An Open Pilot Study Combining Risperidone and a Selective Serotonin Reuptake Inhibitor as Initial Antidepressant Therapy

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Background: Atypical antipsychotics such as risperidone or olanzapine have been reported to be effective when added to a selective serotonin reuptake inhibitor (SSRI) in cases of depression in which treatment with an SSRI alone is not effective. It is possible that the combination of an SSRI and an atypical antipsychotic may be efficacious as an initial treatment for major depression.

Method: Thirty-six subjects who fulfilled DSM-IV diagnostic criteria for major depressive disorder were given fluvoxamine, 50 or 75 mg/day, with risperidone, 0.5 or 1 mg/day, at the start of treatment. The dose of fluvoxamine was increased to 100 or 150 mg/day on the fourth day of the treatment and maintained thereafter. Hamilton Rating Scale for Depression (HAM-D) scores were obtained at baseline and every week for 6 weeks. Remission and response were defined, respectively, as ≥ 75% and 50%–74% reduction from baseline in HAM-D score.

Results: Of 30 subjects who completed the 6-week study, 23 (76%) achieved remission, 5 (17%) achieved response, and 2 (7%) were nonresponsive. Of the 6 patients who did not complete the study, 3 showed remission, 1 showed response, and 2 showed minimal or no response by the time of dropout. The reported adverse effects were mild, and none of the 36 subjects enrolled in the study manifested or reported extrapyramidal symptoms, nausea, or vomiting.

Conclusion: The results suggest that the combination of risperidone and fluvoxamine from the beginning of antidepressant therapy enhances the therapeutic response rate in depression.

(J Clin Psychiatry 2002;63:733–736)

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Selective serotonin reuptake inhibitors (SSRIs) are now widely used and are considered to be first-line drugs for the pharmacologic treatment of depression.[1,2] However, about 30% to 50% of patients do not initially respond to SSRIs,[3–6] and the remission rate in patients treated with SSRIs for 6 weeks is 20% to 30%.[7] Consequently, many patients require a second or third antidepressant to obtain an adequate response or remission,[8] which is the main problem in antidepressant therapy.[9]

Although SSRIs do not produce significant anticholinergic or cardiovascular side effects, they often produce gastrointestinal side effects such as nausea or vomiting.[10–12] Indeed, the presence of adverse gastrointestinal effects is problematic for all SSRIs, and their usefulness as antidepressants may be limited in this respect. Consequently, treatments with fewer side effects and improved efficacy should be pursued.

Antidepressant action was reported following the addition of risperidone to an SSRI in patients who had not responded to SSRI treatment alone.[13,14] In addition, olanzapine, another atypical antipsychotic, has also been reported to be effective in treatment-resistant depression by augmenting the effect of SSRI therapy.[15] In each of these studies, the addition of either risperidone or olanzapine was reported to produce a rapid and efficacious antidepressive effect.

It may be that the combination of an SSRI and an atypical antipsychotic from the beginning of antidepressant treatment enhances the response rate in depression compared with an SSRI alone. However, to our knowledge, there has been no published report of an atypical antipsychotic being administered at the onset of treatment for depression, as opposed to using it as add-on therapy in patients receiving an SSRI.

In this study, we report the efficacy of the combination of risperidone and fluvoxamine in the acute phase of initial treatment for depression. Fluvoxamine was chosen because, compared with other SSRIs, it appears less likely to alter the serum concentration of risperidone via inhibition of the metabolism of risperidone.[16]

METHOD

Subjects were outpatients who fulfilled DSM-IV criteria for major depressive disorder (single episode or recurrent). All subjects were free from pharmacotherapy for depression for no less than a week before the study and had a minimum score of 21 on the 21-item Hamilton Rating Scale for Depression (HAM-D)[17] at the start. Subjects who were pregnant, lactating, or had substance abuse problems were excluded from the study.

