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Lamotrigine augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive–compulsive disorder: a double-blind, placebo-controlled study

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Abstract

The present 16-week double-blind, randomized, placebo-controlled trial had the aim to explore the efficacy of lamotrigine add-on pharmacotherapy on clinical symptomatology and cognitive functioning in a sample of patients with treatment-resistant obsessive–compulsive disorder (OCD) receiving serotonin reuptake inhibitors (SRIs). After clinical and neurocognitive assessments, patients were randomly allocated to receive, in a double-blind design, 100 mg/day of lamotrigine or a placebo. A final sample of 33 patients completed the study. The results obtained indicate that lamotrigine added to stable SRI treatment substantially improved obsessive–compulsive (Yale–Brown Obsessive Compulsive Scale: obsessions, $p < 0.0001$; compulsions, $p < 0.0001$; total score, $p < 0.0001$), and affective symptoms (Hamilton Rating Scale for Depression $p < 0.0001$). Regarding cognitive functions, improvement was observed only in Semantic Fluency ($p = 0.004$). The findings provide evidence that lamotrigine augmentation of SRI treatment is well tolerated and may be proposed as an effective therapeutic strategy to improve outcome in treatment-resistant OCD.

Keywords

Cognitive functions, lamotrigine, obsessive–compulsive disorder, serotonin reuptake inhibitors

Introduction

Serotonin reuptake inhibitors (SRIs), which include clomipramine and selective serotonin reuptake inhibitors (SSRIs), employed in the maximum-tolerated doses for at least 10–12 weeks, are considered first-line pharmacological treatments for patients with obsessive–compulsive disorder (OCD) (Bandelow et al., 2008; Baldwin et al., 2005; Fineberg and Gale, 2005; March et al., 1997), a chronic, disabling disorder affecting 2–3% of the general population (Koran, 2000). Nevertheless, up to 40–60% of patients with OCD do not respond to SRI monotherapy, with some patients showing a substantial degree of residual symptomatology (Goodman, 1999; Pallanti and Quercioli, 2006). In general, treatment options for patients who incompletely respond to a particular agent include switching to a different SRI, or augmenting the given medication with an additional drug of a different class. Augmentation strategies largely consist of the use of atypical antipsychotics (Bloch et al., 2006; Fineberg et al., 2006; Gao et al., 2006; Goodwin et al., 2009), with positive evidence for risperidone, olanzapine, quetiapine, and aripiprazole (D'Amico et al., 2003; McDougle et al., 2000; Muscatello et al., 2011; Vulink et al., 2009). Notwithstanding, the emergence or exacerbation of obsessive–compulsive symptoms in patients with a primary diagnosis of psychosis treated with atypical antipsychotics has been described (de Haan et al., 2002; Lykouras et al., 2003).

The use of anticonvulsants as augmenting agents in the treatment of OCD has also been investigated in few trials involving sodium valproate (Deltito, 1994), carbamazepine (Iwata et al., 2000), gabapentin (Cora-Locatelli et al., 1998), and oxcarbazepine (McMeekin, 2003).

Beyond the hypothesis of a monoaminergic dysfunction that underlies established treatments in OCD (Zohar and Kindler, 1992), several lines of evidence suggest that abnormalities of glutamate neurotransmission in the cortico-striatothalamo-cortical circuitry may have a role in the pathophysiology of OCD. Magnetic resonance spectroscopy (MRS) studies evidenced abnormal Glx measurements in OCD, where 'Glx' is an aggregate measure reflecting levels of glutamate, glutamine, homocarnosine, and GABA (Ross, 1991); In particular, Glx was increased in

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the striatum of patients with OCD, and this increase has been shown to normalize in those subjects with OCD who respond to treatment with SRI medications (Rosenberg et al., 2000). Interestingly, reduced Glx levels in the anterior cingulated in subjects with OCD have been found, thus suggesting an inverse relationship between anterior cingulate and basal ganglia activity in patients with OCD (Rosenberg et al., 2004). Moreover, significantly elevated cerebrospinal fluid glutamate levels were found in subjects with OCD compared with controls (Chakrabarty et al., 2005). As suggested by Greenberg et al. (2000), who demonstrated an increased cortical excitability in subjects with OCD by using transcranial magnetic stimulation, either increased glutamatergic tone or reduced GABA activity in the cortex may have a role in modifying the excitatory–inhibitory balance in the cortex.

Both preclinical data (Simon and Gorman, 2006) and clinical observations support the hypothesis of a glutamatergic dysfunction in those brain regions that are thought to be involved in the pathophysiology of OCD. Consequently, it has been hypothesized that several drugs whose mechanism of action lies in the modulation of glutamate neurotransmission may be a suitable treatment option for patients with SRI-resistant OCD (Coric et al., 2005; Pittenger et al., 2006).

Lamotrigine, an anticonvulsant drug, stabilizes presynaptic neuronal membranes, reducing excessive glutamate release via inhibition of axonal voltage-gated sodium and calcium channels (Burstein, 1995). Evidence concerning the use of lamotrigine as an augmenting agent in OCD treatment is still sparse and conflicting. In a 4-week case series of eight patients with OCD who previously failed to respond to SSRIs, lamotrigine add-on at the maximum dose of 100 mg/day only benefited one patient (Kumar and Khanna, 2000).

