Risperidone: Review of Its Therapeutic Utility in Depression

By Joyce E. Myers, MD, and Michael E. Thase, MD

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**ABSTRACT** – There is extensive evidence to implicate dysregulation of noradrenergic, serotonergic, and dopaminergic neurotransmission in the pathophysiology of mood disorders. The receptor profile for risperidone, an atypical antipsychotic with demonstrated efficacy in schizophrenia, is consistent with possible antidepressant activity. Specifically, risperidone is a potent antagonist of central 5-HT$_{2A}$ receptors, addressing symptoms such as insomnia, agitation, and weight loss and may indirectly enhance 5-HT$_{1A}$-mediated neurotransmission. A search of the worldwide medical literature published through December 2000 revealed 24 publications pertinent to the clinical use of risperidone in the treatment of patients with depressive symptomatology. In schizophrenia, in which depression is a common comorbid condition, the results of eight randomized, blinded, and controlled trials consistently demonstrated that treatment with risperidone significantly reduced scores on various measures of depressive symptoms. Moreover, these effects were distinct from improvements in negative and positive symptoms. Antidepressant effects also were observed in two large meta-analyses of trials in patients with schizophrenia or schizoaffective disorder. Observations from uncontrolled studies and case reports of risperidone therapy of other psychiatric disorders were similarly suggestive of antidepressant activity. Collectively, the evidence we present in this review indicates that risperidone's therapeutic benefits in psychiatric medicine extend beyond potent and effective antipsychotic activity and may include effectiveness in treating depression and related affective disorders. Systematic studies are now needed to evaluate the utility of concomitant therapy with an atypical antipsychotic in psychotic, bipolar, and treatment-resistant depressive syndromes. Psychopharmacology Bulletin. 2001;35(4):109-129

**KEY WORDS**: antidepressant, atypical antipsychotic, depression, risperidone, schizophrenia

**INTRODUCTION**

Risperidone was among the first of the class of atypical antipsychotics to demonstrate therapeutic advantages over conventional neuroleptics. These advantages include a broader spectrum of efficacy for both the positive and negative symptoms of schizophrenia,$^{1,2}$ as well as a lower propensity to cause extrapyramidal symptoms.$^{3,4}$ Like other atypical antipsychotics, the therapeutic benefits of risperidone...
for treating schizophrenia are thought to be the result of simultaneous modulation of effects on serotonergic, dopaminergic, and noradrenergic neurotransmission. Despite broad similarities, however, each member of this class is distinguished by a unique profile of potencies across monoamine systems. Thus, the effects of each novel antipsychotic on the neurotransmitter systems implicated in depression must be evaluated in the treatment of mood disorders having a depressive component.

In this article, we critically analyze the available evidence pertaining to the potential antidepressant effects of risperidone. In addition to summarizing the relevant basic pharmacologic data, we review the results of controlled trials, open studies, and anecdotal reports of risperidone treatment of depressive mood disorders. These reports encompass patients having a wide range of mental disorders, including schizophrenia, schizoaffective disorder, major depression, bipolar disorder, and obsessive-compulsive disorder (OCD). Overall, the evidence collected to date indicates that risperidone has antidepressant effects and suggests that more systematic studies of this compound are needed in the forms of depression most likely to benefit from concomitant treatment with an atypical antipsychotic agent.

**Basic Pharmacologic Profile of Risperidone**

Multiple lines of evidence indicate that dysregulation of noradrenergic and serotonergic corticolimbic neurotransmitter systems are crucial components of the pathophysiology of depression. As reviewed by Ressler and Nemeroff, the involvement of these two monoaminergic systems in depression is likely related to their role in modulating, or being modulated by, other neurobiologic systems that mediate the symptoms of mood disorders. The bulk of the amassed experimental data indicates that depression is associated with decreased serotonergic and overactive noradrenergic function (ie, abnormalities that include abnormal noradrenergic turnover and increased receptor sensitivity). Enhanced serotonin (5-HT) neurotransmission and decreased noradrenergic receptor sensitivity are reproducible findings following long-term administration of various antidepressant medications. Such changes at the synapse may, in turn, be linked to an intracellular cascade that alters second-messenger, neurokinin, and gene activity.

Risperidone produces changes in serotonergic and noradrenergic neurotransmitter systems that are similar to the effects of medications with documented antidepressant effects. In vitro and in vivo receptor-binding studies in brain tissue have shown that risperidone has a high affinity for 5-HT$_{2A}$ and, to a lesser extent, for D$_2$ receptors. At doses resulting in 70% to 90% occupancy of the 5-HT$_{2A}$ receptor, risperidone
enhanced 5-HT concentrations and metabolism (as reflected by levels of 5-HIAA) in the rat frontal cortex. Risperidone also inhibited, in a dose-dependent manner, the spontaneous firing rate of 5-HT neurons in the dorsal raphe nucleus of rats. Subsequent investigations showed that the reduction in 5-HT cell firing by risperidone was associated with an increased availability of 5-HT in the somatodendritic region of neurons that, in turn, led to enhanced 5-HT$_{1A}$ autoreceptor activation and, hence, inhibition of cell firing.

Further studies of the influence of risperidone on central 5-HT systems indicate that the effects on cortical 5-HT neurotransmission are likely related to its ability to act as an antagonist at $\alpha_2$-adrenergic receptors located in the nerve terminal area. The relative ED$_{50}$ values of risperidone for occupying 5-HT$_{2A}$, D$_2$, and $\alpha_2$ receptors following subcutaneous dosing in rats were 0.062, 1.2, and 3.7 mg/kg, respectively. Of possible relevance to its antidepressant potential, chronic administration of risperidone in rats was associated with a sustained increase in neuronal activity of the locus coeruleus accompanied by a significant decrease in norepinephrine levels in the prefrontal cortex.

