 Combined –7.31*** Olanzapine –5.18 Fluoxetine –5.26 Overall Combined –11.60**** Olanzapine –7.55 Fluoxetine –8.73	Remission Combined 24.9[a] Olanzapine 13.1 Fluoxetine 15.2 Response Combined 37.3[b] Olanzapine 21.1 Fluoxetine NR
Papakostas et al, 2004[30]	6-wk open-label; open-label extension	20	Fluoxetine, citalopram, or paroxetine ≥ 20 mg/d; sertraline ≥ 50 mg/d	Ziprasidone 20–80 mg twice daily	Decrease in HAM-D-17 scores from baseline	Remission 25 Response 50
Simon and Nemeroff, 2005[58]	8-wk open-label	15	Various SSRIs or SNRIs	Aripiprazole 2.5–30 mg	Decrease in HAM-D-17 scores from baseline	Remission 60 (intent-to-treat) 88 (completers)

*p = .03 vs. olanzapine; p = .006 vs. fluoxetine.
**p < .05 vs. olanzapine or fluoxetine.
***p = .013 vs. olanzapine; p = .004 vs. fluoxetine.
****p < .001 vs. olanzapine or fluoxetine.
[a]Reported only as statistically significant in comparison with both olanzapine and fluoxetine; no p values provided.
[b]Reported only as statistically significant in comparison with olanzapine.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, NR = not reported, SNRI = serotonin/norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

nonpsychotic DSM-IV major depressive disorder who had an incomplete response to moderate- to high-dose therapy with an SSRI. They were treated with risperidone (0.5 or 1 mg/day) in addition to paroxetine (10 to 30 mg/day) or fluoxetine (20 to 40 mg/day). Mean HAM-D scores were 20.5 before and 3.7 after initiation of risperidone therapy. Time to response was 1 week or less in all patients, and all patients experienced remission. Improvement was maintained for 3 months or longer in all patients. Improved sexual interest and sleep were reported by some patients. Addition of risperidone to the SSRI was well tolerated, and no extrapyramidal symptoms were noted.

Following this case series, an open-label pilot study[25] of risperidone augmentation of an SSRI was initiated. In this study, the SSRI fluvoxamine was chosen because of its lack of drug-drug interactions with risperidone. Thirty-six outpatients with major depressive disorder were treated with risperidone plus fluvoxamine for 6 weeks; patients older than age 60 years (N = 7) received risperidone 0.5 mg/day and fluvoxamine 100 mg/day, and those aged 60 years or younger (N = 29) received risperidone 1 mg/day and fluvoxamine 150 mg/day. The mean baseline HAM-D score was 28, and 34 of 36 patients had no psychotic features. The primary efficacy measure was a decrease in HAM-D scores at week 6.

Thirty patients completed the study.[25] Remission (defined as 75% or greater reduction in HAM-D scores) was achieved in 23 patients (76%), and response (defined as 50% to 74% reduction in HAM-D scores) was achieved in 5 patients (17%). Two patients (7%) did not respond. Six patients withdrew before the end of the study; of these, 3 achieved remission, 1 responded, and 2 had minimal or no

response at withdrawal. Adverse events were mild, and no extrapyramidal symptoms were identified.

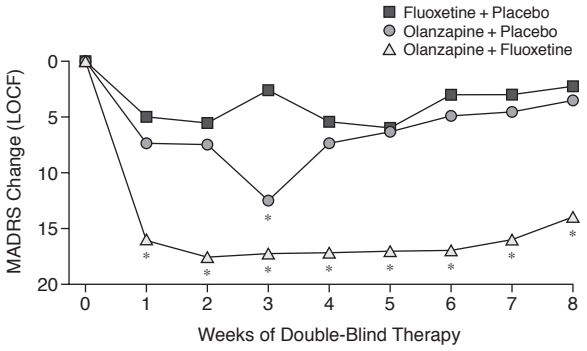
Findings of that study[25] prompted initiation of a trial to evaluate the long-term safety and efficacy of risperidone augmentation of citalopram in patients aged 18 to 85 years with DSM-IV major depressive disorder and a history of nonresponse to at least 1 SSRI.[55,56] An open-label treatment augmentation phase was followed by a double-blind phase to evaluate the efficacy of risperidone augmentation in preventing relapse over a 6-month period. To document nonresponse, patients who were SSRI nonresponders by history were initially treated with citalopram at a target dosage of 40 to 60 mg/day, depending on age, for 4 or 6 weeks; those who had a less than 20% improvement in MADRS score entered the augmentation phase at 4 weeks. During the 4- to 6-week augmentation phase, nonresponders to citalopram received their current citalopram dose augmented with risperidone at a target dose of 0.5 or 1.0 mg/day, depending on age. Patients who achieved remission during the open-label phase were then randomly assigned either to receive citalopram plus placebo or to continue on citalopram plus risperidone for 24 weeks.