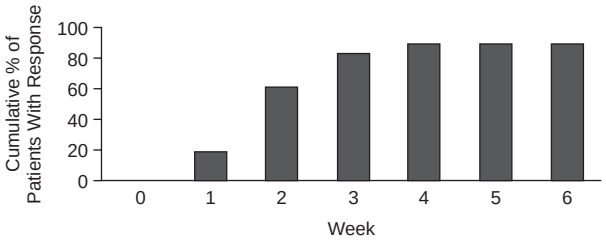
Thirty-six subjects (22 female and 14 male) with a mean age of 47.4 years (range, 18 to 81 years) and a mean HAM-D score of 28.0 (range, 21 to 39) were enrolled after providing informed consent. One male and 1 female subject manifested mood-congruent psychotic features of delusions or hallucinations, but the other 34 subjects had no psychotic features before the study. Thirty-one subjects had never received pharmacotherapy for depression, and the remaining 5 subjects had received pharmacotherapy but were drug-free for at least 1 month prior to the study.

The initial dosages of fluvoxamine and risperidone in the 29 subjects who were less than 60 years old were 75 mg/day and 1 mg/day, respectively. The dosage of fluvoxamine was changed to 150 mg/day on the fourth day of treatment and maintained to the sixth week. The other 7 subjects, who were more than 60 years old, were given 50 mg/day of fluvoxamine and 0.5 mg/day of risperidone at the beginning of treatment, and the dosage of fluvoxamine was changed to 100 mg/day on the fourth day and continued to the sixth week. Patients were allowed to receive 1 mg of flunitrazepam as a hypnotic if requested by the patient, and 24 patients were given flunitrazepam. HAM-D score was rated at baseline and once a week for 6 weeks. Remission, response, minimal response, and no response were defined as reductions in the baseline HAM-D score of 75%–100%, 50%–74%, 25%–49%, and < 25%,[18] respectively.

RESULTS

Thirty of 36 subjects completed the 6-week study. Of the 30 subjects who completed the trial, 23 (76%) achieved remission, 5 (17%) achieved response, and 2 (7%) showed no response to treatment. In the 6 subjects who failed to complete the trial, 1 changed medication after 4 weeks and 1 stopped treatment during the fifth week due to the lack of a sufficient response. Two subjects stopped the medication during the third week with remission and response, respectively, and 2 subjects stopped treatment during the fifth week as a result of remission. Thus, 2 subjects showed minimal or no response, 3 showed remission, and 1 showed response by the time of dropout. The percentages of patients in the intent-to-treat population with ≥ 50% reduction in HAM-D score are presented in Figure 1.

Figure 1. Response (≥ 50% reduction in HAM-D score) to Risperidone and Fluvoxamine in 36 Depressed Patients[a]



[a]Figure represents intent-to-treat population.
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

Nine of 36 subjects reported adverse effects, which included headache, insomnia, drowsiness, sexual dysfunction, general malaise, and asthenia in the legs. These adverse effects were all mild and did not lead to discontinuation of the treatment. None of the 36 subjects reported nausea or vomiting, and no extrapyramidal side effects were identified. Six of 24 subjects who received flunitrazepam at the beginning discontinued it before the end of the study because of improvement of insomnia. The demography of subjects and the course of HAM-D scores are presented in Table 1.

DISCUSSION

The results of this study indicated that the combination of risperidone and fluvoxamine produced a considerable remission rate (76% of the subjects who completed the study). A 50% improvement (≥ 50% reduction in baseline HAM-D score) occurred in about 60% of patients within the first 2 weeks. These results contrast with the low remission rate (20% to 30%)[7] reported in patients receiving an SSRI alone in short-term therapy lasting 6 weeks. The current treatment regimen was considered to be useful to the patients who required certainty of treatment response within a short period of initiating antidepressant therapy. It is possible that the addition of risperidone to the treatment regimen may have produced the observed robust effect. Antidepressant naiveness also may be a factor contributing to the high response rate, since 31 of 36 patients had never received pharmacotherapy for depression before the study. It has been reported that placebo effects do not continue, but subside in a short period.[19] However, placebo effects may or may not fade in 6 weeks. Thus, although the antidepressant effect in the current study continued in most cases to the end of the sixth week, a placebo effect still cannot be excluded from the results.