Other drugs that have potent antagonist effects on 5-HT$_{2A}$ receptors have been shown to be effective antidepressants, which lends further support to the likelihood that risperidone may have antidepressant activity. Nefazodone is a potent 5-HT$_{2A}$ antagonist that also has weak and transient effects as a 5-HT reuptake inhibitor. Like risperidone, nefazodone also enhances 5-HT$_{1A}$-mediated neurotransmission, which is believed to be the primary mechanism underlying its antidepressant efficacy.

Mirtazapine is another newer antidepressant that acts as an antagonist of central 5-HT$_2$ receptors, as well as of $\alpha_2$-adrenergic receptors. Mirtazapine is also a potent blocker of histamine (H$_1$) and 5-HT$_3$ receptors. Antihistaminic effects are unlikely to contribute to antidepressant effects but do significantly influence the tolerability profile of mirtazapine.

In summary, while the pathophysiology underlying depression is complex, there is ample evidence implicating underactivation of serotonergic transmission and overactivation of noradrenergic transmission. Risperidone acts as a potent antagonist of central 5-HT$_{2A}$ and $\alpha_2$-adrenergic receptors. By virtue of its receptor-binding capacity, administration of risperidone may enhance central 5-HT activation and attenuate stress-mediated effects on noradrenergic transmission in a manner similar to that of several antidepressants.

**Clinical Studies**

We searched the worldwide medical literature published through December 2000 using MEDLINE and PUBMED for publications on
the clinical use of risperidone to treat patients with depressive symptoms. Search terms were depression, schizophrenia, schizoaffective disorder, bipolar disorder, mood disorder, affective disorder, and dysthymia. Articles were screened for their relevance to this review and were selected for inclusion if they contained information about the clinical course of depression or depressive symptoms following administration of risperidone. Publications involving schizophrenia or schizoaffective disorder were included only if they contained information on depressive symptoms (eg, if the article presented data on specific outcome measures). Several publications concerning the use of risperidone in bipolar disorders were not included because they were limited to patients with mania. Review articles that failed to present new data were also excluded (ie, Azorin16). A total of 20 publications were selected: 8 controlled investigations, 4 uncontrolled studies, and 8 anecdotal case reports.

Evidence suggestive of antidepressant activity for risperidone is derived primarily from studies involving patients with schizophrenia or schizoaffective disorder. There have been a few small evaluations of risperidone in patients with primary non-affective psychiatric diagnoses other than psychoses (eg, pervasive developmental disorder and OCD). To date, no prospective, controlled investigation of risperidone in patients with major depressive disorder (MDD) has been published, although the results of an open study of risperidone monotherapy that included patients with major depression have been reported, as have anecdotal records of the use of risperidone in combination with selective serotonin reuptake inhibitors (SSRIs) for treating major depression.

Risperidone in Treatment of Depressive Symptoms Associated With Schizophrenia

Many patients with schizophrenia experience depressive symptoms. Among published studies, the modal rate of syndromal or clinically significant depression among schizophrenic patients was reported to be 25%, with rates as high as 75% noted.17 In a study of mid- to late-life patients with schizophrenia, which systematically excluded those with schizoaffective disorder or comorbid major depressive episodes, 13% scored 17 or more on the 17-item Hamilton depression scale (HAM-D),18 which is generally reflective of at least moderate depression. While several factors underpinning the high rate of depression in schizophrenia have been proposed—including a demoralization syndrome, negative symptoms, and consequences of organic factors, substance abuse, and/or neuroleptic treatment—the weight of the available evidence supports the conclusion that depressive symptoms
are a common manifestation of the disease. Moreover, depressive symptomatology in schizophrenia has been linked to poor clinical outcome\textsuperscript{20,21}; diminished quality of life\textsuperscript{22}; and higher rates of relapse, rehospitalization, and suicide.\textsuperscript{23-25}

**Individual Controlled Investigations**

The results of eight randomized, double-blind, and controlled trials of risperidone in patients with schizophrenia or schizoaffective disorders are summarized in Table 1.\textsuperscript{26-33} This table presents key features and results of these trials. One of these trials\textsuperscript{33} enrolled a mixed study group, including some patients with depression associated with psychotic features; this study is discussed separately later. In the remaining seven trials, study populations consisted primarily of adults with confirmed diagnoses of chronic schizophrenia (eg, *Diagnostic and Statistical Manual of Mental Disorders, Third Edition–Revised* [DSM-III-R] or *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [DSM-IV]). Patients meeting inclusion criteria in these seven trials were randomized to double-blind treatment with either risperidone or another neuroleptic. The comparators were

**TABLE 1**

**Comparative, Randomized, Double-Blind, Parallel Design Trials of Risperidone for Depression in Schizophrenia**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient Population</th>
<th>Treatments</th>
<th>Duration of Treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myers et al\textsuperscript{29}</strong></td>
<td>DSM-IV diagnosis of schizophrenia or schizoaffective disorder (N=365)</td>
<td>RIS (4.9 mg/day)*</td>
<td>≥52 weeks</td>
<td>post hoc analysis of mood symptoms showed greater improvements on PANSS anxiety/depression cluster at endpoint with RIS vs HAL (<em>P</em>&lt;.001), and on individual symptoms of guilt (<em>P</em>=.05), anxiety (<em>P</em>=.003), and depressed mood (<em>P</em>=.004).</td>
</tr>
<tr>
<td><strong>Claus et al\textsuperscript{28}</strong></td>
<td>DSM-III-R diagnosis of schizophrenia (N=44)</td>
<td>RIS (12.0 mg/day)*</td>
<td>12 weeks</td>
<td>Significant improvement was found in SADS-C score from baseline to endpoint with RIS (<em>P</em>&lt;.01), and improvement in SADS-C score at endpoint was greater with RIS vs HAL (<em>P</em>=.05).</td>
</tr>
<tr>
<td><strong>Blin et al\textsuperscript{27}</strong></td>
<td>Acute schizophrenia accompanied by psychotic anxiety</td>
<td>RIS (8 mg/day)*</td>
<td>4 weeks</td>
<td>Mean decrease in PAS score was larger with RIS than with HAL (<em>P</em>=.07) or LEVO (<em>P</em>=.02).</td>
</tr>
</tbody>
</table>

