Olanzapine Addition in Obsessive-Compulsive Disorder Refractory to Selective Serotonin Reuptake Inhibitors: An Open-Label Case Series

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Background: Despite the efficacy of selective serotonin reuptake inhibitors (SSRIs) in the treatment of obsessive-compulsive disorder, a significant number of patients show no or only partial remission of symptoms. Some evidence exists to suggest that risperidone augmentation can be helpful in treating this refractory group. The efficacy of other atypical antipsychotic agents, such as olanzapine, in augmenting SSRIs in refractory obsessive-compulsive patients has yet to be systematically investigated.

Method: A series of 10 patients with DSM-IV obsessive-compulsive disorder showing significant residual symptoms following an adequate SSRI trial (12 weeks) were given open-label olanzapine augmentation for a minimum of an additional 8 weeks. Treatment response was assessed using the Yale-Brown Obsessive Compulsive Scale and the Clinical Global Impressions scale.

Results: Nine of the 10 patients in this series treated with olanzapine and an SSRI completed the 8-week augmentation trial. Of these, 4 demonstrated a complete remission or major improvement in obsessive-compulsive symptoms, 3 had partial remission, and 2 experienced no benefit. Nine patients experienced minimal adverse effects, primarily sedation, which did not interfere with continuing treatment. One patient discontinued olanzapine owing to excessive sedation.

Conclusion: The results of this preliminary, open-label trial suggest that olanzapine may be effective in augmenting ongoing SSRI treatment for a portion of patients with obsessive-compulsive disorder refractory to SSRI treatment. Larger, placebo-controlled trials appear warranted to investigate the clinical efficacy and tolerability of olanzapine augmentation of SSRI treatment in SSRI-refractory obsessive-compulsive disorder.

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It has been well established that selective serotonin reuptake inhibitors (SSRIs) are effective for the treatment of obsessive-compulsive disorder (OCD).[1] Despite the benefits gained by many patients receiving SSRI treatment, an estimated 40% to 60% of these patients have persisting symptoms.[2] A number of augmentation strategies have been tried for SSRI-refractory OCD with mixed results. Serotonin-enhancing agents, such as lithium[3] and buspirone,[4] have not proved effective for augmentation, while dopamine antagonists, including pimozide[5] (open-label) and haloperidol[6] (double-blind, placebo-controlled), have been shown to be effective. The addition of haloperidol has proved effective particularly for those SSRI-refractory patients with comorbid chronic tic disorders.[6] Subsequently, due to the preferable side effect profile and safety in long-term use of atypical antipsychotic medications, the potential of these agents has been investigated. When tried as a monotherapy for SSRI-refractory OCD, open-label clozapine was found to be ineffective.[7] In fact, a number of case reports suggest clozapine, as well as risperidone, monotherapy can induce or worsen obsessive-compulsive symptoms in schizophrenic patients.[8] A number of open-label trials have described the efficacy of risperidone addition to ongoing SSRI treatment in patients with SSRI-refractory OCD.[9–12] One double-blind, placebo-controlled investigation of risperidone augmentation of SSRIs in this population documented a 50% response

Table 1. Olanzapine Addition to Selective Serotonin Reuptake Inhibitors[a]

Patient	Age, y	Sex	Chronic Motor Tic Disorder	Comorbid Diagnosis	Primary Obsessive-Compulsive Symptoms	SSRI Dose (mg/day)	Y-BOCS Scores			Dose of Olanzapine (mg/day)	Duration of Olanzapine Tx (wk)	Adverse Effects	CGI Scores at 8 Weeks of Olanzapine Tx[c]
							Pre-SSRI	Pre-Olanzapine	Post-Olanzapine				
1[b]	24	F	No	Major depressive disorder	Religious obsessions	Fluoxetine (80 mg)	30	18	5	20	40	Weight gain	1
2	39	F	No	Major depressive disorder	Checking	Fluvoxamine (300 mg)	32	29	22	5	3	Sedation	N/A
3	50	F	No	Major depressive disorder	Hoarding	Fluvoxamine (300 mg)	33	25	14	10	16	Sedation	3
4	48	M	No	Major depressive disorder/pathological gambling	Checking	Sertraline (100 mg)	31	21	6	2.5	32	None	1
5	48	M	No	None	Contamination	Paroxetine (40 mg)	26	29	31	20	20	Sedation	4
6	40	M	Yes	Generalized anxiety disorder	Contamination	Sertraline (200 mg)	27	31	28	7.5	16	Sedation	4
7	48	M	Yes	Major depressive disorder	Arranging	Fluvoxamine (300 mg)	22	22	14	2.5	12	Sedation	2
8	31	M	Yes	None	Contamination	Fluvoxamine (300 mg)	35	32	19	2.5	10	Sedation	3
9	48	M	Yes	Major depressive disorder	Sexual obsessions	Sertraline (200 mg)	30	21	10	1.25	12	Sedation	2
10	27	M	No	Schizotypal personality disorder	Somatic obsessions	Fluvoxamine (200 mg)	32	29	12	1.25	8	Sedation	1

