Evidence for Using Atypical Antipsychotics in Mood and Anxiety Disorders

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At present, there are more small, open-label trials than large, double-blind, placebo-controlled studies of atypical antipsychotics in the treatment of nonpsychotic psychiatric illnesses. Existing evidence indicates both the safety and the efficacy of relatively low doses of the dopaminergic/serotonergic atypical antipsychotics as adjunctive, or augmentation, therapy for patients with nonpsychotic mood and anxiety disorders. In psychiatric practice, atypical antipsychotics are widely used to enhance the action of antidepressants or mood stabilizers in the management of many illnesses, including psychotic and nonpsychotic major depression, bipolar disorder (especially mania), posttraumatic stress disorder, and obsessive-compulsive disorder. Such use of atypical antipsychotics in the primary care setting remains a relatively new concept. Several studies indicate that atypical antipsychotics such as risperidone and olanzapine can improve clinical outcome when used to augment antidepressants or mood stabilizers. *(Primary Care Companion J Clin Psychiatry 2003;5[suppl 3]:27–32)*

Antipsychotics have historically been used to treat patients with schizophrenia, but their efficacy is not limited to psychotic disorders. Antipsychotics, particularly as adjunctive therapy, also are useful in treating patients with mood and anxiety disorders. The frequent and serious side effects of the older, conventional antipsychotics include weight gain and both reversible and chronic drug-induced movement disorders, which discourage their use. Individuals with primary mood disorders, such as bipolar disorder, are thought to be particularly vulnerable to the development of tardive dyskinesia resulting from antipsychotic treatment.[1] In fact, rates of tardive dyskinesia may be twice as high among mood disorder patients as among schizophrenic patients treated with conventional antipsychotics. The newer, atypical antipsychotics present a more benign side effect profile and thus a more favorable risk:benefit ratio; however, significant weight gain is a relatively frequent side effect of the atypical antipsychotics.[2–5] At present, there are more small, open-label trials than large, double-blind, placebo-controlled studies of atypical antipsychotics in the treatment of nonpsychotic psychiatric illnesses. But in clinical psychiatry practice, atypical antipsychotics at relatively low doses are widely used to augment antidepressants or mood stabilizers in the management of severe or resistant mood and anxiety disorders.

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EVIDENCE FOR THE USE OF ATYPICAL ANTIPSYCHOTICS

Major Depression

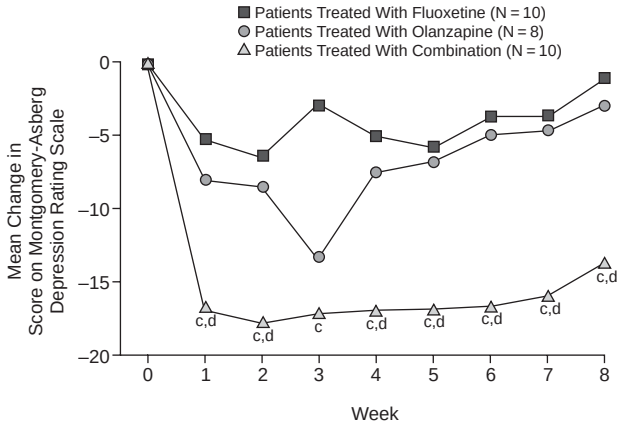
Psychotic depression (including depression with delusions of guilt) is rarely responsive to antidepressants alone; symptom resolution may require augmentation of the antidepressant with an antipsychotic. Augmentation describes the addition of a second drug to the initial drug in order to enhance the action of the initial drug. Some augmenting agents may have intrinsic effects as well. Importantly, augmentation with antipsychotics also has proved effective against resistant or refractory depression without psychotic features. At low doses, the atypical antipsychotic risperidone antagonizes excitatory serotonergic ($5\text{-}HT_2$) receptors and thus may enhance the inhibitory effects of serotonin and augment the action of selective serotonin reuptake inhibitors (SSRIs). Ostroff and Nelson[5] observed a small sample of 8 patients with nonpsychotic, treatment-resistant depression who were candidates for electroconvulsive therapy by virtue of their unresponsiveness to pharmacotherapy. The addition of risperidone to the patients' ongoing SSRI treatment vastly improved outcome, resulting in reduced scores on the Hamilton Rating Scale for Depression (HAM-D) and remission of symptoms within 1 week or less (Table 1).