*continued on next page*
<table>
<thead>
<tr>
<th>Reference</th>
<th>PATIENT POPULATION</th>
<th>TREATMENTS</th>
<th>DURATION OF TREATMENT</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceskova and Svestka (^{26})</td>
<td>ICD-9 diagnosis of schizophrenia (n=49) or schizoaffective disorder (n=13)</td>
<td>RIS (2.5–9.5 mg/day); HAL (2.9–9.9 mg/day)</td>
<td>8 weeks</td>
<td>Mean BPRS anxiety/depression factor score with RIS was improved beginning at week 1 and was maintained through week 8 (P&lt;.001). Mean BPRS anxiety/depression factor score at week 8 was less with HAL than with RIS (P&lt;.02).</td>
</tr>
<tr>
<td>Conley and Mamoud (^{26})</td>
<td>DSM-IV diagnosis of schizophrenia (n=325) or schizoaffective disorder (n=52)</td>
<td>RIS (4.8 mg/day); OLAZ (12.4 mg/day)</td>
<td>8 weeks</td>
<td>Greater improvements were seen at week 8 with RIS vs OLAZ on PANSS anxiety/depression cluster (P&lt;.02).</td>
</tr>
<tr>
<td>Tollefson et al (^{11})</td>
<td>DSM-IV diagnosis of schizophrenia, schizoaffective/schizophreniform psychosis (N=339)</td>
<td>RIS (7.2 mg/day); OLAZ (17.2 mg/day)</td>
<td>28 weeks</td>
<td>post hoc analysis found a greater proportion of OLAZ (59%) vs RIS (45%) patients showing a &gt;7-point decrease in PANSS anxiety/depression cluster score at week 8 (P&lt;.05).</td>
</tr>
<tr>
<td>Breier et al (^{26})</td>
<td>DSM-IV diagnosis of schizophrenia (N=29)</td>
<td>RIS (5.9 mg/day); CLOZ (403.6 mg/day)</td>
<td>6 weeks</td>
<td>No significant treatment difference in mean percentage decrease between RIS and CLOZ in HAM-D scores (P=0.25) or BPRS anxiety/depression factor score (P=0.74) at week 6 was found. Within-group change in these scores was significant for CLOZ (P&lt;.01) but not for RIS (P&gt;0.05).</td>
</tr>
<tr>
<td>Muller-Siecheneder et al (^{13})</td>
<td>DSM-III-R diagnosis of schizophrenia with major depressive symptoms (n=19), schizoaffective disorder (n=66), major depression with psychotic features (n=38)</td>
<td>RIS (6.9 mg/day); HAL (9.0 mg/day) plus AMI (180 mg/day)</td>
<td>6 weeks</td>
<td>A larger mean decrease in BRMS score at endpoint in the HAL/AMI group (-18.4) vs RIS group (-13.1) (P=0.0013) was found. Mean decrease in BPRS anxiety/depression factor score was also larger in the HAL/AMI group (-10.4) than in the RIS group (-7.1) (P&lt;.001).</td>
</tr>
</tbody>
</table>

RIS=risperidone; HAL=haloperidol; CLOZ=clozapine; OLAZ=olanzapine; AMI=amitriptyline; LEVO=levomepromazine; BPRS= Brief Psychiatric Rating Scale; BRMS=Bech-Rafaelsen Melancholia Scale; HAM-D=Hamilton depression scale; PAS=Psychiatric Anxiety Scale; PANSS=Positive and Negative Syndrome Scale for Schizophrenia; SADS-C=Schedule for Affective Disorders and Schizophrenia—Change Version; ICD-9=International Classification of Disease, 9th revision. \(^*\)

*Mean modal dose.
\(^{1}\)Median (or mean) daily dose at endpoint.
\(^{2}\)Mean minimum to mean maximum daily dose.

haloperidol in four trials,\textsuperscript{26-29} olanzapine in two trials,\textsuperscript{30,31} and clozapine in one trial.\textsuperscript{32} Treatment durations ranged from 4 to 52 weeks.

Different assessment scales were used in these trials to evaluate the effects of risperidone on mood symptoms. These included the anxiety/depression subscale cluster of the Positive and Negative Syndrome Scale for Schizophrenia (PANSS), the Brief Psychiatric Rating Scale (BPRS), the HAM-D, the Schedule for Affective Disorders and Schizophrenia–Change Version and the Psychiatric Anxiety Scale.

In three of the four haloperidol-controlled studies, there was evidence of a greater effect for risperidone on depressive symptoms. Risperidone was superior to haloperidol for the treatment of depressive symptoms in two studies.\textsuperscript{28,29} In a third study, the advantage of risperidone over haloperidol approached significance (\(P=.07\)). In the fourth trial,\textsuperscript{26} both drugs were associated with significant improvements (within subjects), although the mean BPRS anxiety/depression subscale score at endpoint was lower in the haloperidol group (1.23) than in the risperidone group (1.75; \(P=.02\)).

