SRIs Augmentation with Cariprazine In Patients with Treatment Resistant Obsessive-Compulsive Disorder: A Retrospective Observational Study

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Introduction

Obsessive–compulsive disorder (OCD) has been considered for decades a chronic, poorly responsive disorder until the introduction of Serotonin Reuptake Inhibitors (SRIs); these medications are well established as first-line pharmacotherapeutic treatment for OCD across consensus guidelines. However, despite the excellent safety profile and demonstrated efficacy of SRIs, a substantial proportion of individuals with OCD fails to attain sufficient benefit. Although the proportion of patients who may be considered treatment resistant or intolerant is difficult to define, it may be approximately estimated to be between 40 and 50 percent after an adequate medication treatment trial (1). In recent years, prompted researchers to investigate possible strategies for treatment-resistant patients. One of the most studied and promising strategies, to date, is the addition of antipsychotics to SRI treatment (2 - 4). Several studies examining antipsychotic augmentation have demonstrated the efficacy of these agents in patients with treatment resistant OCD: risperidone has been reported as being the most effective in treating OCD symptoms in meta- analyses (5, 6); aripiprazole has also been shown to be effective (7, 8); quetiapine and olanzapine efficacy have been examined, although the results are inconsistent and multiple meta-analyses have been unable to demonstrate their superiority vs. placebo (5; 9 – 11); paliperidone has been studied in treatment-resistant OCD patients in one randomized, placebo-controlled trial of 8 weeks showing significant baseline to post-treatment reductions in Y-BOCS, yet between group differences did not meet the threshold for significance (12). A more recent network meta-analysis investigating different pharmacological agents used in augmentation strategies for treatment resistant OCD found that, amongst atypical antipsychotics, aripiprazole and risperidone achieved significant efficacy in Y-BOCS scores reduction (13).

Cariprazine is a partial agonist of dopamine D2/D3 receptors (with higher affinity for D3) and serotonin 5HT1A/5HT2A receptors (14).This unique receptor profile may play a role in its efficacy and tolerability and is believed to be involved in its antipsychotic, antidepressant, antianhedonic and pro-cognitive effects (15, 16). FDA has approved cariprazine as an adjunctive treatment for unipolar depression (1.5 – 3 mg/day). However, in Europe it has been approved only for schizophrenia. Given that cariprazine is a third generation antipsychotic and that it has a unique pharmacologic profile involving serotoninergic activity, it might also be effective in OCD, in combination with SRIs. Up to date there is no data regarding the use of cariprazine as an augmentation strategy in patients with OCD who failed to respond to SRI treatment. In this retrospective observational study, we show outcomes for patients with OCD who failed to respond to SRIs and were subsequently treated with low dose cariprazine ~~(CPZ)~~ as an add-on.

Material and Methods

Clinical records of inpatients and outpatients with an OCD diagnosis according to DSM-5 criteria treated in the Mental Health Department of Alba and Bra (Italy) and the Mental Health Department of Naples (Italy) from June 2022 to April 2023 were analyzed. Patients included in the analysis had to have a Yale-Brown Obsessive-Compulsive Scale (YBOCS)

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total score ≥16, had to be resistant to at least one adequate trial with a SRI (clomipramine, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), and subsequently treated with cariprazine as an add-on at a starting dose of 1,5 mg/day. There were no exclusion criteria applied. However, neither psychiatric comorbidity nor substance abuse were detected during data collection.

Treatment resistance was defined as a failure to show an improvement ≥25% at the YBOCS total score compared to the beginning of the SRI trial. The trial was considered adequate if it lasted at least 12 weeks with an adequate dose of SRIs according to American Psychiatric Association guidelines. ~~Patients underwent a twelve-week cariprazine augmentation trial. Cariprazine's starting dose was 1,5 mg/day for all patients.~~ Dosage changes were implemented according to clinical judgment (dosage variation was established in relation to efficacy and tolerability observed). ~~The SRI dose remained unchanged during add-on weeks.~~ All subjects referred to our Service signed their written informed consent to have their anonymously treated clinical data potentially used for teaching or search purposes. Written consent was also collected for off-label treatment. Socio-demographic, clinical and safety information were collected for each subject from medical reports. Patients underwent follow-up visits according to clinical judgement. All psychiatric diagnoses and clinical assessments were made by psychiatrists with several years of experience. For the purpose of this report, medical records have been analyzed at the start of cariprazine treatment and at the endpoint. Treatment response was measured by the change from baseline to final value within the 12 weeks of the study. The primary efficacy measures were the YBOCS total score and the Clinical Global Impression-Severity (CGI-S) score, which were completed at baseline and every two weeks. The percentage of patients who responded to the augmentation with cariprazine was calculated. For the purpose of the this study we considered responders patients who had an improvement ≥25% at the YBOCS total score with respect to the beginning of the addition phase. During each visit, the UKU Side Effect Rating Scale was used to record all adverse effects reported by patients or investigators. Paired t-tests were used to evaluate differences in YBOCS and CGI-S scores between baseline and the end of the 12-week trial. Significance was set at $p<0.05$. The Statistical analysis was conducted using SPSS® software version 19.

