Risperidone Augmentation of Selective Serotonin Reuptake Inhibitors in Major Depression

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Background: At low doses, risperidone acts as a 5-HT_2 antagonist. Preclinical data suggest 5-HT_2 antagonists may enhance the action of serotonin. This report examines the clinical use of risperidone to augment selective serotonin reuptake inhibitor (SSRI) antidepressants in patients who have not responded to SSRI therapy.

Method: In 8 patients with major depressive disorder without psychotic features (DSM-IV) who had not responded to an SSRI, risperidone was added to the ongoing SSRI treatment. Hamilton Rating Scale for Depression scores were obtained before and after the addition of risperidone.

Results: These 8 patients remitted within 1 week of the addition of risperidone. Risperidone also appeared to have beneficial effects on sleep disturbance and sexual dysfunction.

Conclusion: Risperidone may be a useful adjunct to SSRIs in the treatment of depression.

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Although a variety of effective antidepressants are now available, all of these agents are ineffective in some patients. Of patients who complete antidepressant trials, about two thirds respond to the drug therapy; of patients beginning antidepressant trials, about half respond.[1] Faced with a nonresponding patient, the clinician can either switch to another medication or consider one of the augmentation strategies that have been proposed.[2,3] Most of the augmentation strategies are intended to enhance the effects of the initial antidepressant, although some of the augmenting agents have other beneficial effects. For example, lithium also acts as a mood stabilizer, and buspirone has independent effects on anxiety.

The current article describes the use of risperidone as an augmentation strategy. Both preclinical and clinical data provide suggestive evidence that augmentation with risperidone might be effective in treating depression. Risperidone is an atypical antipsychotic, which, at low doses, is about 100 times more potent in antagonizing the 5-HT_{2A} receptor than the D_2 receptor.[4] The 5-HT_{2A} receptor is an excitatory receptor that acts in opposition to the postsynaptic 5-HT_{1A} receptor; thus, antagonism of the 5-HT_{2A} may facilitate the action of serotonin at the 5-HT_{1A} receptor. This was demonstrated by a preclinical study[5] which found that ketanserin, a 5-HT_2 antagonist, enhanced the inhibitory effects of serotonin on prefrontal neurons. This preclinical finding suggests that addition of a 5-HT_2 antagonist to a selective serotonin reuptake inhibitor (SSRI) might augment the effects of the SSRI.

Other clinical findings support the potential utility of this strategy in treating depression. 5-HT_2 antagonists such as nefazodone are effective for treatment of depression.[6,7] 5-HT_2 antagonists such as ritanserin and serazepine appear to be effective for reduction of anxiety and treatment of generalized anxiety disorder.[8,9] Finally, the use of low-dose antipsychotic medication as an adjunctive agent in depression has a long history.[10] Use of the conventional neuroleptics diminished in part because of the potential risk of tardive dyskinesia. However, the relatively low risk of tardive dyskinesia associated with the atypical neuroleptics makes their use in this situation feasible.[11] Thus, the 5-HT_2 antagonism of risperidone may help to reduce symptoms of depression and anxiety, and its antipsychotic actions may confer some of the advantages associated with low-dose antipsychotic use in depression.

In the current study, we describe a series of patients failing SSRI treatment who responded after the addition of a low dose of risperidone to the SSRI.

METHOD

Eight outpatients seen in a private psychiatry practice were included in the sample. The group included 5 men and 3 women, ranging in age from 36 to 75 years. These patients either were referred by other psychiatrists after an incomplete response to SSRI therapy, usually for con-

Table 1. Patient Characteristics and Time to Response

Patient No.	Age (y)	Sex	SSRI Trial	Prior Treatment in This Episode	Risperidone Dose	HAM-D[a] Pre-Risperidone	HAM-D[a] Post-Risperidone[b]	Time to Response
1	46	M	Fluoxetine 20 mg for 6 wk	None	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	Prior trial of desipramine	0.5 mg	17	2	2 d
3	75	M	Paroxetine 20–30 mg for 8 wk	Prior trial of sertraline	0.5 mg for 1 day, increased to 1 mg	27	...[d]	1 wk
4	50	M	Fluoxetine 20–40 mg for 8 wk	3 prior trials	0.5 mg hs	21	3	4 d
5	49	F	Fluoxetine 20 mg for 4 mo	Prior trial of sertraline	0.5 mg hs	18	6	1 wk
6	36	M	Paroxetine 20 mg for 2 wk	None	1.0 mg hs	20	4	1 wk
7	64	F	Paroxetine 10 mg for 2.5 wk	Prior trial of alprazolam 0.25 mg qid	0.5 mg bid	26	4	2 d
8	52	F	Fluoxetine 20 mg for 12 wk	None	0.5 mg hs	16	0	2 d

[a]Hamilton Rating Scale for Depression.
[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.

sideration of electroconvulsive therapy (ECT), or were self-referred. All met DSM-IV criteria for major depressive disorder without psychotic features. All had been treated with an SSRI at a moderate or high dose for 2 to 16 weeks (mean = 7.3 weeks). Hamilton Rating Scale for Depression (HAM-D)[12] scores were obtained prior to the administration of risperidone and at follow-up after risperidone therapy.

RESULTS

Table 1 provides a clinical description of these patients, their drug histories, their treatment with risperidone, and their responses. All 8 of the patients improved dramatically with almost complete remission in 1 week or less. Pre- and post-HAM-D scores are available for all subjects except case 3, who provided follow-up in the form of a letter. All subjects maintained the improvement for at least 3 months.