In a post hoc analysis of mood symptoms from a long-term relapse study involving 365 patients with stable schizophrenia or schizoaffective disorder, treatment with risperidone at a mean modal dose of 4.9 mg/day for an average of 356 days was associated with statistically significantly greater improvements on the PANSS anxiety/depression cluster (four items: depression, anxiety, guilt, and somatic preoccupation).\textsuperscript{29} Significant effects also were observed on individual symptoms of depressed mood, guilt, and anxiety during risperidone therapy as compared with haloperidol administered at a mean modal dose of 11.7 mg/day for an average of 290 days (Figure 1). Additionally, a trend was observed, suggesting a lower risk of relapse among the patients treated with risperidone (\(P=.081\); odds ratio=1.380).\textsuperscript{29}

The two comparative trials involving risperidone and olanzapine yielded contradictory findings. In the 8-week study by Conley and Mamoud,\textsuperscript{30} risperidone administered at a mean dose of 4.8 mg/day was compared to olanzapine at a mean dose of 12.4 mg/day. A statistically significant greater mean decrease in the PANSS anxiety/depression cluster score was observed in the risperidone-treated group (least square mean ± standard error changes of \(-2.8\pm0.2\) versus \(-1.9\pm0.2\); \(P=.02\)). In the other trial, Tollefson et al\textsuperscript{31} reported that the proportion of olanzapine (n=167) and risperidone patients (n=165) exhibiting at least a seven-point decrease in PANSS anxiety/depression cluster score (defined a priori as a clinical response) after 8 weeks was 59\% for olanzapine compared with 45\% for risperidone (\(P=.048\)). Moreover, Tollefson et al\textsuperscript{31} also reported that treatment with risperidone, but not
with olanzapine, was associated with a greater likelihood of relapse during a 20-week maintenance treatment period.

The principal limitation of the Tollefson et al\textsuperscript{31} study is that the mean dose of risperidone (7.2 mg/day) was substantially higher than is now generally used in clinical practice. This may account for the greater incidence of treatment-emergent extrapyramidal symptoms (EPS) (27.3\% versus 15.9\%) and anticholinergic medication use (32.9\% versus 19.8\%; \textit{P}=0.006) in risperidone- versus olanzapine-treated patients, respectively. Higher doses of a neuroleptic combined with EPS, as experienced by up to one third of risperidone patients, has been associated with dysphoria, which in some patients may account for the lack of improvement in mood and decreased overall efficacy for the risperidone-treated group.

In a small trial involving 29 patients, Breier et al\textsuperscript{32} found no statistically significant difference in the change in BPRS anxiety/depression factor scores or HAM-D scores from baseline to 6 weeks of treatment with risperidone or clozapine. Within-group analyses of the improvements in both of these scores, however, were statistically significant only for the clozapine group.

**FIGURE 1**

Mean improvements on Positive and Negative Syndrome Scale for Schizophrenia anxiety/depression cluster and individual items of guilt, depression, and anxiety after long-term administration of risperidone (mean modal dose of 4.9 mg/day) or haloperidol (11.7 mg/day) to patients with chronic schizophrenia or schizoaffective disorder.\textsuperscript{29}

\[\begin{array}{|c|c|c|}
\hline
& Week 1* & Week 52 \\
\hline
Risperidone & n=187 & n=69 \\
Haloperidol & n=198 & n=172 \\
\hline
\end{array}\]

\* \textit{P}=0.14; \textbullet\textbullet \textit{P}=0.005.

The results of an eighth controlled investigation of risperidone in treating depressive symptoms associated with psychosis have been published. This was a 6-week blinded comparison of risperidone to the combination of haloperidol and amitriptyline in a diagnostically mixed population of 123 patients with significant psychotic and depressive symptoms. Both treatments were associated with large reductions in BPRS anxiety/depression factor scores and in Bech-Rafaelsen Melancholia Scale (BRMS) total scores. The magnitude of the reductions in BRMS score ($P = .0013$) and BPRS anxiety/depression factor score ($P < .001$) was significantly greater for the group receiving haloperidol and amitriptyline than for the group treated with risperidone alone. Post hoc analyses suggested that this difference was primarily evident in a subgroup having a primary diagnosis of major depression with psychotic features, while treatment differences were less pronounced in the other diagnostic subgroups (schizoaffective disorder, depressive type, and schizophrenia with major depressive symptoms).

In summary, results from controlled investigations support the effectiveness of risperidone for improving depression associated with schizophrenia or schizoaffective disorders. At doses that were effective in controlling positive and negative symptoms of schizophrenia, risperidone resulted in statistically significant improvements in several validated measures of depressive symptoms. The magnitude of the improvement seen with risperidone was generally greater than that reported for haloperidol. The contradictory findings in the two comparative studies of olanzapine might suggest that both compounds possess antidepressant effects and that relative efficacy may depend on the dosing, patient selection factors, or perhaps some other characteristics. The effects of risperidone were less pronounced than those achieved by combined antidepressant-antipsychotic therapy in one study.

**Pooled Analyses of Controlled Trials**

Data from controlled, blinded trials of risperidone therapy in schizophrenia have been pooled to examine effects on dimensions of affective symptoms. In the first analysis, data were combined from two large controlled trials conducted in North America involving 513 hospitalized patients with chronic schizophrenia who were treated with risperidone (fixed doses of 2–16 mg/day), haloperidol, or placebo for 8 weeks. The second analysis included pooled data from six double-blind trials of risperidone and haloperidol (including the two aforementioned North American trials) involving 1,254 patients with chronic schizophrenia. In both analyses, changes in the PANSS anxiety/depression cluster scores from baseline to study end were compared between the treatment
groups. In the analysis of the combined North American trials, this cluster consisted of individual PANSS items of anxiety, guilt, tension, and depression. In the analysis conducted by Peuskens et al, individual items of somatic concerns, anxiety, feelings of guilt, and depression comprised the PANSS anxiety/depression cluster.