Of 502 patients who entered the study,[56] 445 completed the citalopram monotherapy phase; 434 completers (97.5%) were classified as nonresponders (less than 50% decrease in HAM-D score), and 386 entered the augmentation phase. The augmentation phase was completed by 348 patients (90.2%). In each phase, approximately two thirds of patients were women, mean age was 46.5 years, and approximately 2% had psychotic features.

Significant improvement in mean MADRS scores occurred at each time point in both the citalopram monotherapy and risperidone augmentation phases. When the slopes of improvement during each phase were compared using a regression analysis, rate of improvement was significantly greater with risperidone augmentation than citalopram alone. At the risperidone augmentation endpoint, 68.1% of the patients were treatment responders; that is, they exhibited a 50% or greater improvement in depressive symptom severity.

The incidence of adverse events in patients who received risperidone augmentation was similar to that of the patients receiving citalopram monotherapy. Adverse events occurring in 10% or more of patients were headache (19.2%) and nausea (11.0%) in the monotherapy phase, and dry mouth (12.9%) and headache (12.9%) during the augmentation phase. Scores on the Simpson-Angus Scale,[57] Barnes Akathisia Scale, and AIMS were low at baseline and did not change significantly during either treatment. Mean change in body weight during the augmentation phase was +1.4 ± 2.5 kg. Scores on the Global Impressions of Sexual Function decreased significantly in men ($p < .01$) and nonsignificantly in women during the citalopram phase and improved significantly in both men and women ($p < .02$) in the risperidone augmentation phase, suggesting that risperidone may ameliorate the sexual dysfunction associated with citalopram.

Figure 3. Mean Change From Baseline in Montgomery-Asberg Depression Rating Scale (MADRS) Scores for Olanzapine, Fluoxetine, and Olanzapine and Fluoxetine Combined in Patients With Treatment-Resistant Unipolar Depression[a]



[a]Reprinted with permission from Shelton et al.[26]
*$p < .05$ vs. fluoxetine + placebo.
Abbreviation: LOCF = last observation carried forward.

In the second phase of the study,[55] responders were randomized to continued treatment with risperidone and citalopram or placebo and citalopram. Kaplan-Meier analysis revealed that the time to relapse in the patients treated with risperidone and citalopram was significantly longer than that in the placebo and citalopram group in the patients who had a less than 25% response to citalopram alone.[55]

An additional 2-site (Brown University and Emory University), placebo-controlled study of risperidone augmentation of SSRI antidepressants in patients with unipolar depression is nearing completion, with a target accrual of 84 patients.

Among studies of olanzapine augmentation is a double-blind study by Shelton et al.[26] of olanzapine in combination with fluoxetine in patients with nonpsychotic, treatment-resistant unipolar depression who did not respond to treatment with antidepressants of 2 different classes. After a 6-week open-label phase in which patients received fluoxetine (20 to 60 mg/day), nonresponders were randomly assigned to receive olanzapine (5 to 20 mg/day) plus placebo (N = 8), fluoxetine (20 to 60 mg/day) plus placebo (N = 10), or olanzapine (5 to 20 mg/day) plus fluoxetine (20 to 60 mg/day) (N = 10) for 8 weeks. Patients who completed the double-blind phase were eligible to enter an 8-week open-label extension phase of treatment with olanzapine and fluoxetine. Among patients assigned to double-blind therapy, 75% were women, 96% were white, and the mean age was 42 years.