The combination of fluvoxamine and risperidone was considered well tolerated. The most common adverse effects produced by fluvoxamine are nausea and vomiting,[20–22] with a reported incidence of 20% to 70%.[20,23–26] These adverse effects can result in the discontinuation of

Table 1. The Demography of Subjects and the Course of HAM-D Scores[a]

			HAM-D Total Score									
				Week								
Case	Sex	Age (y)	Baseline	1	2	3	4	5	6	% Reduction[b]	Hypnotic	Side Effect
1	M	26	36	30	26	10	10	7	7	81	–	…
2	F	75	25	10	6	6	4	0	0	100	(+)	…
3	F	53	21	15	11	8	4	4	4	81	+	Headache
4	F	50	23	12	9	9	5	5	5	78	+	…
5	F	24	23	20	17	17	17	18	18	22	+	General malaise
6	M	36	30	27	13	11	1	1	5	83	–	…
7[c]	M	24	28	25	21	18	10	4	4	86	–	Headache
8	F	59	38	19	3	3	2	2	2	95	+	…
9	F	32	34	19	18	11	9	9	9	74	+	…
10	F	53	29	7	6	0	0	0	0	100	–	…
11	F	39	39	23	18	5	5	5	5	87	+	…
12	M	51	34	28	15	10	7	2	0	100	(+)	…
13	F	61	22	22	11	10	9	9	7	68	+	Asthenia in the legs
14	M	59	26	26	26	26	25	25	24	8	+	Insomnia
15	F	62	22	16	13	6	1	0	0	100	–	…
16	F	40	28	20	18	14	10	7	7	75	+	…
17	M	40	26	13	10	10	8	8	8	69	(+)	…
18	F	51	25	16	4	Stopped[d]	…	…	…	…	–	…
19	M	56	30	16	13	8	4	4	4	87	+	…
20	M	36	28	18	12	7	7	0	0	100	(+)	Erectile disturbance
21	F	75	26	26	26	26	25	Switched[e]	…	…	+	…
22	F	38	23	23	24	22	23	Stopped[f]	…	…	+	…
23	F	18	22	16	9	6	2	1	1	95	(+)	Headache
24	M	49	29	14	6	6	4	Stopped[d]	…	…	–	…
25	F	53	21	7	21	16	12	4	0	100	+	…
26	M	29	34	25	19	11	7	4	3	91	(+)	…
27	M	51	22	16	8	Stopped[d]	…	…	…	…	–	Drowsiness
28	F	31	27	20	18	14	10	7	7	74	–	Insomnia
29	F	58	22	17	8	8	5	4	4	82	–	…
30	M	74	22	19	16	4	4	3	3	86	+	…
31[c]	F	52	37	27	5	2	2	2	2	94	–	…
32	F	64	31	21	12	5	0	0	0	100	+	…
33	F	35	29	19	16	12	10	10	9	69	+	…
34	M	22	23	4	1	1	1	Stopped[d]	…	…	+	…
35	M	50	35	27	10	10	6	6	5	86	+	…
36	F	81	38	28	21	9	8	8	8	79	–	…

[a]Abbreviation: HAM-D = Hamilton Rating Scale for Depression. Symbols: + = hypnotic was used, – = no hypnotic was used, (+) = hypnotic was discontinued by the end of the study due to improvement of insomnia.
[b]Percentage reduction in HAM-D score from baseline at endpoint.
[c]Patients 7 and 31 had psychotic features at baseline.
[d]Stopped taking drug because of improvement of symptoms.
[e]Switched to another antidepressant because of lack of efficacy.
[f]Stopped taking drug because of lack of efficacy.

treatment at an early stage.[20,21,27] Thus, the adverse effects may prevent the rapid dose escalation of fluvoxamine at the beginning of treatment,[21,27,28] potentially increasing the time required to obtain an effective response.[29] In the current study, none of the 36 subjects manifested nausea or vomiting in spite of the relatively rapid escalation of the dose of fluvoxamine, including dropouts who continued the medication for 2 to 4 weeks. Although the number of subjects in this study was small, the lack of appearance of slight nausea or vomiting may have been related to the action of risperidone. Risperidone is reported to have an antiemetic action,[30] which is most likely due to its antagonism of dopamine D_2 receptors. Thus, a low dose of risperidone may potentially counteract the nausea or vomiting produced by an SSRI, and this may have contributed to the robust response rate in the current study.