Table 1. Risperidone + SSRI for Resistant Depression: Patient Characteristics and Time to Response[a]

Patient No.	Age (y)	Sex	SSRI Trial	Risperidone Dose	HAM-D Pre-Risperidone	HAM-D Post-Risperidone[b]	Time to Response
1	46	M	Fluoxetine 20 mg for 6 wk	0.5 mg hs for 1 day, increased to 1 mg[c]	19	0	1 d
2	53	M	Fluoxetine 20 mg for 2 mo	0.5 mg	17	2	2 d
3	75	M	Paroxetine 20–30 mg for 8 wk	0.5 mg for 1 day, increased to 1 mg	27	...[d]	1 wk
4	50	M	Fluoxetine 20–40 mg for 8 wk	0.5 mg hs	21	3	4 d
5	49	F	Fluoxetine 20 mg for 4 mo	0.5 mg hs	18	6	1 wk
6	36	M	Paroxetine 20 mg for 2 wk	1.0 mg hs	20	4	1 wk
7	64	F	Paroxetine 10 mg for 2.5 wk	0.5 mg bid	26	4	2 d
8	52	F	Fluoxetine 20 mg for 12 wk	0.5 mg hs	16	0	2 d

[a]Adapted with permission from Ostroff and Nelson.[5]
[b]HAM-D performed at first follow-up visit; time to response based on patient's report of when the major change occurred.
[c]Dose increased by the patient because of apparent benefit.
[d]No return visit and no HAM-D score obtained; patient and referring psychiatrist noted complete remission.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, SSRI = selective serotonin reuptake inhibitor.

Figure 1. Weekly Change From Baseline in Response Rate for Depressed Patients Treated With Fluoxetine, Olanzapine, or a Combination of Both[a,b]



[a]Reprinted with permission from Shelton et al.[3]
[b]Combination superior to fluoxetine or olanzapine ($p < .05$).
[c]Significantly superior to fluoxetine ($p < .05$).
[d]Significantly superior to olanzapine ($p < .05$).

Hirose and Ashby[6] found that the combination of risperidone and fluvoxamine from the start of treatment for major depressive disorder enhances therapeutic response. In their study, 36 patients received up to 150 mg/day of the SSRI fluvoxamine plus up to 1 mg/day of risperidone for 6 weeks. Of the 30 patients who completed the trial, 23 achieved remission of symptoms, 5 achieved response (as defined by a 50%–74% reduction in baseline HAM-D score), and 2 failed to achieve response. Remission and response were prompt, and rate of remission was substantially higher than is usually achieved in brief trials of an SSRI alone. The combination was well-tolerated; however, it remained to be determined whether risperidone in combination with an SSRI should be continued as maintenance therapy or discontinued after remission is achieved.

In the first placebo-controlled, double-blind trial[3] of an atypical antipsychotic for nonpsychotic resistant depression, the atypical antipsychotic olanzapine plus the SSRI fluoxetine was compared with olanzapine alone and fluoxetine alone. The patients taking olanzapine plus fluoxetine achieved greater improvement from baseline on the Montgomery-Asberg Depression Rating Scale (MADRS) than patients taking either monotherapy (Figure 1). Scores on the HAM-D and the Clinical Global Impressions-Improvement (CGI-I) scale were better among patients taking the combination than among patients taking olanzapine alone. However, HAM-D and CGI-I scores among patients taking olanzapine plus fluoxetine were not significantly better than among patients taking fluoxetine alone. Clinical responses to the combination therapy became evident by the first week, indicating rapid onset of action. In an open-label extension of this study, olanzapine plus fluoxetine was administered to completing patients. Patients who had taken olanzapine plus fluoxetine in the double-blind phase maintained their response in the open-label extension, but patients who had taken either monotherapy in the first phase did not improve significantly during the second phase. The researchers concluded that a synergistic antidepressant effect occurred neurochemically with the combination of olanzapine plus fluoxetine and that this synergy showed promise in the treatment of patients with nonpsychotic, treatment-resistant depression. Further research is needed to determine whether combinations of other atypical antipsychotics with other SSRIs are similarly effective.

