



# Possible treatment with Second Generation Antipsychotic as Supplementary Management to Treatment-Resistant Obsessive Compulsive Disorder, a Pilot Study



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## Abstract

**Introduction:** 40%-60% of the patients with obsessive-compulsive disorder remain unimproved by Serotonin-Reuptake inhibitors. The objective of this study was to examine whether addition of the atypical antipsychotic, olanzapine, to serotonin reuptake inhibitor is useful for patients with OCD who do not respond to antidepressant monotherapy.

**Method:** Eleven patients with obsessive compulsive disorder who had not responded to at least 2 previous treatments with a serotonin reuptake inhibitor at maximum dose and duration were assigned to receive olanzapine in addition to antidepressant for 8 weeks in an open-label study. Treatment response was assessed using the Yale-Brown Obsessive-Compulsive Scale (YBOCS).

**Results:** six of 11 patients respond to the olanzapine addition. The mean  $\pm$  SD baseline YBOCS score of 33.45  $\pm$  4.47 dropped to a mean of 25  $\pm$  5.98 at endpoint with a mean reduction of 24.56%.

**Conclusion:** Treatment-refractory OCD Patients may benefit from addition of olanzapine to ongoing antidepressant therapy.

## Introduction

Serotonin Reuptake Inhibitors (SRI) is the most effectual drug treatment accessible for obsessive-compulsive disorder (OCD) [1]. Clomipramine, citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline have been proved to be effective against obsessive and compulsive symptoms independent of their antidepressant activity [2-4]. Nevertheless, 50%-60% of patients with OCD fail to respond to a single trial of an SRI, and 20-40% does not respond sufficiently after several medication trials [1]. Moreover, although the selective serotonin reuptake inhibitors (SSRIs) are generally considered to be secure and well tolerated, still a proportion of subjects do experience intolerable side effects and discontinue treatment prematurely. Also, No single drug acting on different neurotransmitter systems has yet proved an absolute efficacy against obsessive-compulsive symptoms.

Therapeutic strategies in these resistant cases usually consist of augmentation therapies with, tryptophan, buspirone, clonazepam and lithium or the addition of antipsychotic drugs. But the final results with these tactics were not encouraging so

far and have remained somewhat experimental than crucial. The addition of low-dose antipsychotics to standard antidepressant treatment has shown to be effective in some cases, but extrapyramidal side effects have limited the use of typical antipsychotics. Therefore treatment with atypical antipsychotic that shows fewer extrapyramidal symptoms might be a useful alternative for treatment-refractory OCD patients. Beneficial effects of adding risperidone to SSRIs has been observed in some cases of treatment-resistant obsessive-compulsive disorder [5,6]. In prior reports (four open and one double-blind studies) positive results with the addition of olanzapine to the regular antidepressant treatment of the patients [7-11] have been displayed. In the present study a new trial with olanzapine has been performed in a non-western patient population with treatment-resistant OCD.

## Method:

Eleven female outpatients, after full explanation of the procedure for them and obtaining assigned informed consent, entered the study. The mean  $\pm$  SD age of the subjects was

39.2+/- 9.08 years. Patients were diagnosed as OCD according to the DSM-TR criteria. Inclusion criteria in the present study consisted:1) OCD symptoms of at least 3 years duration and 2) a score on the YBOCS [12] of at least 18. The subject's mean +/- SD baseline score on the YBOCS was 33.45 +/- 4.47 and the mean duration of illness was 16.3+/-7.35 years. All of the patients had both obsessions and compulsions.

All patients failed at least 2 adequate treatments with an SRI at maximum dose (clomipramine 250 mg/day, fluvoxamine 300 mg /day, fluoxetine 80 mg/day, sertraline 200 mg/day, citalopram 80 mg/day) and enough duration (12 weeks). Failure was defined as a less than 25% improvement on the YBOCS.

In an 8-week trial, all patients continued to take their current SRI at the maximum dose during trial. Four patients received clomipramine (250 mg/day), three patients received fluvoxamine (300 mg/day), two patients received fluoxetine (80 mg/day), one patient received sertraline (200 mg/day) and one patient received citalopram (80 mg/day). Olanzapine (generic form tablets) addition was initiated at a dose of 2.5 mg/day and then increased by 2.5 mg increments in weekly meetings, to a maximum of 10 mg by week4, and then this dose was held

constant up to the end of the assessment. No other psychotropic drug or psychosocial intervention was permitted during the evaluation. Subjects were seen by the same trained assessor at baseline (week 0) and at the end of weeks 4 and 8 at which times clinical response and adverse events were evaluated. The assessor was not blind to the treatment and its goals. The primary efficacy parameter was YBOCS score [12]. Full response to treatment was prospectively defined as at least 50% decrease in YBOCS score and partial response as at least 25% decrease in YBOCS score from beginning. Adverse events were assessed at each visit by means of patients' spontaneous reports and clinical examination by psychiatrist.

**Results**

Two patients were full responders with a mean decrease of 51% in YBOCS score. Four patients were partial responders with at least a 25% decrease. Five patients experienced no change in their obsessive-compulsive symptoms (Table 1) (Figure 1). In those who benefited from the treatment, improvement started within the first two weeks of olanzapine addition. In general patients mean YBOCS score decreased significantly (by 24.56%) from baseline to endpoint ( $t = 4.23, df = 10, p < 0.002$ ) (Figure 2).