[a]Abbreviations: CGI = Clinical Global Impressions Global Improvement item, SSRI = selective serotonin reuptake inhibitor, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.
[b]Patient 1 reported in reference 15.
[c]CGI scores: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse.

rate and found that, in contrast to the findings with haloperidol addition, OCD patients with and without comorbid chronic tics showed improvement.[13]

At present, there is limited information regarding the efficacy of olanzapine monotherapy or augmentation for the treatment of OCD. In 2 groups of 25 schizophrenic subjects treated with olanzapine or placebo who were followed prospectively over a 6-week period, no emergence of obsessive-compulsive symptoms was observed in the active or placebo group.[14] A single case report from our group exists in which the subject experienced a full remission of obsessive-compulsive symptoms when treated with olanzapine augmentation for her SSRI-refractory OCD[15] (subject 1 of the series presented here). In this article, we describe a series of 10 patients with SSRI-refractory OCD who were treated with olanzapine augmentation.

METHOD

Ten outpatients (3 women and 7 men) from the Yale Adult OCD Clinic (New Haven, Conn.) were included in this case series (Table 1). Their ages ranged from 24 to 50 years (mean ± SD = 40.3 ± 9.8 years). All patients were diagnosed with OCD according to DSM-IV criteria by clinical interview. Most patients carried comorbid diagnoses including major depressive disorder (N = 6), generalized anxiety disorder (N = 1), pathological gambling (N = 1), and schizotypal personality disorder (N = 1). Four patients, all male, were diagnosed with chronic motor tic disorder, and none had Tourette's disorder.

All patients included in this series had completed a trial of an SSRI (fluvoxamine, 5 patients; sertraline, 3 patients; paroxetine, 1 patient; and fluoxetine, 1 patient) for a duration of at least 12 weeks at adequate doses (see Table 1). Six of the 10 patients enrolled in the trial had shown essentially no improvement at the end of the SSRI trial alone, while 4 had demonstrated a partial response. For this latter group, decreases in Yale-Brown Obsessive Compulsive Scale (Y-BOCS)[16,17] scores ranged from 8 to 12 points, but all patients continued to experience interfering and disabling obsessive-compulsive symptoms, and the Y-BOCS scores remained equal to or greater than 18. Two patients received additional low-dose benzodiazepines for anxiety. No other psychoactive medications were used.

Patients were eligible for olanzapine augmentation if they had a Y-BOCS score greater than 16 and experienced no more than minimal improvement according to the Clinical Global Impressions Global Improvement item (CGI) after at least 12 weeks of treatment with an SSRI. Olanzapine augmentation was initiated at a dose of 1.25 or 2.5 mg/day and then titrated as tolerated and clinically indicated (mean ± SD final dose = 7.3 ± 7.3 mg/day; range, 1.25–20 mg/day). Obsessive-compulsive symptoms were assessed during the 8-week augmentation trial using the Y-BOCS and CGI.