Bipolar Disorder

Bipolar disorder is characterized by alternating periods of mania, depression, and relative mood stability. The disparate nature—the polarity—of the bipolar phases complicates management of this disorder. For example, a pharmacotherapy for bipolar depression is unsatisfactory if it provokes a switch into mania. Appropriate drug therapy

for bipolar disorder does not increase the rate of switching between depression and mania (called "cycling"). Typically, bipolar disorder has been treated with mood stabilizers, including lithium and the anticonvulsant divalproex, often in combination with antidepressant drugs like SSRIs. Antipsychotics too have shown acute and prophylactic efficacy in treating bipolar disorder, particularly in combination therapy when a mood stabilizer was suboptimally effective.

Mania manifests as irritability, agitation, impulsiveness, aggression, and sometimes psychosis. To date, there has been more research directed at the role of atypical antipsychotics in the treatment of mania than of bipolar depression, and evidence suggests that antipsychotics have antimanic qualities apart from their efficacy in controlling psychosis. In fact, olanzapine is approved by the U.S. Food and Drug Administration (FDA) for the treatment of mania.

A double-blind, placebo-controlled study[4] tested olanzapine in 139 patients with acute mania, half of whom showed psychotic symptoms. In this study, the atypical antipsychotic did not augment a mood stabilizer but instead was administered as monotherapy. Subjects were allowed to adjust their dosage within the allowed range of 5 to 20 mg/day. Half the patients receiving placebo and 25% of the patients receiving olanzapine discontinued due to inefficacy before the end of the trial. Compared with placebo, olanzapine was associated with significantly greater improvement on the Young Mania Rating Scale (YMRS), the CGI-Severity (CGI-S) scale for bipolar mania, and the total and positive scores of the Positive and Negative Syndrome Scale (PANSS). There was no significant difference between olanzapine and placebo on the HAM-D, implying that the antimanic effect of olanzapine did not initiate or exacerbate depression in the bipolar subjects.

In a double-blind study[7] lasting 3 weeks, 262 manic patients were randomly assigned to receive either placebo or risperidone monotherapy at a flexible, once-daily dose of 1 to 6 mg (mean dose, 4.1 ± 0.1 mg/day). Patients with and without psychotic features who received risperidone showed significantly greater improvements in YMRS total score than patients receiving placebo, suggesting to researchers that the antimanic effect of risperidone is independent of its antipsychotic effects. Symptom improvement was noted at day 3 and was sustained for the duration of the study with only minimal change in MADRS scores.

Antipsychotics have also been compared to and tested in combination with mood stabilizers for the treatment of bipolar disorder. In a 4-week, double-blind study[8] of 45 manic patients with and without psychotic symptoms, the atypical antipsychotic risperidone, the conventional antipsychotic haloperidol, and the mood stabilizer lithium were found to have equivalent antimanic efficacy. Sachs et al.[9] conducted a 3-week comparison of risperidone with haloperidol in a double-blind, placebo-controlled study of 156 patients. All patients were experiencing a manic episode, and all were being treated concomitantly with a mood stabilizer (lithium or divalproex). Over the course of the trial, 35% of the patients receiving adjunctive risperidone, 49% of the patients receiving placebo, and 53% of the patients receiving adjunctive haloperidol discontinued, leaving 80 subjects in the data. Adverse events were reported least frequently among patients receiving adjunctive risperidone, but weight gain among these patients was significantly greater than weight gain among patients receiving placebo or haloperidol. The occurrence of extrapyramidal symptoms did not differ significantly between risperidone and placebo but was significantly more frequent with haloperidol. According to the YMRS, there was greater improvement among patients taking risperidone or haloperidol plus a mood stabilizer than among patients taking placebo plus a mood stabilizer, regardless of which mood stabilizer was involved. On the CGI-S, an endpoint rating of "very much improved" was reported by 25% of patients receiving adjunctive risperidone, 16% of patients receiving adjunctive haloperidol, and no patients receiving placebo. The clinical significance of the superiority by some measures of risperidone over haloperidol is enhanced by the fact that risperidone is an atypical antipsychotic with a relatively mild side effect profile (although weight gain was significantly greater among patients receiving risperidone).