Results

Thirteen patients fulfilled the entry criteria and were eligible for the study. Table 1 shows the socio-demographic and clinical characteristics of the 13 patients included. A mean age of 40,9±15,9 years was recorded among the patients; 7 (53,8%) were female and 6 (46,2%) were male. The majority of them were married (61,5%) and were highly educated (69,2% ≥13 years). Mean age at OCD onset was 17,2±4,0 years while mean illness duration was 30,8±11,4 years.

All patients completed the 12-week open label, flexible dose phase. 10 out of 13 patients took the minimum dose (1,5 mg/die) of cariprazine; three patients took 3 mg/die. The SRI dose remained unchanged during the add-on weeks for all patients.

Patients showed significant improvement over the 12-week study period (Fig.1)(paired t-test for mean Y-BOCS total score at week 12 compared to baseline: $t=8.266$, $df=12$, $p<0.001$). When examining obsessions and compulsions subscales of the YBOCS we also found a significant improvement at week 12 compared to baseline (paired t-test for mean YBOCS obsession subscale: $t=7.015$, $df=12$, $p<0.001$; paired t-test for mean YBOCS compulsion subscale: $t=6.446$, $df=12$, $p<0.001$). Analysis of variance revealed a significant treatment effect over the 12-week trial period for time ($F=19.682$, $p<0.001$); similar results emerged for the YBOCS obsession subscale ($F=14.571$, $p=0.001$) and the YBOCS compulsion subscale ($F=15.192$, $p<0.001$). Table 2 shows the YBOCS scores of the 13 OCD subjects who completed the 12-week observational period. Examining the CGI-S score we found a significant improvement at week 12 compared to baseline (paired t-test for mean CGI-S score $t=6.008$, $df=12$, $p<0.001$); analysis of variance of CGI-S scores revealed a significant treatment effect over the 12-week trial period for time ($F=10.241$, $p=0.002$). At the end of the study eight patients (61.5%)

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met the response criteria of ≥25% improvement in YBOCS total score vs. baseline. Overall, adverse effects were reported by 11 patients (84.6%). All the side effects reported were mild. The most common adverse event recorded was a sense of inner tension which was experienced by 3 (23.1%) patients. Table 3 summarizes all adverse events that occurred in the sample.

Discussion

To the best of our knowledge, this is the first report evidencing that the addition of low doses of cariprazine to ongoing SRI treatment can improve obsessive-compulsive symptoms in patients who were resistant to SRI alone. There is only a single case report in literature describing cariprazine as an add-on to long-acting paliperidone treatment in a patient with schizophrenia who developed OCD symptoms (17). ~~With regards to efficacy measures,~~ More than two thirds of patients satisfied response criteria at the end of the 12-week study period. From a pharmacological perspective, Cariprazine is a partial agonist ~~of exerts its pharmacological action through partial agonism of~~ of dopamine and serotonin receptors, and it could be through this mechanism of action that OCD symptoms improve. ~~This could be the mechanism for ameliorating obsessive symptoms~~. Although there is a recent report in literature of cariprazine-induced OCD (18), which could be mediated by the drug interaction with D3 receptors, in our sample there was no evidence exacerbation of OCD symptoms which could be linked to cariprazine treatment.

Due to lack of data about cariprazine as augmentation strategy in patients with OCD, it is not possible to compare our findings with the existing literature. However, our responder rate of 61.5% was significantly superior to that of the other antidopaminergic agents usually found to be effective in one-third of patients with treatment-resistant OCD (19, 20). Several limitations should be considered when interpreting these results: the small sample size; the retrospective nature of the data collected; and the absence of a control group.

Nevertheless, cariprazine augmentation was well tolerated. The most common adverse event was inner tension. No severe adverse events emerged during the study; no patients discontinued treatment during the 12-week period. Most notably, only one patient showed weight gain. This aspect is in line with a recent retrospective study of electronic health reports in which cariprazine treatment revealed a neutral weight and metabolic profile (21). This is a critical issue given the significant long-term metabolic risk of atypical antipsychotic medications and the consequent increased cardiovascular risk.

In conclusion, our preliminary results suggest that cariprazine may be a potentially effective and well-tolerated SRI augmentation strategy for treatment-resistant OCD. The results of this study need to be replicated in larger, randomized controlled trials.

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Competing Interests

Authors declare no competing interests in

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Table 1: Socio-demographic and clinical characteristics of the sample