RESULTS

With at least 8 weeks of olanzapine augmentation, 4 patients (subjects 1, 4, 9, and 10) were "responders" (at least a 50% decrease in Y-BOCS score and a rating of "much improved" or "very much improved" on the CGI [rated as 2 and 1, respectively]), 3 (subjects 3, 7, and 8) were "partial responders" (at least a 30% drop in Y-BOCS score and/or a CGI rating of "much improved" or "very much improved"), and 2 patients had no change in their obsessive-compulsive symptoms (subjects 5 and 6). One patient (subject 2) discontinued olanzapine treatment after only 3 weeks owing to excessive sedation despite apparent onset of improvement in obsessive-compulsive symptoms. Symptomatic improvement generally began within the first 2 weeks of treatment. Those patients who experienced a robust response demonstrated improvement within the first week. The group of responders were treated with the full range of doses of olanzapine, varying from 1.25 mg/day to 20 mg/day. These 4 patients maintained their clinical responses to the time of this report at 10 to 40 weeks of treatment.

Response did not appear to be related to gender, type of obsessive-compulsive symptoms, or comorbid diagnoses, including the presence of comorbid chronic tics. The 1 patient in the series with comorbid schizotypal personality disorder (subject 10) was deemed to be 1 of the 4 responders to olanzapine augmentation.

The experience of adverse effects from olanzapine augmentation varied among the 10 patients. Among the patients who completed the 8-week trial, 1 patient reported no side effects, 7 complained of sedation, and 1 experienced weight gain of 8 lb (3.6 kg) after 8 weeks of olanzapine treatment (subject 1). Discontinuation of olanzapine occurred in 2 cases because of severe sedation (subjects 2 and 8 at weeks 3 and 10, respectively). Response did not appear to be dose related, and adverse effects were observed at doses as low as 1.25 mg/day.

DISCUSSION

This case series provides preliminary evidence that olanzapine augmentation may be efficacious and well tolerated for patients with SSRI-refractory OCD. After the addition of olanzapine to ongoing SSRI treatment, 7 (70%) of 10 SSRI-refractory patients showed at least moderate symptomatic improvement, and 4 (40%) had nearly full responses. The results from this study should be interpreted with caution due to its nonblinded, open-label design and small sample size.

Evidence exists to suggest that typical neuroleptics have greater efficacy in augmentation of SSRI treatment for OCD patients with comorbid chronic tics[5,6] or comorbid schizotypal personality disorder.[5] However, in the double-blind, placebo-controlled study of risperidone augmentation for SSRI-refractory OCD, there was no difference in treatment response between patients with and without comorbid chronic tics.[13] McDougle et al.[13] hypothesized that the broader range of effective treatment with risperidone may be due to risperidone's potent antagonism of serotonin-2A (5-HT_{2A}) and dopamine-2 (D_2) receptors. Olanzapine, likewise, binds to 5-HT_{2A} and D_2 receptors with high affinity. Its apparent efficacy for treating a broad range of patients with OCD would be consistent with this hypothesis.

In general, olanzapine augmentation was well tolerated in this group of patients, with a discontinuation rate due to adverse effects of 20%. Sedation was reported by 80% of patients and was the reason for discontinuation in 2 cases. The finding that only 1 patient experienced weight gain was surprising since on average there exists a reported weight gain during 6 to 8 weeks of olanzapine treatment of 4 to 8 lb (2 to 3 kg).[18]

It is possible that the improvement observed here with olanzapine augmentation of SSRI treatment was due to olanzapine alone. However, results have not been promising for the use of other atypical antipsychotics as monotherapy for the treatment of OCD.[15] It also is possible that the improvement seen was due to prolonged use of the SSRI or to a pharmacokinetic drug interaction affecting the blood SSRI levels. However, patients were given at least 12 weeks of SSRI treatment and were observed to have a stable baseline prior to starting olanzapine augmentation. In addition, it is possible that the metabolism of olanzapine was slowed in patients who were also taking fluvoxamine since fluvoxamine acts as a potent inhibitor of the cytochrome P450 1A2 enzyme, the same enzyme that is important for the breakdown of olanzapine. It is notable that subject 2, the only patient unable to complete the 8-week trial of olanzapine augmentation because of excessive sedation, was treated with fluvoxamine. Moreover, the mean dose of olanzapine tolerated by the 5 patients also taking fluvoxamine was less than half the mean dose tolerated by those taking other SSRIs. Additional research is needed to investigate the possible pharmacokinetic interactions between olanzapine and SSRIs.