A similar but open-label prospective study[10] examined the atypical antipsychotic quetiapine alone and in combination with a mood stabilizer. All 20 subjects were diagnosed with either bipolar disorder or schizoaffective disorder. All had been taking conventional antipsychotics for 6 months or more and were unable to discontinue them without clinical worsening; 13 of 20 subjects were also taking a mood stabilizer. Quetiapine was started at 25 mg b.i.d. and could be increased as tolerated to a maximum of 800 mg/day. Following initiation of quetiapine, the previous, conventional antipsychotic therapy was tapered and removed. The switch to quetiapine resulted in significantly improved scores on the Brief Psychiatric Rating Scale (particularly in regard to conceptual disorganization and suspiciousness), the YMRS, and the HAM-D, suggesting that an atypical antipsychotic can have efficacy for symptoms of both bipolar mania and bipolar depression.

Posttraumatic Stress Disorder

Individuals with the anxiety, avoidance, physiologic arousal, and cognitive disturbance of posttraumatic stress disorder (PTSD) are likely to present to primary care physicians early in the course of their illness, when they are most treatable. Although combat veterans make up a large number of those with PTSD, sufferers also include the victims of more commonplace traumas, like discovery of a dead loved one or catastrophic loss of a late-term pregnancy. Traumatic events are not uncommon; about half the

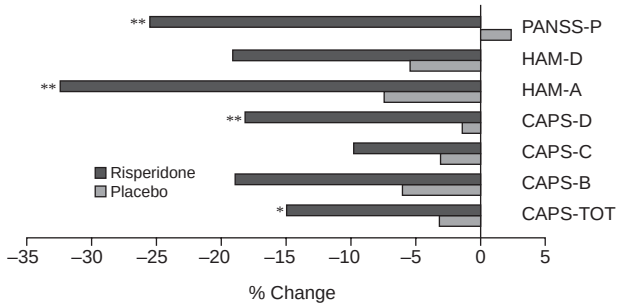
population of the United States will at some point be exposed to an event such as a man-made or natural disaster, rape, assault, or serious accident.[11] Nonetheless, combat veterans are particularly at risk for chronic PTSD that is unresponsive to SSRI treatment and worsened by psychotic symptoms such as hallucinations. Although pharmacology is not and should not be the only treatment for patients with PTSD, early treatment with appropriate medication can empower patients to engage in the psychosocial treatment they require.

In primary care settings, pharmacotherapy for PTSD relies upon serotonergic antidepressants as the preferred initial medication. The frequent presence, however, of intrusive, psychotic-like symptoms in PTSD suggests the usefulness of an antipsychotic agent with serotonergic properties in patients who do not respond promptly to an SSRI alone. Likewise, the antidepressant and anxiolytic properties of atypical antipsychotics may offer efficacy in the avoidant/depressive and hyperaroused/anxious symptom clusters in PTSD.[12] Petty et al.[12] conducted an uncontrolled, open, 8-week trial of olanzapine as monotherapy for PTSD. Olanzapine was started at 5 mg/day and increased, as necessary, up to 20 mg/day, stabilizing at week 4. Thirty subjects completed the trial; among the 16 noncompleters, almost half experienced intolerable side effects. Primary efficacy measures were the Clinician Administered PTSD Scale (CAPS) and the CGI-I. With olanzapine treatment, total CAPS scores decreased by approximately 30%: intrusive symptoms decreased by 31%, avoidant symptoms decreased by 31%, and hyperaroused symptoms decreased by 28%.