During double-blind treatment, patients in the olanzapine-fluoxetine group had greater improvement from baseline in MADRS scores than did patients in either monotherapy group ($p = .03$ vs. olanzapine; $p = .006$ vs.

fluoxetine) (Figure 3). The response was maintained throughout the 8-week open-label extension period. Improvement in mean HAM-D scores was also significantly greater in the olanzapine-fluoxetine group than in the olanzapine group (–11.7 and –5.9, respectively; p = .03) but did not attain statistical significance versus the fluoxetine group (–3.8; p = .07). The percentages of patients classified as responders, as defined by a 50% or greater improvement in MADRS scores, were 60%, 10%, and 0% in the olanzapine-fluoxetine group, fluoxetine group, and olanzapine group, respectively.[26]

Both drugs were well tolerated. The most frequently reported adverse events in any group were somnolence, increased appetite, asthenia, weight gain, headache, dry mouth, and nervousness; increased appetite and weight gain were significantly more frequent in patients treated with olanzapine than fluoxetine alone.[26]

Limited results from additional studies of olanzapine in combination with fluoxetine compared with monotherapy with either agent in patients with treatment-resistant depression have been published in abstract form. In the largest of these, a meta-analysis was performed of data from one 8-week and one 12-week double-blind study that included 797 patients with nonpsychotic treatment-resistant unipolar depression who had not responded to both an SSRI and a non-SSRI antidepressant.[29] Improvement in MADRS scores was significantly greater at week 1 in patients receiving olanzapine plus fluoxetine (–7.31) than in those receiving monotherapy with either olanzapine (–5.18; p = .013) or fluoxetine (–5.26; p = .004). This difference was maintained throughout 8 weeks of treatment (–11.60, –7.55, –8.73; p < .001 for both between-group comparisons). Remission rates at endpoint were significantly greater in the combined treatment group than in the olanzapine or fluoxetine monotherapy groups (24.9%, 13.1%, and 15.2%, respectively). Endpoint response rates were significantly greater in the combined group than in the olanzapine group (37.3% and 21.1%, respectively) but not in the fluoxetine group.

A recently published open-label study investigated the efficacy of ziprasidone augmentation of SSRIs in 20 patients with nonpsychotic major depressive disorder who had not responded to at least a 6-week trial of an adequate dose of an SSRI.[30] Ziprasidone (20 mg–80 mg twice daily) was added to the SSRI for 6 weeks. Mean patient age was 41.9 years, and 35% of patients were women.

Thirteen patients (65%) completed the study. Four patients (20%) discontinued because of intolerance of study medication. On intent-to-treat analysis, 10 patients (50%) were classified as responders as defined by a 50% or greater decrease from baseline in the 17-item HAM-D (HAM-D-17) score at 6 weeks, and 5 (25%) achieved remission, defined as a HAM-D-17 score of 7 or less. Of the 6 responders who remained on the same therapy and were followed up for a mean of 15.3 weeks, 2 additional patients achieved remission and 1 relapsed; the remaining patients maintained their previous response or remission status. The most common adverse events were fatigue in 10 patients (50%), sleep disturbance in 6 (30%), and restlessness, tremor, and bruxism in 3 (15%) each.

Finally, 15 patients nonresponsive to SSRIs or serotonin/norepinephrine reuptake inhibitors were treated with aripiprazole in an open-label study.[58] Although higher doses (15 to 30 mg) of aripiprazole were associated with high rates of akathisia, lower doses (2.5 to 5 mg) were associated with a high rate of conversion of SSRI nonresponders to responders.

To date, there are no published data on the use of quetiapine or clozapine as augmentation therapy in the management of bipolar depression or treatment-resistant unipolar depression.

EFFICACY OF ATYPICAL ANTIPSYCHOTICS IN OBSESSIVE-COMPULSIVE DISORDER AND GENERALIZED ANXIETY DISORDER

A relatively limited database from clinical trials suggests that atypical antipsychotics are effective augmenting agents in patients with refractory OCD.[59,60] In one open-label trial,[61] 23 patients with OCD resistant to a 6-month trial of fluvoxamine 300 mg/day received augmentation with olanzapine 5 mg/day for an additional 3 months. Mean scores on the Yale-Brown Obsessive Compulsive Scale (YBOCS)[62] decreased significantly (–8.0; p < .0005), and 10 patients (43.5%) were classified as responders at endpoint. In a subsequent study,[60] 10 patients with OCD unresponsive to ≥ 60 mg/day of fluoxetine for 12 weeks or longer received olanzapine augmentation (maximal dosage, 10 mg/day) for 8 weeks; patients had previously not responded to a mean of 3.3 antidepressant drug treatment trials. The YBOCS scores improved 68%, 30%, and 29%, respectively, in 3 of the 9 completers, and 1 patient was rated as "much improved" on the CGI-Improvement scale.

