Original Article

Role of Lamotrigine Augmentation in Treatment-Resistant Obsessive Compulsive Disorder: A Retrospective Case Review from South Asia

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ABSTRACT

Background: Resistance to pharmacotherapy is one of the major challenges in the management of obsessive-compulsive disorder (OCD). OCD being a quite prevalent disorder, this resistance adds to the disability. Different strategies are being employed to counter this resistance, one of them being augmentation with glutamatergic modulators. Lamotrigine is being used for same since the recent past with mixed results. **Objective:** The aim was to study the role of lamotrigine augmentation in serotonin reuptake inhibitor (SRI) resistant OCD patients. **Methodology and Results:** This study was carried by studying the case sheets of SRI resistant cases having already completed the treatment. A total of 22 cases sheets over 2 years met the study criteria with a mean age of mean age of 34.14 years. Over a period of 16 weeks, with a mean lamotrigine dose of 150 mg/day, 20 out of 22 patients had shown a significant response. The mean decrease in Yale-Brown Obsessive Compulsive Scale score was 67.23% with a baseline score of 28.87. There was a similar change on different domains of World Health Organization quality of life ($P = 0.00564$). **Conclusion:** Lamotrigine augmentation to on-going treatment with SRIs may be an effective move in case of SRI resistant OCD patients.

Key words: *Augmentation, lamotrigine, obsessive-compulsive disorder, serotonin reuptake inhibitor resistance*

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a chronic, disabling disorder affecting 2-3% of the general population.[1] Serotonin reuptake inhibitors (SRIs) which include clomipramine and selective SRIs (SSRIs), are being considered the first line of pharmacological treatment in this disorder as is supported by the literature.[2-4] However, the majority (40-50%) of patients are resistant to this mono-therapeutic treatment approach which poses a major issue in the management of OCD.[5] Current options for such treatment-resistant OCD include switching to an alternative SSRI or augmentation with dopamine antagonists or other agents or cognitive-behavioural therapy.[6] When such options are not suitable, available or effective, augmentation of the on-going SSRI with another compound represents the preferable strategy.[5]

Apart from the monoaminergic dysfunction that forms the basis of present day treatments in OCD, several evidences suggest that abnormalities of other neurotransmitters may have a role in the pathophysiology of OCD. Evidence from genetic, behavioral, and neuroimaging studies have shown the abnormally high glutamatergic concentrations in caudate nucleus of patients in OCD.[7] Moreover this

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evidence has led to the hypothesis that glutamate modulating drugs may be a suitable treatment option for patients with SRI-resistant OCD.[8,9]

Lamotrigine, an antiepileptic drug and a mood stabilizer, also having anti-glutamanergic properties has been occasionally has been occasionally used in OCD treatment.[10] Two small open studies used lamotrigine for treating obsessive symptoms, one in schizophrenia and another in bipolar disorder.[11,12] A small open study of augmentation of SRIs with 100 mg/day of lamotrigine in eight patients reported negative results.[13] A case report of lamotrigine augmentation using up to 150 mg/day in a patient with a stable dose of clomipramine (225 mg/day) described a remarkable improvement.[14] A 16 weeks double-blind, randomized, and placebo-controlled trial of lamotrigine augmentation (up to 100 mg/day) in patients receiving SSRIs has shown positive results at large.[15]

To the best of our knowledge, there is no study from South Asia contesting the role of lamotrigine augmentation in SRI resistant OCD. With this aim in mind and the recent data showing an association between decreased caudate glutamatergic concentrations and a reduction in OCD symptoms, we initiated an investigation of adjunctive lamotrigine in treatment-resistant OCD.

MATERIALS AND METHODS

The study included a retrospective chart review of a consecutive series of patients over a period of 2 years diagnosed with Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) OCD, and was treated at the Department of Psychiatry, Government Medical College, Srinagar, Jammu and Kashmir, India. Only those case sheets were reviewed, which were complete and met the requirements of the review. All patients were evaluated by a consultant psychiatrist using a semi-structured clinical interview for DSM-IV diagnosis to determine Axis I diagnoses. Patients were considered to be treatment-resistant if they were nonresponsive or partially responsive to an adequate trial (14 weeks) of open, flexible-dose treatment of an SRI at maximal doses (fluoxetine 80 mg/day, paroxetine 60 mg/day, fluvoxamine 300 mg/day, clompiramine 250 mg/day, or sertraline 200 mg/day) or to highest dose tolerated.[15]

Patients having any other primary Axis I psychiatric diagnosis were not included in this review; that is, OCD must be the disorder that caused the most disability and impairment to the patient. Patients taking concurrent benzodiazepines, antipsychotics, sedative hypnotics, or antidepressant medications were not excluded from this case series provided that they had been on a stable dose of these medications for at least 8 weeks prior, and had not changed the dose of the concurrent medication over the course of the treatment period. Lamotrigine was started at dose of 25 mg/day and gradually increased to 200 mg by 8 weeks with weekly increment of 25 mg. The SRI was continued, and the doses were changed minimally were needed. Lamotrigine was stopped in some patients owing to the development of rash. In total 22 patients who had completed follow-up for a minimum of 16 weeks were assessed for this study. This study included in-patients as well as out-door patients.