Both reports found that risperidone produced significantly larger improvements in anxiety/depression cluster scores compared with haloperidol (or placebo) (Figure 2). Using pooled data from the North American trials, Marder et al. showed that the magnitude of the treatment effect on the anxiety/depression cluster score for risperidone (6 mg/day) relative to placebo (defined as the change from baseline with risperidone minus the change from baseline with placebo, divided by the pooled standard deviations) was 4.71 ($P < .001$). The treatment effect for risperidone relative to haloperidol was almost as large, equaling 3.95 ($P < .001$). Even at a dose of 2 mg/day, risperidone was statistically superior to placebo in improving scores on the PANSS anxiety/depression cluster. Finally, this analysis found significantly greater improvements among risperidone-treated patients (combined doses of 6–16 mg/day) compared with haloperidol-treated patients on three (depression, anxiety, tension) of the four individual items comprising the cluster.

Similar results were reported by Peuskens et al. Changes from baseline in the anxiety/depression cluster scores averaged -2.1 in the risperidone group compared with -1.5 ($P < .001$) and -0.4 ($P < .001$) in the haloperidol and placebo groups, respectively. Risperidone was also significantly more effective than either haloperidol or placebo ($P < .01$) among patients who had high anxious/depressive symptoms at baseline (Figure 2). Significant symptom reduction was evident after only 1 week of therapy in patients treated with risperidone.

Clinical Evidence Supportive of Risperidone’s Antidepressant Activity

Findings suggestive of antidepressant activity for risperidone from the controlled investigations and meta-analyses in schizophrenia or schizoaffective disorders are supported by results of additional controlled and uncontrolled studies and anecdotal case reports. The patient groups evaluated in these supportive reports include individuals with schizoaffective disorders, major depression with or without psychotic features, bipolar disorder, OCD, pervasive developmental disorders, dysthymia with comorbid borderline personality disorder, and Alzheimer’s disease.
Supportive Controlled Trials

Two double-blind, placebo-controlled trials of risperidone in treating depressive symptoms associated with antidepressant-resistant OCD or pervasive developmental disorders have been published (Table 2). In both of these trials, risperidone was significantly superior to placebo in reducing depressive symptoms as well as in effecting improvement in other features of the disorder under evaluation.

In the first study, 36 patients with a primary diagnosis of OCD who were refractory to various SSRIs were randomized to 6 weeks of double-blind adjunctive treatment with risperidone (2.2 mg/day) or placebo. Twenty-nine of these patients met criteria for comorbid major depressive episode. HAM-D scores were reduced from baseline (11.7±7.8 to 7.6±4.9) after 6 weeks of adjunctive risperidone treatment \((P=0.02)\). By

**FIGURE 2**

Mean change from baseline in Positive and Negative Syndrome Scale for Schizophrenia (PANSS) anxiety/depression cluster scores following double-blind treatment with risperidone, haloperidol, or placebo in patients with chronic schizophrenia. (A) Results of pooled analysis involving 513 patients. Data for risperidone reflect patients receiving treatment of 6 mg/day. (B) Results of pooled analysis involving 1,254 patients. The anxious/depressed subgroup consists of 576 patients with a baseline PANSS cluster score of greater than or equal to the median score of 11.

contrast, HAM-D scores in the placebo group were not significantly changed after 6 weeks (12.2±5.0 to 15.2±8.7).

In the second controlled trial, 31 adults with pervasive developmental disorder were randomized to 12 weeks of treatment with risperidone or placebo. No concomitant psychotropic medications were permitted. None of the patients met DSM-IV diagnostic criteria for schizophrenia or had psychotic symptoms. Depressed affect was rated by clinicians using a 100-mm visual analog scale. Risperidone treatment, administered at a mean dose of 2.9 mg/day, resulted in statistically significant greater reductions relative to baseline in clinician-rated depression at endpoint relative to placebo (mean values of 23.8–8.5 versus 23.1–19.4, respectively; P<.03).

Uncontrolled Studies

Four uncontrolled studies involving risperidone treatment of patients with depressive symptomatology have been published (Table 2). One of these studies was conducted in patients with a diagnosis of schizoaffective disorder, depressed type, or major depression with psychosis according to DSM-III-R; one in patients with Alzheimer’s disease, and the remaining two in patients with a confirmed primary diagnosis of bipolar disorder.

<table>
<thead>
<tr>
<th>Reference</th>
<th>PATIENT POPULATION</th>
<th>TREATMENT*</th>
<th>DURATION OF TREATMENT</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>McDougle et al. 38</td>
<td>OCD refractory to SSRI (N=36)</td>
<td>RIS (2.2 mg/day)</td>
<td>6 weeks</td>
<td>RIS was superior to placebo in reducing HAM-D scores (P&lt;.005 on day 15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td></td>
<td>in addition to OCD and anxiety symptoms (P&lt;.01).</td>
</tr>
<tr>
<td>McDougle et al. 39</td>
<td>Autism (n=17) or other pervasive</td>
<td>RIS (2.9 mg/day)</td>
<td>12 weeks</td>
<td>RIS was superior to placebo in reducing depression (P&lt;.03) in addition</td>
</tr>
<tr>
<td></td>
<td>developmental disorder NOS (n=14)</td>
<td>Placebo</td>
<td></td>
<td>to aggression, repetitive behavior, irritability, anxiety, and autistic</td>
</tr>
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<td></td>
<td></td>
<td></td>
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<td>symptoms (P&lt;.02).</td>
</tr>
</tbody>
</table>

OCD=obsessive-compulsive disorder; SSRI=selective serotonin reuptake inhibitor; NOS=not otherwise specified; RIS=risperidone; HAM-D=Hamilton depression scale.