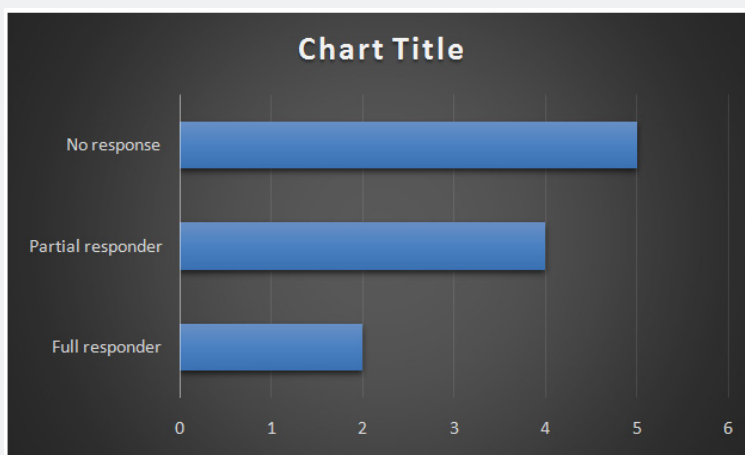


Figure 1: Response of treatment-refractory OCD cases.

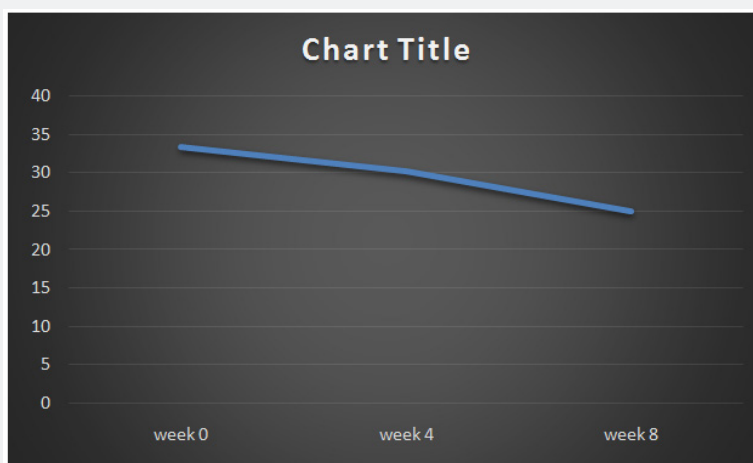


Figure 2: Decrease of YBOCD between baseline and week 8.

**Table 1:** Participants' Characteristics and Outcome.

Patient No.	Age (y)	Sex	Duration of OCD(y)	Type of OCD Symptoms	Comorbid Diagnosis	Current SRI	Daily SRI Dose (mg)	YBOCS (Baseline)	YBOCS (Endpoint)	% Change	t	P Value
1	42	F	10	contamination	OCPD	Fluoxetine	80	39	19	51.28		
2	38	F	20	contamination	None	Fluoxetine	80	32	24	25		
3	34	F	15	contamination	GAD	citalopram	80	31	28	9.67		
4	23	F	7	Checking	None	Sertraline	200	40	35	12.5		
5	47	F	15	contamination	OCPD	Fluvoxamine	300	32	18	43.75		
6	37	F	11	contamination	None	Fluvoxamine	300	29	28	3.44		
7	50	F	26	Precision	None	Fluvoxamine	300	37	18	51.35		
8	39	F	18	contamination	None	Clomipramine	250	33	31	6.06		
9	28	F	9	Checking	OCPD	Clomipramine	250	25	18	28		
10	54	F	31	contamination	None	Clomipramine	250	33	29	12.12		
11	40	F	18	contamination	None	Clomipramine	250	37	27	27.02		
Mean	39.2		16.3					33.45	25	24.56	4.23	0.002
SD	9.08		7.35					4.47	5.98			

Abbreviations: GAD: Generalized anxiety disorder; YBOCS: Yale-Brown Obsessive Compulsive Scale; OCD: Obsessive-compulsive disorder; OCPD: Obsessive-compulsive personality disorder.

The most common adverse effects of olanzapine in our samples were weight gain (2), somnolence (3), dizziness (2), dyspepsia (2), tremor (1), and constipation (1). Since the side effects were mild and well tolerated, no one dropped out owing to medication intolerance.

### Discussion

This study provides additional evidence that addition of olanzapine to ongoing SRI treatment may be efficacious for therapy-refractory OCD patients. There are, however, limitations to the data presented due to the small sample size and open-label design. In all, the results of our study are consistent with the findings of previous addition trials with risperidone and olanzapine [5-11]. Supplementing SRIs with atypical antipsychotics shows benefits, but the main problem here is that there is some inconsistency in the definition of treatment refractoriness. Most studies included patients who had failed to respond to only one SRI trial. They should rather be qualified as treatment resistant. The dilemma of deficient response is an area under discussion and merits further investigation. Furthermore, a clear criteria for no response needs to be agreed upon because frequently the standards for response rates differ to a great extent. For example, Weiss et al. [7] used a cutoff of 50% decrease in YBOCS score as responders, while Francobandiera [10] chose a cutoff of 25%. McDougle et al. [6], on the other hand, used a more restrictive criterion with a cutoff of 35% for YBOCS decrease and a final score of 16 on the YBOCS in combination with a final Clinical Global Impressions scale rating of much

improved or very much improved. Such differences nullify the comparison of effect sizes between different studies.

Atypical antipsychotics may enhance the action of SRIs through serotonin receptor blockade. The broader range of effective treatment with the addition of atypical antipsychotics may be due to a D2 blockade, or a combined serotonergic-dopaminergic blockade, particularly 5-HT2A and D2 antagonism [5]. Anyhow, addition of atypical antipsychotics to SRIs seems a promising pharmacotherapy intervention for treatment – refractory OCD patients. No doubt, further studies as regards the mechanism of action of these augmentative strategies for OCD are warranted.

### Conclusion

Treatment-refractory OCD Patients may benefit from addition of olanzapine to ongoing antidepressant therapy.

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