The progress of symptoms was assessed using Yale-Brown Obsessive Compulsive Scale (YBOCS) symptom checklist and severity rating scale which is a 10 item scale with scores varying from 0 to 4 for each item with a high validity and reliability.[16]

The general wellbeing and quality-of-life (QoL) was assessed using the World Health Organization (WHO)-QoL (BREF version). The WHO-QoL (BREF version) is a 26-item self-administered questionnaire, which emphasizes the subjective responses of patients in physical, psychological, environmental and social domains. The score for each domain was computed on a 0-100 scale. The psychometric property is comparable to that of the full version of WHO-QoL.[17]

The data were tabulated, and the individual results of the cases were studied statistically. Mean/average and the deviations were calculated using the latest version of Statistical Package for Social Sciences. Chi-square tests were applied to study the change in scores. Statistical significance was set at $P < 0.05$.

RESULTS

Twenty-two patients met the selection criteria, having a complete follow-up with fully maintained case sheets along with relevant rating scales. The sample included 14 males and 6 females with a mean age of 34.14 ± 5.66 years (22-52 years). The mean duration of illness was 15.82 ± 5.87 years (5-30 years). Before the initiation of lamotrigine, the mean YBOCS score was 28.87 suggesting a severely ill state of most of these patients [Table 1]. This was further evident from the mean baseline score of the different domains of WHO-QoL viz., 51.77, 51.45, 53.95, 56 for physical, psychological, social, environmental respectively [Table 2]. Other variables, treatment history and treatment response, are noted in Table 1.

All the patients were treated at least 16 weeks of lamotrigine augmentation among whom twenty showed a significant response and two of them did not respond. A significant change of more than 60% was seen both

Table 1: Clinical profile and YBOCS score

Patient	Age	Sex	Duration of illness (years)	Number of failed SRI trials	Lamotrigine dose (mg/day)	YBOCS score at 0 week	YBOCS score 4 weeks	YBOCS score 8 weeks	YBOCS score 12 weeks	YBOCS score 16 weeks
1	40	Female	20	2	100	35	35	30	18	12
2	27	Male	10	2	150	32	30	26	17	11
3	32	Male	15	3	150	28	27	20	15	10
4	38	Male	14	4	200	26	26	18	12	8
5	42	Female	22	2	150	27	23	16	11	6
6	32	Male	17	3	100	27	24	16	11	7
7	27	Male	13	2	150	32	30	24	16	10
8	42	Male	22	4	100	24	23	19	15	10
9	45	Female	23	3	150	33	30	23	17	11
10	28	Female	12	1	200	26	24	18	12	6
11	27	Male	13	1	200	27	25	19	13	6
12	32	Male	14	2	100	24	21	16	11	5
13	34	Male	16	3	200	32	29	24	20	20
14	47	Male	24	5	150	29	27	20	16	11
15	22	Male	5	2	200	32	28	20	14	9
16	52	Female	30	4	200	34	30	22	16	7
17	25	Female	7	2	100	30	28	22	14	9
18	29	Male	11	2	150	25	22	16	10	6
19	34	Male	14	1	150	32	30	27	25	24
20	32	Male	16	1	100	30	28	20	16	9
21	31	Male	14	2	150	26	24	17	10	6
22	33	Male	16	1	150	24	21	16	11	5
Mean	34.14		15.82	2.37	150	28.87	26.60	20.41	14.55	9.46
SD	5.66		5.87	1.13	37.80	3.48	3.60	3.96	3.64	4.63

YBOCS – Yale-Brown obsessive compulsive scale; SD – Standard deviation; SRI – Serotonin reuptake inhibitors

Table 2: WHO-QoL scores

Patient	WHO-QOL score at week 0 (domain wise)				WHO-QOL score at week 16 (domain wise)			
	Physical QoL on 0-100 scale	Psychological QoL on 0-100 scale	Social QoL on 0-100 scale	Environmental QoL on 0-100 scale	Physical QoL on 0-100 scale	Psychological QoL on 0-100 scale	Social QoL on 0-100 scale	Environmental QoL on 0-100 scale
1	38	44	31	44	75	81	75	88
2	44	44	44	50	81	88	94	94
3	50	56	56	56	88	88	81	94
4	56	50	56	56	81	94	94	88
5	63	56	69	63	88	94	94	88
6	56	56	56	56	81	94	88	94
7	63	63	69	63	75	81	88	75
8	50	50	56	56	88	94	81	81
9	38	44	44	56	81	75	88	81
10	56	50	56	56	88	81	81	94
11	44	50	56	50	81	75	81	88
12	56	44	44	63	75	81	88	88
13	50	56	69	63	75	63	69	69
14	56	50	56	56	75	88	81	88
15	56	50	56	56	81	81	88	94
16	44	44	44	50	88	94	88	81
17	50	56	56	63	88	94	94	81
18	56	50	56	63	75	81	88	88
19	44	50	56	56	63	75	69	69
20	50	56	44	50	75	88	88	88
21	63	63	69	50	88	81	88	94
22	56	50	44	56	81	88	75	81
Mean	51.77	51.45	53.95	56	80.50	84.50	84.59	85.72