In a randomized, double-blind, placebo-controlled study, McDougle et al.[59] assessed risperidone augmentation in 36 patients with OCD resistant to an initial 12-week SSRI trial. Mean total YBOCS scores decreased 31.8% (from 27.4 to 18.7; p < .001) in the risperidone augmentation group (N = 20) at 6 weeks; no significant change in scores occurred in the placebo group (N = 16). Of 18 completers in the risperidone group, 9 (50%) were classified as responders compared with none of the 15 completers in the placebo group. Hamilton Rating Scale for Anxiety scores also decreased significantly in the risperidone group (p = .007). Augmentation with risperidone was generally well tolerated.

Atypical antipsychotics may also be useful as augmentation therapy in patients with treatment-resistant generalized anxiety disorder. In a 6-week, randomized, double-

blind, placebo-controlled study,[63] 40 nondepressed patients with HAM-A scores of 18 or more at baseline who had not responded to an antianxiety agent were given risperidone 0.5 to 1.5 mg/day in addition to an anxiolytic drug. Compared with patients in the placebo group, those in the risperidone augmentation group had significantly greater decreases in HAM-A total scores (–9.8 vs. –6.2; p = .034) and HAM-A psychic anxiety factor scores (–6.3 vs. –3.8; p = .047).

DISCUSSION AND CONCLUSIONS

Although the entire database is relatively small, it is rapidly expanding, and results of available studies provide preliminary evidence that atypical antipsychotics appear to be a useful addition to the treatment options available for patients with difficult-to-treat unipolar or bipolar depression and patients with OCD or generalized anxiety disorder. In particular, results of open-label trials of risperidone augmentation in patients with treatment-resistant unipolar depression demonstrated remission rates of 60% to 76%[25,56]; a large double-blind trial is under way to confirm these findings. A large trial of olanzapine augmentation of fluoxetine in treatment-resistant unipolar depression reported remission rates of 25% for combination therapy compared with 15% for fluoxetine alone.[29] Although the decreases in MADRS scores at week 1 and overall appeared to be superior with a combination of olanzapine and fluoxetine when compared with either fluoxetine or olanzapine alone, endpoint values have not yet been reported. The utility of olanzapine in this clinical setting remains unclear but promising, and publication of the results of this trial is likely to clarify this issue. Data supporting the use of ziprasidone and aripiprazole in depression are limited, but the 2 published studies,[30,58] 1 with each agent, showed encouraging results.

In patients with bipolar depression, there is increasing evidence for efficacy of both atypical antipsychotic drug monotherapy[54] and combination atypical antipsychotic-SSRI augmentation strategies.[28] The efficacy and safety of olanzapine in combination with fluoxetine are supported by a large double-blind trial with remission and response rates of approximately 50% and 56%, respectively; no comparison was made with fluoxetine alone in this study.[28] Of note is the absence of treatment-emergent mania, with no differences from placebo in mean YMRS scores.[28] Several case reports have been published concerning the apparent induction of mania or hypomania associated with olanzapine or risperidone, but post hoc analyses of placebo-controlled olanzapine and risperidone trials in acute mania found no evidence that either drug worsens manic symptoms.[64] Although preliminary studies do not suggest that induction of mania or rapid cycling is a concern when combining an atypical antipsychotic with an antidepressant, further studies of combination therapy will be necessary to adequately evaluate this possibility.

In the studies reviewed here, the principal and, in many cases, the only evaluation of efficacy was change in depressive symptoms severity as measured by depression rating scales. Indeed, most clinical trials in depression do not include instruments that measure quality of life and other dimensions, including social and occupational functioning.[65] Pain, another dimension rarely evaluated in depression therapy trials, is a common component of major depressive disorder.[66] Evaluation of such dimensions can provide broader, more real-world assessment of the total burden of illness than can depression rating scales alone, and future studies to evaluate treatments for refractory depression may benefit by using assessment tools that measure these aspects of the illness.

In conclusion, considerable preliminary evidence suggests that atypical antipsychotics may be a safe and effective therapeutic option for patients with difficult-to-treat bipolar or unipolar depression. Further clinical trials are certainly warranted.

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin and others), carbamazepine (Carbatrol, Equetro, and others), citalopram (Celexa and others), clozapine (Clozaril, FazaClo, and others), fluoxetine (Prozac and others), lamotrigine (Lamictal), lithium (Lithobid, Eskalith, and others), olanzapine (Zyprexa), olanzapine-fluoxetine (Symbyax), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, aripiprazole, lithium, olanzapine, risperidone, and ziprasidone are not approved by the U.S. Food and Drug Administration for the augmentation of antidepressant therapy, and bupropion is not approved for use in combination with selective serotonin reuptake inhibitors.

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