Although the adverse effects were monitored for only 6 weeks in this study, none of the patients had symptoms of extrapyramidal side effects. The absence of acute extrapyramidal symptoms has been suggested to predict a low risk for subsequent tardive dyskinesia.[31,32] It has been reported that the risk of tardive dyskinesia with low doses of risperidone (0.5–1 mg/day) is extremely low.[33–35] Therefore, if risperidone is administered only in low doses for a short period of time with an SSRI, the use of this combination at the start of treatment may be relatively safe. However, the continued use of risperidone as maintenance therapy should be cautiously weighed against the risk of extrapyramidal side effects. Furthermore, it remains to be determined whether risperidone should be continued or discontinued when remission is achieved at an early stage.

In conclusion, the results suggest that the combination of risperidone and fluvoxamine from the beginning of treatment may enhance the therapeutic response rate at an early stage. The results also suggest that risperidone may suppress nausea or vomiting elicited by fluvoxamine. Consequently, these results suggest that the combination of fluvoxamine and risperidone at the beginning of therapy may represent a new strategy for the treatment of depression. However, effects due to placebo or a coadministered hypnotic cannot be excluded in this study, which was an open trial and had no placebo control group. Also, other variables such as the degree of skill in clinical rating and the antidepressant naiveness of the patients may have influenced the outcome of the current study. Consequently, double-blind, placebo-controlled studies with a more rigorous trial design are required to validate the findings of this study.

Drug names: fluvoxamine (Luvox and others), olanzapine (Zyprexa), risperidone (Risperdal).