*Median (or mean) daily dose at endpoint.

In a study by Hillert et al., seven patients with major depression with psychotic features and three with schizoaffective disorder, depressed type, received monotherapy with risperidone for 6 weeks at doses of 4–10 mg/day (mean dose of 6.6 mg/day). Improvement relative to baseline was apparent for scores on the BRMS after 1 week of risperidone treatment (26.8–18.8). This improvement continued across the remainder of the 6-week treatment course with a significant reduction from baseline in BRMS scores at endpoint of 26.8–11.1 ($P < .015$). Eight patients completed 6 weeks of risperidone monotherapy. Two patients with a diagnosis

### TABLE 2B

**Uncontrolled Studies Evaluating Antidepressant Effects of Risperidone**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient Population</th>
<th>Treatment*</th>
<th>Duration of Treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hillert et al</td>
<td>DSM-III-R diagnosis of schizoaffective disorder, depressed type (n=3) or major depression with psychotic features (n=7)</td>
<td>RIS (6.6 mg/day) (Monotherapy)</td>
<td>6 weeks</td>
<td>There was a significant reduction in BRMS score ($P &lt; .015$) at endpoint. Seven of 10 patients showed a clinically meaningful decrease in BRMS score (from baseline scores of 20–32 to endpoint scores of 0–7). Two patients had suicidal ideation and were discontinued from the study.</td>
</tr>
<tr>
<td>Jacobsen</td>
<td>DSM-IV diagnosis of acute exacerbation of MDD (N=4)</td>
<td>RIS (1–6 mg/day) (Monotherapy, n=2; add-on to antidepressants, n=2)</td>
<td>12–19 weeks</td>
<td>There was a complete response in all four patients.</td>
</tr>
<tr>
<td>Ghaemi and Sachs</td>
<td>DSM-III-R diagnosis of bipolar disorder with breakthrough symptoms of depression (n=2) or mixed (n=1)</td>
<td>RIS (2 or 3 mg/day) (Add-on to lithium or valproate)</td>
<td>12–64 weeks</td>
<td>Two patients demonstrated improvement with RIS (CGI-I rating of much improved). One patient exhibited worsening of symptoms and was discontinued for sedation.</td>
</tr>
<tr>
<td>Barcia et al</td>
<td>Alzheimer’s disease with psychotic and/or affective symptomatology (N=235)</td>
<td>RIS (1.23 mg/day) (Monotherapy in 43%)</td>
<td>6 months</td>
<td>There was significant improvement in mean total scores of GDS as well as CDR and CGI ($P &lt; .05$).</td>
</tr>
</tbody>
</table>

MDD=major depressive disorder; RIS=risperidone; HAM-D=Hamilton depression scale; BRMS=Bech-Rafaelsen Melancholia Scale; CGI-I=Clinical Global Impression-Improvement scale; GDS=Geriatric Depression Scale; CDR=Clinical Deterioration Rating.

*Median (or mean) daily dose at endpoint.

of major depression developed suicidal ideation and were withdrawn prematurely because of symptomatic worsening.

A study of 235 patients with Alzheimer’s disease accompanied by psychosis and/or affective symptomatology evaluated the effects of 6 months of low-dose risperidone treatment (mean dose of 1.23 mg/day). In almost one half of the patients (43.4%), risperidone was administered as monotherapy. The effect of therapy on depressive symptoms was evaluated with the Geriatric Depression Scale (GDS). The researchers reported a statistically significant reduction in GDS total scores at day 15 (P<.005) that was sustained throughout the remainder of the 6-month trial. The mean GDS score was 12.8 at month 6 compared with an average score of 15.5 at baseline.

A discussion of the results of two uncontrolled studies of risperidone, one in mood disorders and obsessive-compulsive disorder and the second in bipolar disorder, is limited to those patients reported to have target symptoms of depression. Both of these studies were conducted in individuals who either failed to show an adequate response to existing medications or suffered breakthrough symptoms, and risperidone was administered as adjunctive therapy in all cases. In the study by Jacobsen, 4 of the 25 patients had depression as the primary target symptom. All patients with a primary diagnosis of MDD demonstrated a complete response (ie, total symptom resolution) to treatment with risperidone at doses of 1–6 mg/day. In two patients, the response occurred following the addition of risperidone to their existing medications (imipramine plus thyroid supplementation in one patient and sertraline plus trazadone in the other patient). In these patients, risperidone was administered as needed for 12–19 weeks.

Of the 12 patients with bipolar disorder treated with risperidone by Ghaemi and Sachs, the primary target symptom was depression for two and a mixed episode for one. Two of these three patients experienced breakthrough symptoms while on lithium, and the remaining patient had an acute relapse while on valproate. Following the addition of risperidone at a daily dose of 2 or 3 mg, improvement was seen in two of the three patients, as evidenced by Clinical Global Impression (CGI)-Improvement ratings of much improved and increases in Global Assessment of Function ratings relative to baseline scores. The remaining patient withdrew from the study after 6 weeks of risperidone therapy because of lethargy.