Representative Cases

Case 1. The first case was a 46-year-old white man who was referred by his internist because of a partial response to fluoxetine. The patient reported a 6-month history of depressed mood, crying spells, difficulty performing his work because of poor concentration, difficulty sleeping, and loss of libido. He had been started on fluoxetine 20 mg/day and showed slight improvement after 6 weeks. At the time of our initial evaluation, his HAM-D score was 19. He stated that his mood was better, but he still did not "feel quite right." He felt his sleep was never adequate and that he still had trouble "focusing." There were no psychotic symptoms. He was continued on 20 mg/day of fluoxetine and risperidone 0.5 mg h.s. was added. He called 2 days later to say that he felt the best he had felt in 6 months. He described feeling improved after the first night's dose but not completely well. Consequently, he increased his risperidone to 1 mg the second night. He reported that the morning after his first dose of risperidone, he awoke with his first erection in months and that his libido had returned. When seen at the office follow-up 2 weeks later, his HAM-D score was 0.

Case 2. The patient was a 53-year-old white man with a 1-year history of intractable depression with severe dysphoria, 50-lb (23kg) weight gain, anergia, decreased concentration, insomnia, and an inability to work. He had been on fluoxetine 20 mg/day for 2 months at the time of initial evaluation, with some response. He felt less depressed, but still had problems with sleep, energy, and concentration. He also had intense dread upon awakening in the morning. His HAM-D score was 17 at the time of referral. He was started on risperidone 0.5 mg h.s. During the telephone follow-up 2 days later, he reported feeling almost "back to normal." At the 2 week follow-up in the office, his HAM-D score was 2. Three months later, his response had been sustained. However, he did report a 15-lb (7kg) weight gain.

Case 3. The patient, a 75-year-old married white man, was employed full-time running his own professional office. He was referred for an emergency evaluation for ECT at the request of his treating psychiatrist. He complained of a 3-month history of worsening depression with agitation, rumination, difficulty concentrating, and crying spells. He had severe insomnia with both difficulty falling asleep and early morning awakening. There was a marked diurnal variation to his mood. Morning was characterized by difficulty getting out of bed, with the patient often moaning aloud for several hours that he wanted to die. By midday, he felt well enough to go into work. He also had severe anorexia with a 10-lb (5kg) weight loss over 3 months. He had initially been treated with paroxetine 20 mg/day, which was increased to 30 mg after 1 month. While beginning a medical workup for ECT, the patient was started on 0.5 mg h.s. of risperidone. Telephone contact the next day established that the patient slept better and, subjectively, felt improved. The risperi-

done was increased to 1 mg h.s. Within a week, he reported that his mood had returned to normal. This was confirmed by his treating psychiatrist who saw him in follow-up and felt that he had fully recovered. He was not seen again in our office, and the ECT was canceled.

Two months later, we received an unsolicited letter from the patient, stating

> "I visited your office in a distressed state of mind and utter despair. You prescribed 1 mg of Risperdal with 30 mg of Paxil and the results were instantly miraculous. I have been able to sleep peacefully and my appetite has returned. I have also been able to cope patiently with the daily anxieties at work and home and actually look forward to a productive routine."

DISCUSSION

The 8 cases in our study illustrate the beneficial effects of the addition of risperidone to an ongoing SSRI. In most cases, the patients noted improvement within days.

Most of the patients had a relatively complete response, and, as a result, it did not appear that the effects of the addition of risperidone were limited to certain types of symptoms. A related question, however, is whether the presenting characteristics of the patients differed from a typical cross-section of depressed patients. Some of the patients were quite ruminative, anxious, or even agitated and were similar to patients for whom low-dose neuroleptics have been prescribed. Two prior reports suggest near-delusional patients may respond less well to desipramine[13] or phenelzine.[14] In near-delusional patients failing desipramine, a low-dose neuroleptic did appear useful and sometimes rapidly effective.[13] However, other patients in the current sample did not have these characteristics. Thus, the advantage of risperidone did not appear limited to a particular type of patient.

The addition of risperidone was well tolerated, particularly at the low doses used. No patients developed extrapyramidal symptoms. In fact, the addition of risperidone appeared to have other advantages. Two patients noted improvement in sexual interest and performance. It was unclear if the risperidone had a direct effect on sexual functioning or whether the decrease in depressive symptoms resulted in improved sexual interest and performance. Four patients also noted dramatic improvement in sleep. The apparent beneficial effects of risperidone on sexual dysfunction and sleep are similar to those reported for nefazodone, a 5-HT_2 antagonist.[15,16]

The data from this open trial were not controlled. It is possible the addition of a new medication resulted in placebo-like effects. It is also possible that the additional duration of treatment was helpful; although most of the patients had received the SSRI for several weeks, they improved within a matter of days after receiving risperidone. Two patients had received the SSRI for only 2 weeks; however, they remitted within a week of the addition of risperidone. This limited additional duration of treatment seemed an unlikely explanation for the beneficial effects. Although the patients included in this report responded to the addition of risperidone, we do not mean to suggest that all patients will respond to risperidone augmentation. It is possible that this patient selection was biased. A larger sample would need to be studied to determine overall effectiveness. In addition, this study does not address the question of the efficacy of this augmentation strategy in patients who are clearly treatment resistant or treatment refractory. The patients in this sample varied in terms of their treatment resistance. It is likely that the effectiveness of this strategy would be reduced in clearly refractory patients.

In summary, these 8 cases illustrate the potential beneficial effects of augmenting an SSRI with risperidone. Clearly, a controlled study is needed, and is in fact being pursued.

Drug names: alprazolam (Xanax), buspirone (BuSpar), desipramine (Norpramin and others), fluoxetine (Prozac), nefazodone (Serzone), paroxetine (Paxil), phenelzine (Nardil), risperidone (Risperdal), sertraline (Zoloft).

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