REFERENCES

1. Bernstein JG. Handbook of Drug Therapy in Psychiatry. St. Louis, Mo: Mosby Year Book; 1995
2. Olfson M, Klerman GL. Trends in the prescription of antidepressants by office-based psychiatrists. Am J Psychiatry 1993;150:571–577
3. Barbui C, Hotopf M. Amitriptyline v the rest: still the leading antidepressant after 40 years of randomised controlled trials. Br J Psychiatry 2001; 178:129–144
4. Clinical Practice Guideline Number 5: Depression in Primary Care, vol 2. Treatment of Major Depression. Rockville, Md: US Dept Health Human Services, Agency for Health Care Policy and Research; 1993. AHCPR publication 93-0551
5. Thase ME, Kupfer DJ. Recent developments in the pharmacotherapy of mood disorders. J Consult Clin Psychol 1996;64:646–659
6. Nelson JC. A review of the efficacy of serotonergic and noradrenergic reuptake inhibitors for treatment of major depression. Biol Psychiatry 1999;46:1301–1308
7. Ferrier IN. Treatment of major depression: is improvement enough? J Clin Psychiatry 1999;60(suppl 6):10–14
8. DeVane CL. Pharmacologic characteristics of ideal antidepressants in the 21st century. J Clin Psychiatry 2000;61(suppl 11):4–8
9. Fawcett J, Barkin RL. Efficacy issues with antidepressants. J Clin Psychiatry 1997;58(suppl 6):32–39
10. Masand PS, Gupta S. Selective serotonin-reuptake inhibitors: an update. Harv Rev Psychiatry 1999;7:69–84
11. Edwards JG, Anderson I. Systematic review and guide to selection of selective serotonin reuptake inhibitors. Drugs 1999;57:507–533
12. Spigset O. Adverse reactions of selective serotonin reuptake inhibitors: reports from a spontaneous reporting system. Drug Saf 1999;20:277–287
13. Ostroff RB, Nelson JC. Risperidone augmentation of selective serotonin reuptake inhibitors in major depression. J Clin Psychiatry 1999;60: 256–259
14. O'Connor M, Silver H. Adding risperidone to selective serotonin reuptake inhibitor improves chronic depression [letter]. J Clin Psychopharmacol 1998;18:89–91
15. Shelton RC, Tollefson GD, Tohen M, et al. A novel augmentation strategy for treating resistant major depression. Am J Psychiatry 2001;158: 131–134
16. Sproule BA, Naranjo CA, Brenmer KE, et al. Selective serotonin reuptake inhibitors and CNS drug interactions: a critical review of the evidence. Clin Pharmacokinet 1997;33:454–471
17. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967;6:278–296
18. Trivedi MH, Baker SM. Clinical significance of monitoring early symptom change to predict outcome. J Clin Psychiatry 2001;62(suppl 4):27–33
19. Quitkin FM, Rabkin JG, Ross D, et al. Identification of true drug response to antidepressants: use of pattern analysis. Arch Gen Psychiatry 1984;41: 782–786
20. Wagner W, Zaborny BA, Gray TE. Fluvoxamine: a review of its safety profile in world-wide studies. Int Clin Psychopharmacol 1994;9:223–227
21. Ware MR. Fluvoxamine: a review of the controlled trials in depression. J Clin Psychiatry 1997;58(suppl 5):15–23
22. DeVane CL. Comparative safety and tolerability of selective serotonin reuptake inhibitors. Hum Psychopharmacol 1995;10:S185–S193
23. Lapierre YD, Browne M, Horn E, et al. Treatment of major affective disorder with fluvoxamine. J Clin Psychiatry 1987;48:65–68
24. Feighner JP, Boyer WF, Meredith CH, et al. A placebo-controlled inpatient comparison of fluvoxamine maleate and imipramine in major depression. Int Clin Psychopharmacol 1989;4:239–244
25. Dominguez RA, Goldstein BJ, Jacobson AF, et al. A double-blind placebo-controlled study of fluvoxamine and imipramine in depression. J Clin Psychiatry 1985;46:84–87
26. Norton KR, Sireling LI, Bhat AV, et al. A double-blind comparison of fluvoxamine, imipramine and placebo in depressed patients. J Affect Disord 1984;7:297–308
27. Freeman CP. Fluvoxamine: clinical trials and clinical use. J Psychiatr Neurosci 1991;16:19–25
28. Wilde MI, Plosker GL, Benfield P. Fluvoxamine: an updated review of its pharmacology, and therapeutic use in depressive illness. Drugs 1993;46: 895–924
29. Gelenberg AJ, Chesen CL. How fast are antidepressants? J Clin Psychiatry 2000;61:712–721
30. Janssen PAJ, Niemegeers CJE, Awouters F, et al. Pharmacology of risperidone (R64766), a new antipsychotic with serotonin-S2 and dopamine-D2 antagonistic properties. J Pharmacol Exp Ther 1988;244:685–693
31. Kane JM, Woerner M, Lieberman J. Tardive dyskinesia: prevalence, incidence, and risk factors. J Clin Psychopharmacol 1988;8:52S–56S
32. Barnes TR, McPhillips MA. Novel antipsychotics, extrapyramidal side effects and tardive dyskinesia. Int Clin Psychopharmacol 1998;13 (3, suppl):S49–S57
33. Gutierrez-Esteinou R, Grebb JA. Risperidone: an analysis of the first three years in general use. Int Clin Psychopharmacol 1997;12(suppl 4): S3–S10
34. Brecher M, Kane JM, Okamoto A, et al. Low frequency of tardive dyskinesia in elderly patients with dementia exposed to risperidone for up to one year. Presented at the 151st annual meeting of the American Psychiatric Association; May 30–June 4, 1998; Toronto, Ontario, Canada
35. Casey DE. The relationship of pharmacology to side effects. J Clin Psychiatry 1997;58(suppl 10):55–62