Risperidone Augmentation of Serotonin Reuptake Inhibitors in Obsessive-Compulsive and Related Disorders

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Background: While serotonin is the neurotransmitter most commonly implicated in obsessive-compulsive and related disorders, there is also evidence for dopaminergic mediation of these conditions. Indeed, augmentation of serotonin reuptake inhibitors with the atypical neuroleptic risperidone has been suggested to be useful in obsessive-compulsive disorder (OCD).

Method: Charts of all patients treated in our OCD clinic with the combination of a serotonin reuptake inhibitor and risperidone were reviewed. Demographic details of patients and clinical response to this pharmacotherapeutic strategy were tabulated.

Results: A series of patients with OCD (N = 8), trichotillomania (N = 5), and Tourette's syndrome (N = 3) who were refractory to treatment with serotonin reuptake inhibitors had received risperidone augmentation. In a number of cases, this strategy proved clinically effective. However, a minority of patients experienced significant adverse effects.

Conclusion: Patients with OCD and related disorders are not infrequently refractory to treatment with serotonin reuptake inhibitors. Controlled trials of risperidone augmentation in such patients seem warranted. In particular, it is necessary to determine an appropriate dose range to minimize adverse effects.

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Since early reports of the efficacy of the serotonin reuptake inhibitor clomipramine in the treatment of obsessive-compulsive disorder (OCD),[1] a range of research has confirmed that serotonin plays a significant role in the mediation of this condition.[2] In addition, serotonin reuptake inhibitors appear selectively effective in a range of disorders that appear to have phenomenological characteristics in common with OCD—including trichotillomania[3] and body dysmorphic disorder.[4]

Nevertheless, serotonin reuptake inhibitors are not effective in all patients with OCD and related disorders,[5,6] suggesting that other neurochemical systems may also be important in these conditions. McDougle and colleagues[7] have recently reported that OCD patients refractory to serotonin reuptake inhibitors may respond to augmentation of these agents with neuroleptics, particularly if tics are present. Similarly, this combination of agents has been reported effective in trichotillomania[8] and Tourette's syndrome.[9]

These findings are consistent with a range of preclinical and clinical evidence indicating that dopamine plays a role in OCD and possibly related disorders such as Tourette's syndrome.[10,11] Furthermore, the recent introduction of atypical neuroleptics with favorable adverse effect profiles, such as risperidone, has encouraged the use of augmentation strategies with these agents in the treatment of OCD,[12–15] as well as in the treatment of trichotillomania[14] and Tourette's syndrome.[16]

In this paper, the charts of patients seen in an OCD clinic and treated with the combination of a serotonin reuptake inhibitor and risperidone are reviewed.

METHOD

Charts of all patients seen in the OCD clinic of a teaching hospital (Tygerberg, South Africa) were reviewed to determine whether the combination of a serotonin reuptake inhibitor and risperidone had been used. Where this combination of agents had in fact been employed, details were tabulated for each patient (Table 1).

Patients in our clinic are routinely assessed with the Yale-Brown Obsessive Compulsive Scale,[17] as well as

Table 1. Risperidone Augmentation of Serotonin Reuptake Inhibitors (SRIs)*

Sex	Age (y)	DSM-IV Diagnosis	SRI Trial	Y-BOCS Score Pre-Risperidone	Risperidone Trial	Y-BOCS Score Post-Risperidone	CGI Score
F	54	Obsessive-compulsive disorder	Paroxetine 60 mg/d × 14 wk	24	2 mg/d × 4 wk	16	2
F	28	Obsessive-compulsive disorder	Paroxetine 60 mg/d × 12 wk	28	1 mg/d × 1 wk	28	4
M	43	Obsessive-compulsive disorder	Paroxetine 60 mg/d × 9 mo	20	1 mg/d × 4 wk	16	2.5
M	27	Obsessive compulsive disorder	Clomipramine 200 mg/d × 6 mo	28	2 mg/d × 4 wk	28	4
M	19	Obsessive-compulsive disorder	Fluoxetine 40 mg/d × 12 wk	28	1 mg/d × 4 wk	29	4
F	59	Obsessive-compulsive disorder	Clomipramine 250 mg/d × 7 mo	14	1 mg/d × 4 wk	4	1
M	33	Obsessive-compulsive disorder	Citalopram 60 mg/d × 3 mo	18	1 mg/d × 4 wk	8	1
F	40	Obsessive-compulsive disorder	Clomipramine 250 mg/d × 9 mo	18	1 mg/d × 4 wk	18	4
F	22	Trichotillomania	Clomipramine 200 mg/d × 8 mo	5	1 mg/d × 4 wk	3	2
M	45	Trichotillomania	Clomipramine 50 mg/d × 12 mo	5	1 mg/d × 4 wk	3	2.5
F	43	Trichotillomania	Citalopram 40 mg/d × 36 mo	8	1 mg/d × 4 wk	8	4
F	31	Trichotillomania	Clomipramine 175 mg/d × 12 wk	8	1 mg/d × 4 wk	4	2
F	23	Trichotillomania	Clomipramine 100 mg/d × 6 mo	6	1 mg/d × 4 wk	3	2
M	20	Tourette's syndrome	Citalopram 60 mg/d × 10 mo	24	4 mg/d × 4 wk	14	OCD: 2 tics: 2
M	16	Tourette's syndrome	Fluoxetine 40 mg/d plus pimozide 4 mg/d × 12 mo	0	4 mg/d × 4 wk	0	OCD: 4 tics: 2
M	24	Tourette's syndrome	Citalopram 60 mg/d plus pimozide 8 mg/d × 18 mo	20	3 mg/d × 4 wk	20	OCD: 4 tics: 4

Abbreviations: CGI = Clinical Global Impression Change Scale (1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change), OCD = obsessive-compulsive disorder, Y-BOCS = Yale-Brown Obsessive-Compulsive Scale (compulsion scale only in trichotillomania patients).

with a Clinical Global Impressions (CGI)[18] change score. Effect of treatment on these measures was also tabulated (Table 1).