QoL – Quality of life; WHO – World health organization

in YBOCS and WHO-QoL (P = 0.00564) [Table 3]. The endpoint mean score for YBOCS was 9.46 and the mean score for physical, psychological, social and environmental domains of WHO-QoL was 80.50, 84.50, 84.59 and 85.72, respectively. Both YBOCS and WHO-QoL showed a significant improvement in overall state of health of these patients.

The mean time for responders to achieve a 25% reduction on YBOCS score was 9.2 ± 2.2 weeks at a mean dose of 150 mg/day of lamotrigine. The mean dose of lamotrigine at endpoint was 150 ± 37.8 mg/day, with a dose range of 100-200 mg/day with a 67.23% decline in YBOCS score with 20 (out 22) patients showing a full response of more than 35% reduction in scores.

Augmentation of lamotrigine was carried on the different SRIs, which included fluvoxamine, sertaline, clomipramine and escitalopram, but due to the small number of subjects, statistical analyses were not feasible to evaluate differences between subgroups. The combination of lamotrigine-SRIs was generally well-tolerated. A few adverse effects were documented which included headache (three patients), sedation (four patients), fatigue (one patient), and benign skin rash (one patient). These effects were generally mild and transient and did not force discontinuation.

DISCUSSION

This case series provides a basic evidence for the potential effectiveness of lamotrigine augmentation in patients with OCD who are refractory to standard SRI therapy. There are, however, obvious limitations to the presented data, including a retrospective case series design, small sample size, and reliance on case sheets. However, the use of a specific scale for OCD (YBOCS), WHO-QoL and continuous follow-up make a strong case to bet on its results.

The results obtained from the present study indicate that lamotrigine added to stable SRIs treatment substantially improved obsessive-compulsive symptoms in patients who were resistant to SRI alone. A mean 67.23% reduction in YBOCS total score was observed at the end of 16 weeks of adjunctive lamotrigine. The rate of responders in our sample was 90.9% when the response criterion of 25% improvement or greater in YBOCS total score was considered; a full response (>35% YBOCS total score reduction) was also observed in the same percentage. The percentage of full responders was more than observed in previously conducted studies.[11,15] The probable reasons of this high response was higher dose of lamotrigine used for a longer duration of time than in the previous attempts. However, a trial of eight patients with OCD refractory to SRI treated with adjunctive lamotrigine, had not shown benefit.[13] However, this negative result could be due to the low doses of lamotrigine used in that study.

There is some evidence that glutamate dysregulation and the subsequent glutamanergic modulation by lamotrigine may explain this therapeutic relationship. There are similar evidences with regard to efficacy of other glutamanergic modulators such as riluzole and topiramate in the management of refractory OCD.[8,18,19] Further the augmenting role of lamotrigine by glutamanergic modulation is supported indirectly by the fact that SRIs may indirectly attenuate glutamatergic activity through inhibitory effect of serotonin on corticostriatal glutamate release.[9]

The clinical phenomenology of OCD in these resistant cases could provide another plausible explanation of this therapeutic benefit. As was observed by authors, features such as diurnal variation in symptom severity, family history of mood disorder, rapid mood changes, rapid popping out from severe illness and predominance of religious and blasphemous obsessions. The response at bipolar doses of lamotrigine further points toward the affect of some of these clinical features in this response-relationship. However, this needs to be studied separately and at a wider clinical sample.

Our study provides evidence that the lamotrigine augmentation to on-going treatment with SRIs may be a beneficial strategy for SRI resistant OCD patients. The mechanism behind this anti-obsessional activity looks likely to be multi-pronged synergistic action on neurotransmitter systems involved in obsessional symptoms.[20] However, these results may be interpreted cautiously in view of weakness and strengths already discussed.

Table 3: Change in severity scores

Mean score	Baseline score 0 week	Final score 16 weeks	Percentage change	*P*
Mean YBOCS score at baseline	28.87	9.46	–67.23	0.00564
Physical QoL on 0-100 scale	51.77	80.50	64.31	
Psychological QoL on 0-100 scale	51.45	84.50	60.89	
Social QoL on 0-100 scale	53.95	84.59	63.78	
Environmental QoL on 0-100 scale	56	85.72	65.33	

YBOCS – Yale-Brown Obsessive Compulsive Scale; QoL – Quality of life

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