In a study by Bartzokis et al.,[13] 73 combat veterans with PTSD were recruited from a psychosocial treatment program and randomly assigned to receive risperidone or placebo. In most cases, risperidone was added to an existing drug regimen (usually consisting of antidepressants); in other cases, the subject was free of psychotropic medications at study start. Risperidone treatment was initiated at 1 mg/day, increased to 3 mg/day over a 2-week period, and then maintained at 3 mg/day for the remainder of the 16-week trial. Seventy percent of the patients completed the study through follow-up. Outcome measures included the CAPS, the Hamilton Rating Scale for Anxiety, the HAM-D, and the PANSS-positive subscale. Adjunctive risperidone was superior to placebo on all outcome measures and was significantly superior on 4 of them (Figure 2). The researchers concluded that risperidone improved the psychiatric symptoms of PTSD even when overt psychosis was absent.

Anger regulation deficits and explosiveness are particularly common among combat veterans with PTSD. In a study[14] exploring the effects of adjunctive risperidone on irritable aggression coinciding with PTSD, 15 veterans received up to 2 mg/day of risperidone or placebo in addition to their current psychotropic regimen for 6 weeks.

Figure 2. Percentage Change in PTSD Symptom Scores From Baseline to Endpoint[a]



[a]Reprinted with permission from Bartzokis et al.[13]
*p < .05, **p < .01 vs. placebo.
Abbreviations: CAPS-B = Clinician Administered PTSD Scale, Reexperiencing Symptoms; CAPS-C = Clinician Administered PTSD Scale, Avoidance Symptoms; CAPS-D = Clinician Administered PTSD Scale, Arousal Symptoms; CAPS-TOT = Clinician Administered PTSD Scale, Total; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; PANSS-P = Positive and Negative Syndrome Scale, Positive Symptoms; PTSD = posttraumatic stress disorder.

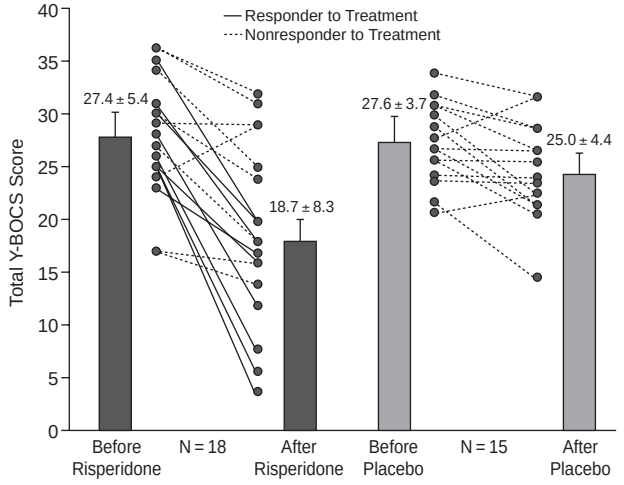
They were evaluated using the PTSD Checklist Military Version and the Overt Aggression Scale-Modified for Outpatients (OAS-M). Adjunctive risperidone was well tolerated and significantly reduced irritability and intrusive thoughts compared with placebo. Aggression as measured by the OAS-M decreased significantly from baseline scores in the group receiving risperidone, but when compared with the placebo group the change in aggression did not reach statistical significance. Avoidance and hyperarousal also decreased, though not significantly compared with placebo, among patients receiving risperidone.

Current data suggest that atypical antipsychotics are effective as augmentation therapy—and possibly as monotherapy—for patients with combat-induced PTSD. However, combat-induced PTSD is especially refractory and frequently accompanied by psychotic symptoms, aggression, and paranoid personality traits.[13] The question remains whether results related to combat-induced PTSD can be extrapolated to a civilian population.