Case Reports

Three of the seven anecdotal case reports of risperidone for the treatment of depressive symptoms involved risperidone monotherapy in individuals with a primary diagnosis of schizoaffective disorder or
major depression with psychotic features. The remaining four publications concerned the use of risperidone as an add-on to existing antidepressant therapy in patients with a primary diagnosis of major depression without psychotic features. Table 3 summarizes the main features of these case reports.

The largest series of anecdotal reports of risperidone treatment of inpatients displaying depressive symptoms was a retrospective analysis of records for 144 psychiatric inpatients conducted by Keck and colleagues. They presented information on the treatment course of individuals with DSM-III-R diagnoses of schizoaffective disorder, depressed type (n=23) or major depression with psychotic features (n=3). For all but 5 of these 26 patients, risperidone was administered as an adjunct to antidepressant medication(s). An interview with a psychiatrist revealed that 20 of the 21 patients receiving adjunctive risperidone treatment (including all 3 with major depression) and 3 of the 5

<table>
<thead>
<tr>
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<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keck et al44</td>
<td>DSM-III-R diagnosis of schizoaffective disorder, depressed type (n=23) or major depression with psychotic features (n=3)</td>
<td>Not specified</td>
<td>Monotherapy (n=5); add-on to antidepressants (n=21)</td>
<td>There was a moderate to marked response to RIS (based on psychiatric interview) in 17 of 21 patients with schizoaffective disorder and in all 3 patients with psychotic depression.</td>
</tr>
<tr>
<td>Ghaemi et al45</td>
<td>DSM-III-R diagnosis of bipolar disorder with breakthrough symptoms of depression (n=2) or mixed (n=5)</td>
<td>RIS (mean dose 2.8 mg/day)</td>
<td>Add-on to lithium or valproate</td>
<td>Two patients with depression and two with mixed episode demonstrated improvement with RIS (CGI-I rating of much improved). Three patients were minimally improved (n=2) or unchanged (n=1).</td>
</tr>
<tr>
<td>Dwight et al46</td>
<td>DSM-III-R diagnosis of schizoaffective disorder (bipolar type, n=6; depressed type, n=2)</td>
<td>6–8 mg/day</td>
<td>Monotherapy (n=6); add-on to lithium or valproate (n=2)</td>
<td>All six patients with substantial pretreatment of depression (HAM-D scores of 15–21) showed meaningful reductions following RIS therapy (HAM-D scores of 1–6). Six bipolar patients exhibited a transient increase in manic symptoms within 1 week of starting RIS.</td>
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*continued on next page*
patients receiving risperidone monotherapy improved significantly. Although details of risperidone treatment were not provided according to a diagnosis subgroup, the average length of risperidone treatment among all responders was 8 weeks and the mean dose was 6 mg/day.

### TABLE 3 CONTINUED

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<tr>
<td>Myers and Thase</td>
<td>Major depression with psychotic features refractory to conventional treatment (N=1)</td>
<td>4 mg/day</td>
<td>Monotherapy</td>
<td>Mood disturbances and psychotic symptoms resolved within 1 week of starting RIS; patient remained symptom-free during 8 months of treatment. Cessation of RIS was accompanied by reemergence of depression and psychosis, which responded to reinstatement of RIS.</td>
</tr>
<tr>
<td>Ostroff and Nelson</td>
<td>DSM-IV diagnosis of MDD without psychosis refractory to SSRI treatment (N=8)</td>
<td>0.5–1 mg/day</td>
<td>Fluoxetine or paroxetine</td>
<td>All eight patients improved with almost complete remission within ≤1 week of starting RIS. HAM-D scores decreased while on RIS in all patients from baseline values of 16–26 to on-therapy values of 0–6.</td>
</tr>
<tr>
<td>Szigethy and Schultz</td>
<td>Dysthymia and borderline personality disorder unresponsive to conventional treatment (N=1)</td>
<td>1 mg/day</td>
<td>Fluvoxamine</td>
<td>There was sustained improvement in mood disturbances and remission of ritualistic compulsions and paranoia during the 3-month treatment period. An attempt to initiate RIS monotherapy led to relapse. Reinstatement of RIS-fluvoxamine combination again led to improvements.</td>
</tr>
<tr>
<td>Welner</td>
<td>Depression and anxiety refractory to conventional treatment (N=1)</td>
<td>1–3 mg/day</td>
<td>Phenelzine</td>
<td>Depressive symptoms and severe anxiety/agitation resolved within 2 weeks of starting RIS. Occurrence of dystonia and orthostatic hypotension led to discontinuation of RIS, but the patient remained symptom-free for 2 months after RIS was withdrawn.</td>
</tr>
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</table>

RIS=risperidone; MDD= major depressive disorder; SSRI=selective serotonin reuptake inhibitor; CGI-I=Clinical Global Impression-Improvement scale; HAM-D=Hamilton depression scale.

Ghaemi et al\textsuperscript{45} reviewed clinic charts on patients with bipolar I disorder (N=14) who had received risperidone following breakthrough symptoms while taking mood stabilizers. Among those patients, five had presented with a mixed episode and two with depression. After receiving an average dose of 2.8 mg/day for 6 weeks, both patients with depression and two patients with mixed symptoms were rated on the CGI as much improved. The three remaining patients experienced minimal improvement (n=2) or were unchanged (n=1) at the end of the 6 weeks of treatment.