RESULTS

Eight patients who met DSM-IV criteria for OCD had received augmentation of serotonin reuptake inhibitors with risperidone. None of these patients had tics or a history of tics. None of these patients met diagnostic criteria for schizotypal personality disorder. After risperidone augmentation, three patients reported very much or much improvement in OCD symptoms, one patient noted minimal to much improvement, three patients had no change in symptoms, and one patient was unable to tolerate side effects of increased anxiety and irritability. Two of the three responders elected to continue the medication, and improvement has been maintained for 10 and 3 months, respectively. The patient with minimal to much response elected to discontinue risperidone 2 months later, after experiencing significant "slowing down" of thought processes.

Five patients who met DSM-IV criteria for trichotillomania, but not for OCD, had received augmentation of serotonin reuptake inhibitors with risperidone. None of these patients had tics or a history of tics. On this regimen, three patients reported significant clinical improvement, a fourth reported minimal to much improvement, and a fifth patient experienced no change. Two of the responders have maintained improvement for some months on this regimen, but a third elected to discontinue risperidone 3 months later after noticing increased symptoms of depression.

Three patients who met DSM-IV criteria for Tourette's syndrome, and who had comorbid OCD symptoms, had received augmentation of serotonin reuptake inhibitors with risperidone. In one patient, there was significant improvement of both tic and OCD symptoms after addition of risperidone. However, after 2 months of treatment, the patient noted dramatic worsening of mood, and the risperidone was discontinued. In the second patient, OCD symptoms were already fully controlled when risperidone was used in place of pimozide. On this regimen, the patient experienced no change in OCD symptoms and further improvement in tics. In the third patient, OCD symptoms had shown some improvement on the combination of a serotonin reuptake inhibitor and pimozide, and replacement of pimozide with risperidone did not result in further change.

CONCLUSION

Given the advantageous adverse effect profile of risperidone compared with classical neuroleptics,[19] evidence that this agent is similarly effective in the augmentation of serotonin reuptake inhibitors in treatment-refractory OCD would have obvious clinical importance. A review of a series of cases of patients with OCD, trichotillomania, and Tourette's syndrome suggests that in patients refractory to treatment with serotonin reuptake inhibitors, risperidone augmentation may indeed be effective for some within a relatively short space of time. At the relatively low doses of risperidone used, extrapyramidal side effects were not problematic, but other adverse effects such as increased depression did at times lead to discontinuation of this agent.

Clearly, there are significant limitations to the data presented here. These include the limited sample size and the lack of a placebo- or dose-controlled treatment design. It might be argued that increased duration of exposure to serotonin reuptake inhibitors rather than risperidone augmentation was responsible for clinical improvement, although in all patients duration of monotherapy was at least 12 weeks. Alternatively, it is possible that risperidone alone has anti-OCD effects, although there are few data to suggest that neuroleptic monotherapy is effective in this disorder.[20–22] In addition, early response to pharmacotherapy, perhaps particularly in trichotillomania,[23] is not always long-lasting. Conclusions from the data here can be only extremely tentative.

It is theoretically possible that risperidone augmentation results in increased blood levels of the serotonin reuptake inhibitor and thereby leads to a therapeutic response.[24] Although risperidone and haloperidol are chemically unrelated, in their study of haloperidol augmentation McDougle et al.[7] found no relationship between the blood level of the serotonin reuptake inhibitor and treatment response. Furthermore, response to the combination of a serotonin reuptake inhibitor and an atypical neuroleptic is consistent with preclinical data indicating involvement of both serotonergic and dopaminergic systems in stereotyped movements.[10] In addition, this finding is consistent with reports of the use of serotonin reuptake inhibitors with typical neuroleptics in OCD,[7] trichotillomania,[8] and Tourette's syndrome,[9] as well as with previous reports of risperidone augmentation in these disorders.[12–16] As in this study, the previous literature has indicated that the response to dopaminergic augmentation occurs relatively quickly.

There are, however, also several anecdotal reports of exacerbation of OCD symptoms by atypical neuroleptics.[25–27] Experimental administration of metergoline,[28] a 5-HT_1/5-HT_2 antagonist, or of ritanserin,[29] a 5-HT_{2A}/5-HT_{2C} antagonist, during serotonin reuptake inhibitor treatment can reverse the therapeutic effects of serotonin reuptake inhibitor treatment. It is similarly possible that clozapine and risperidone, both of which are 5-HT_2 antagonists, may on occasion exacerbate OCD. In our series, although risperidone did not worsen obsessive-compulsive symptoms, a number of patients experienced increased depression after addition of this agent. There is evidence that particular effects of combined serotonergic-dopaminergic blockade are observed in only a narrow dose range,[30] perhaps accounting for these apparently divergent data.

In conclusion, further research is necessary to determine the indications for and optimal dosage and duration of risperidone augmentation of serotonin reuptake inhibitors in OCD and related disorders. It is possible that this augmentation strategy might be most effective in patients with both OCD and tics,[7] although this has not clearly been shown here or elsewhere.[13] Risperidone augmentation may also be useful in OCD spectrum disorders characterized by stereotypical kinds of symptoms. Nevertheless, attention to the possible adverse affects of risperidone augmentation is also warranted.

Drug names: clomipramine (Anafranil), clozapine (Clozaril), haloperidol (Haldol and others), pimozide (Orap), risperidone (Risperdal), ritanserin (Tiserton).

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