Pt	Age (yy)	Gender	Educational level (yy)	Marital Status	OCD		SRI		YBOCS		CGI-S	
					Age at onset (yy)	Duration (yy)	Type	Dose (mg/d)	baseline	end of the SRI-alone trial	baseline	end of the SRI-alone trial
1	21	F	13	married	21	23	Fluvoxamine	300	30	27	**6**	5
2	27	M	11	married	15	32	Fluvoxamine	300	32	30	**7**	6
3	55	F	13	single	19	3	Fluoxetine	60	29	24	**6**	5
4	56	F	8	single	12	25	Clomipramine	225	29	25	**6**	5
5	70	F	13	single	10	29	Escitalopram	30	32	32	**7**	6
6	36	M	13	married	17	40	Clomipramine	225	33	29	**7**	6
7	34	M	18	married	16	39	Clomipramine	225	31	30	**7**	6
8	38	M	8	married	22	32	Sertraline	200	26	23	**5**	5
9	36	F	13	single	17	30	Fluoxetine	60	33	29	**7**	6
10	21	F	13	married	25	25	Sertraline	200	28	26	**5**	5
11	27	F	13	married	16	47	Paroxetine	60	30	24	**6**	5
12	55	M	5	married	18	46	Clomipramine	225	28	26	**5**	5
13	56	M	13	single	16	29	paroxetine	60	33	31	**7**	6

OCD: Obsessive-Compulsive Disorder
YBOCS: Yale-brown Obsessive-Compulsive Scale
SRI: Serotonin Re-Uptake Inhibitor
CGI-S: Clinical Global Impression – Severity Scale

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Table 2: Efficacy results for patients with obsessive-compulsive disorder who received cariprazine as add-on therapy.

Participant	YBOCS total score			YBOCS obsessions score			YBOCS compulsions score		
	Baseline	Endpoint	Change (%)	Baseline	Endpoint	Change (%)	Baseline	Endpoint	Change (%)
1	27	20	25,9	13	8	38,5	14	12	14,3
2	30	22	26,7	15	12	20,0	15	10	33,3
3	24	18	25,0	14	10	28,6	10	8	20,0
4	25	22	12,0	13	12	7,7	12	10	16,7
5	32	23	28,1	14	11	21,4	18	12	33,3
6	29	28	3,4	15	14	6,7	14	14	0,0
7	30	22	26,7	15	11	26,7	15	11	26,7
8	23	20	13,0	12	11	8,3	11	9	18,2
9	29	20	31,0	16	12	25,0	13	8	38,5
10	26	19	26,9	11	10	9,1	15	9	40,0
11	24	16	33,3	12	9	25,0	12	7	41,7
12	26	22	15,4	13	11	15,4	13	11	15,4
13	31	21	32,3	17	13	23,5	14	8	42,9
Mean (SD)	27,4 (3,0)	21,0 (2,9)	23,1 (9,1)	13,8 (1,7)	11,1 (1,6)	19,7 (9,7)	13,5 (2,1)	9,9 (2,0)	26,2 (13,2)

YBOCS: Yale-brown Obsessive-Compulsive Scale

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Table 3: adverse events reported in patients with obsessive-compulsive disorder who received cariprazine as add-on therapy.

Adverse events	n (%)
Tension/Inner unrest	**3 (23.1)**
Sleepiness/Sedation	**2 (15.4)**
Tremor	**2 (15.4)**
Constipation	**1 (7.7)**
Headache	**1 (7.7)**
Reduced duration of sleep	**1 (7.7)**
Weight gain	**1 (7.7)**
Rigidity	**1 (7.7)**

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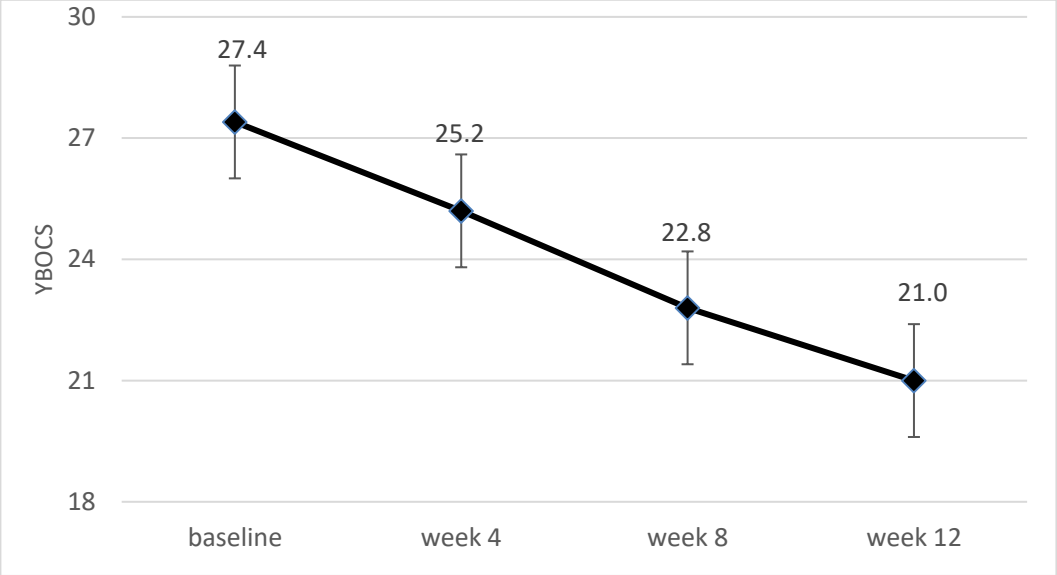
Fig. 1 Mean reduction in Yale-Brown Obsessive-Compulsive Scale (YBOCS) scores during the twelve week observation period



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