A third case series of risperidone involved eight patients with a \textit{DSM-III-R} diagnosis of schizoaffective disorder, two with depressed type and six with bipolar type.\textsuperscript{46} The HAM-D and Young Mania Rating Scale (YMRS) were administered to these hospitalized patients prior to risperidone treatment and every other day during treatment (duration unspecified) by a single, unblinded rater. Most of the patients received risperidone as monotherapy (six of the original eight). Baseline HAM-D scores indicated substantial depression in six patients (scores of 15–21); each of these six exhibited clinically meaningful improvements in depression following risperidone treatment at doses of 6 or 8 mg/day (HAM-D scores of 1–6). Three of the patients who were depressed at the time of risperidone administration demonstrated a switch into mania during risperidone treatment, as reflected by an increase in YMRS scores from 0, 4, or 5 at baseline to peak values of 22, 10, and 14, respectively. Manic symptoms spontaneously resolved in these patients, and they were discharged on risperidone monotherapy.

This small case series, along with other sporadic case reports on the induction of mania,\textsuperscript{47} supports the antidepressant effects of risperidone. Risperidone, like other atypical agents with similar receptor profiles, and all conventional antidepressants have the potential to induce mania as a side effect of their antidepressant action.\textsuperscript{48,49} While this side effect is supportive of risperidone’s antidepressant efficacy, it is an uncommon event that generally resolves with discontinuation of the drug, reduction of dose, or addition of a mood stabilizer.\textsuperscript{49}

Risperidone monotherapy was reported to be effective in a person with major depression with psychotic features that was refractory to several different antidepressant treatment strategies, including the combined use of fluoxetine, trifluoperazine, and electroconvulsive shock therapy.\textsuperscript{50} After a 1-week trial with 4 mg/day of risperidone, all symptoms resolved and the patient was able to be discharged from the hospital. When risperidone was withdrawn after 8 months, the patient experienced a relapse of psychotic depression that again responded rapidly to the reinstatement of risperidone monotherapy.
Four publications presented observations from patients in whom risperidone was added to existing antidepressant medication (Table 3). In three papers, risperidone was prescribed as an adjunct to SSRI therapy; in the fourth, it was an adjunct to treatment with a monoamine oxidase inhibitor. A notable feature of each of these anecdotal reports was the rapidity with which depressive symptoms resolved following the addition of low doses of risperidone (0.5–3 mg/day). For example, Ostroff and Nelson reported significant improvement in remission of symptoms of depression within 1 week or less of adding risperidone in eight outpatients with DSM-IV–confirmed MDD who had not responded to adequate trials of either fluoxetine or paroxetine. The HAM-D scale was collected for seven of these patients to quantify improvement. Prior to adding risperidone, HAM-D scores ranged from 16 to 26; at the first follow-up visit after beginning risperidone, scores had decreased to 0–6.

O’Connor and Silver reported that addition of risperidone to existing SSRI therapy in four patients was sufficient to control suicidal ideation, agitation, and disturbances in eating and sleeping behaviors. Each of these patients had met criteria for MDD, and three also fulfilled diagnostic criteria for dysthymia. One of the patients in this series suffered a relapse following cessation of adjunctive risperidone treatment that remitted rapidly following its reinstatement.

**Conclusion**

By virtue of its ability to block central serotonin 5-HT$_{2A}$, α$_2$-adrenergic, and dopamine D$_2$ receptors, risperidone has the potential to exert profound changes in central monoaminergic neurotransmission. Of relevance to antidepressant effects, administration of risperidone to rats stimulates cortical 5-HT neurotransmission and decreases noradrenergic availability. These changes in serotonergic and noradrenergic neurotransmission are similar to the effects of chronic administration of various antidepressants. Together, these actions suggest that risperidone’s therapeutic benefits may extend beyond antipsychotic activity.

A review of the literature yielded a number of publications that pertain to the antidepressant activity of risperidone. Review of these publications, which included both controlled and uncontrolled studies in schizophrenia and nonpsychotic psychiatric disorders as well as case reports of patients with mood disorders, indicate that risperidone has significant effects on depressive symptoms. In schizophrenia, in which depression is a common comorbid condition, the results of eight randomized, blinded, and controlled trials demonstrated that treatment with risperidone resulted in significant reductions in depressive symptoms that were distinct from improvements in negative and positive
symptoms. This finding was confirmed by the findings of two large meta-analyses of trials in schizophrenia.

The results of these controlled investigations of risperidone in treating depression associated with schizophrenia are relatively clear-cut, yet the trials to date are subject to criticism because of a number of design features. First and foremost, none of the trials had a predefined objective of demonstrating antidepressant efficacy. Second, analyses of depression/anxiety outcome measures typically were done post hoc. Third, most of the patients in these controlled trials did not have severe levels of depressive symptoms. Rather, the studies excluded patients with severe depression. Finally, it may be argued that depression, as considered from the perspective of a syndrome, may be different in the population studied than in patients with primary mood disorders. Still, few would argue that the observed effects of risperidone on depressive symptoms are not clinically significant.

Although the data are limited and largely uncontrolled, risperidone shows promise as an add-on treatment to antidepressants for more refractory primary depressive disorders of both psychotic and nonpsychotic subtypes. Available evidence suggests that risperidone may be effective at lower doses (ie, 1–3 mg) than those generally required to treat schizophrenia and schizoaffective disorder. This improvement appears to be achieved rapidly, often within the first 2 weeks of treatment. Similar findings have recently been reported in a small but well-controlled study of olanzapine.

For antidepressant-treated patients with a diagnosis of major depressive disorder, it appears that lower doses of risperidone (eg, 0.5–3 mg/day) may be effective for treating depressive symptomatology. Moreover, anecdotal case reports suggest that the combination of low-dose risperidone and an SSRI may be an effective and well-tolerated strategy for managing patients with major depression that is refractory to SSRI treatment alone.

In conclusion, the collective evidence from pharmacologic studies and clinical investigations highly suggests an antidepressant activity for risperidone, and future clinical research is needed to confirm this observation.

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