Obsessive-Compulsive Disorder

Like PTSD, obsessive-compulsive disorder (OCD) is categorized as an anxiety disorder. The obsessive thinking that defines OCD is experienced by the sufferer as intrusive, and the distress and anxiety involved in obsessive thinking necessitate the individual's compulsive performance of ritualized countermeasures. First-line therapy for OCD relies on SSRIs or clomipramine (a tricyclic antidepressant), but 40% to 60% of patients with OCD are not clinically responsive to adequate treatment with these drugs.[15] Thus, atypical antipsychotics have been widely used as augmentation therapy in the treatment of refrac-

Figure 3. Change in Y-BOCS Scores Among Patients With Refractory OCD After Adding Risperidone or Placebo to SSRI for 6 Weeks[a]



[a]Adapted with permission from McDougle et al.[20]
Abbreviations: OCD = obsessive compulsive disorder, SSRI = selective serotonin reuptake inhibitor, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

tory OCD, though large-scale, double-blind, placebo-controlled studies remain few.

In a small, open-label study,[16] 9 nonresponding patients augmented their current SSRI or clomipramine treatment with up to 5 mg/day of olanzapine. Three patients showed marked improvement and 3 showed mild-to-moderate improvement in response to the augmentation. However, other research has found that olanzapine,[17] risperidone,[18] or clozapine[19] administered singly lack efficacy in treating OCD or actually worsen obsessive-compulsive symptoms.

In an open, prospective study[2] of risperidone in the treatment of refractory OCD, patients were titrated to a dose of 6 mg/day of risperidone in addition to the existing regimen of sertraline or clomipramine. All patients reported dramatic improvement, which was reflected by marked improvement in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores. A double-blind study by McDougle et al.[20] compared low-dose risperidone with placebo as adjunctive therapy for patients whose symptoms of OCD did not respond to treatment with SSRI monotherapy. Fifty percent of patients who added risperidone to their SSRI regimen achieved treatment response, which was defined as ≥ 35% improvement on the Y-BOCS from addition of risperidone, a final CGI rating of "much improved" or "very much improved," and clinician consensus that the patient's symptoms were improved (Figure 3).

Interestingly, between 20% and 30% of individuals with OCD have current or past tics, and comorbidity with Tourette's disorder is high.[21] Patients with Tourette's disorder generally respond to conventional antipsychotics, but adverse effects limit their use. Of note is research that found both risperidone[22] and olanzapine[23] to suppress, with few side effects, the motor and vocal tics caused by Tourette's disorder. In addition to tics, risperidone reduced the depressive, anxious, and obsessive-compulsive symptoms associated with Tourette's.[22]

CONCLUSION

In-depth discussion of the use of atypical antipsychotics in treating mood and anxiety disorders is indeed constrained by the lack of large-scale, placebo-controlled, double-blind studies. More data are needed. Nonetheless, existing evidence strongly suggests both the safety and the efficacy of dopaminergic/serotonergic atypical antipsychotics as augmentation therapy for psychotic and nonpsychotic major depression, bipolar disorder (especially mania), combat-induced PTSD, and OCD. When considering antipsychotics, the clinician must remember that a dose that would be subtherapeutic for a patient with schizophrenia can be an ample dose for a patient with a mood or anxiety disorder.

Drug names: clomipramine (Anafranil and others), clozapine (Clozaril and others), divalproex (Depakote), fluoxetine (Prozac and others), haloperidol (Haldol and others), olanzapine (Zyprexa), paroxetine (Paxil), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, clozapine, olanzapine, and quetiapine are not approved by the U.S. Food and Drug Administration for the treatment of depression and anxiety disorders; clomipramine, divalproex, haloperidol, and sertraline are not approved for the treatment of anxiety disorders; and lithium is not approved for the treatment of depression.

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