In summary, these data suggest that further investigation of the efficacy of olanzapine for the treatment of SSRI-refractory OCD is warranted.

Drug names: buspirone (BuSpar), clozapine (Clozaril and others), fluoxetine (Prozac), fluvoxamine (Luvox), haloperidol (Haldol and others), olanzapine (Zyprexa), paroxetine (Paxil), pimozide (Orap), risperidone (Risperdal), sertraline (Zoloft).

REFERENCES

1. McDougle CJ, Goodman WK, Leckman JF, et al. The psychopharmacology of obsessive-compulsive disorder: implications for treatment and pathogenesis. In: Dunner DL, ed. Psychiatric Clinics of North America, vol 16. 4th ed. Philadelphia, Pa: Saunders; 1993:749–766

2. Goodman WK, Price LH, Rasmussen SA, et al. Efficacy of fluvoxamine in obsessive-compulsive disorder: a double blind comparison with placebo. Arch Gen Psychiatry 1989;46:36–43
3. McDougle CJ, Price LH, Goodman WK, et al. A controlled trial of lithium augmentation in fluvoxamine-refractory obsessive-compulsive disorder: lack of efficacy. J Clin Psychopharmacol 1991;11:175–184
4. McDougle CJ, Goodman WK, Leckman JF, et al. Limited therapeutic effect of addition of buspirone in fluvoxamine-refractory obsessive-compulsive disorder. Am J Psychiatry 1993;150:647–649
5. McDougle CJ, Goodman WK, Price LH, et al. Neuroleptic addition in fluvoxamine-refractory obsessive-compulsive disorder. Am J Psychiatry 1990;147:652–654
6. McDougle CJ, Goodman WK, Leckman JF, et al. Haloperidol addition in fluvoxamine-refractory obsessive-compulsive disorder: a double blind, placebo-controlled study in patients with and without tics. Arch Gen Psychiatry 1994;51:302–308
7. McDougle CJ, Barr LC, Goodman WK, et al. Lack of efficacy of clozapine monotherapy in refractory obsessive-compulsive disorder. Am J Psychiatry 1995;152:1812–1814
8. Potenza MN, McDougle CJ. Potential of atypical antipsychotics in the treatment of nonpsychotic disorders. CNS Drugs 1998;9:213–232
9. McDougle CJ, Fleischmann RL, Epperson CN, et al. Risperidone addition in fluvoxamine-refractory obsessive-compulsive disorder: three cases. J Clin Psychiatry 1995;56:526–528
10. Saxena S, Wang D, Bystritsky A, et al. Risperidone augmentation of SRI treatment for refractory obsessive-compulsive disorder. J Clin Psychiatry 1996;57:303–306
11. Ravizza L, Barzega G, Bellino S, et al. Therapeutic effect and safety of adjunctive risperidone in refractory obsessive-compulsive disorder (OCD). Psychopharmacol Bull 1996;32:677–682
12. Stein DJ, Bouwer C, Hawkridge S, et al. Risperidone augmentation of serotonin reuptake inhibitors in obsessive-compulsive and related disorders. J Clin Psychiatry 1997;58:119–122
13. McDougle CJ, Epperson CN, Pelton GH, et al. A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive-compulsive disorder. Arch Gen Psychiatry. In press
14. Baker RW, Ames D, Umbricht DSG, et al. Obsessive-compulsive symptoms in schizophrenia: a comparison of olanzapine and placebo. Psychopharmacol Bull 1996;32:89–93
15. Potenza MN, Wasylink S, Longhurst JG, et al. Olanzapine augmentation of fluoxetine in the treatment of refractory obsessive-compulsive disorder [letter]. J Clin Psychopharmacol 1998;18:423–424
16. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale (Y-BOCS), I: development, use, and reliability. Arch Gen Psychiatry 1989;46:1006–1011
17. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale (Y-BOCS), II: validity. Arch Gen Psychiatry 1989; 46:1012–1016
18. Beasley CM Jr, Tollefson GD, Tran PV. Safety of olanzapine. J Clin Psychiatry 1997;58(suppl 10):13–17