It should also be noted there have been case reports for lamotrigine potentially causing obsessive–compulsive symptoms, blepharospasm, and tourettism in a patient with major depression (Alkin et al., 2007), and, in two patients affected by bipolar II disorder, intrusive, repetitive phrases (Kemp et al., 2007), and obsessional symptoms (Kuloglu et al., 2008), respectively. More recently, an 8-week, open-label trial evaluated the efficacy and tolerability of lamotrigine in schizophrenia and schizoaffective patients with comorbid obsessive–compulsive symptoms (Poyurovsky et al., 2010). Lamotrigine up to 200 mg/day (starting dose: 25 mg/day) was added to ongoing psychotropic drugs in schizophrenia ($n = 5$) and schizoaffective disorder ($n = 6$) patients with clinically significant obsessive–compulsive symptoms (Yale–Brown Obsessive-Compulsive Scale (Y-BOCS) score > 16). At the end of the trial, five patients, all with schizoaffective disorder, showed a ≥ 35% a decrease in Y-BOCS total score; a significant improvement in depressive symptoms, assessed with the Calgary Depression Scale for Schizophrenia, was also observed. The beneficial effect of lamotrigine (up to 150 mg/day) added to a stable dose of clomipramine (225 mg/day) in a patient with treatment-resistant OCD was also reported (Uzun, 2010).

Regarding cognitive functioning, lamotrigine was less commonly associated with the cognitive impairment observed with many other anticonvulsants (Aldenkamp and Baker, 2001), even in older adults (Chung et al., 2009). Moreover, the glutamatergic-attenuating effect of lamotrigine may have the potential to improve cognitive function related to motor response inhibition problems (Anand et al., 2000). A functional magnetic resonance imaging study designed to examine lamotrigine effect on brain circuitry function underlying response inhibition in bipolar patients showed that lamotrigine monotherapy enhanced prefrontal and temporal lobe activity during a response inhibition task (Pavuluri et al., 2010). To the best of our knowledge, no double-blind, placebo-controlled trials have been performed to examine the clinical effect of lamotrigine augmentation in patients with OCD demonstrating a sub-optimal response therapeutic response to SRIs alone.

Based on evidence from the literature, the present study was aimed to test whether or not lamotrigine would be more effective than placebo on clinical symptomatology and cognitive functioning in a sample of patients with OCD who had not responded or not fully responded to SRI treatment alone.

Methods

Subjects

The study was carried out at the Psychiatry Unit of the University Hospital of Messina, Italy. Outpatients who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision criteria (American Psychiatric Association, 2000) for OCD and demonstrated persistent obsessive–compulsive symptoms despite an adequate trial with an SRI (American Psychiatric Association, 2007) for at least 12 weeks were considered for an augmentation trial with lamotrigine. Eligible subjects had to have a Y-BOCS total score of 16 or greater (Goodman et al., 1989a, 1989b).

All patients were diagnosed as having OCD as their primary disorder by a senior psychiatrist using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Axis I disorders (Spitzer et al., 1995).

Dosages of SRIs had been stable for at least 2 months before the study and were left unchanged throughout the study. During the study, no additional medications were allowed. Patients with any other major psychiatric disorder, significant concurrent medical illnesses, organic brain disorder, or history of substance and alcohol abuse, mental retardation and pregnant or lactating women were excluded. Patients were also excluded if they received concomitant specific psychotherapies.

All the patients provided written informed consent after a full explanation of the protocol design, which had been approved by the local ethics committee. The patients were recruited from February 2010, and the follow-up was completed by January 2011.

Study design

This trial was a 16-week, double-blind, randomized, placebo-controlled trial of adjunctive fixed-doses of lamotrigine to SRI therapy in OCD. After baseline evaluation, patients fulfilling inclusion criteria were randomly assigned to receive adjunctive treatment with either lamotrigine or placebo under double-blind conditions. The allocation to parallel groups was determined by pre-randomized codes generated by a computer. Coded treatments were allocated sequentially to subjects in order of their registration for the trial. During the study, the randomization list was held securely and none of the research personnel, who enrolled, assessed, and treated the patients, were aware of the patient assignments until the study was concluded. Lamotrigine and placebo were dispensed in identical-appearing capsules; patients randomized to placebo took the same number of capsules as those assigned to lamotrigine.

The dose of lamotrigine was increased from 25 mg/day to 100 mg/day at week 4, in increments of 25 mg/week. This dosage was maintained until the end of the trial at week 16; the maximum dose of 100 mg per day was established according to Kumar and Khanna (2000). Plasma levels of lamotrigine have not formally assessed; the US prescribing information (Prescribing information: Lamictal®) states that a therapeutic plasma concentration range has not been established for lamotrigine.

Treatment response was measured by the change from baseline to final value at week 16 of the study. The following instruments were used as primary efficacy measures: Y-BOCS (Goodman et al., 1989a, 1989b), Clinical Global Impression-Severity (CGI-S) (Guy, 1976), and Hamilton Rating Scale for Depression (HDRS) (Hamilton, 1960). Response to lamotrigine was defined as clinical improvement in the obsessive–compulsive component (> 25% decrease in the total Y-BOCS score).

Neurocognitive functioning was assessed with the Wisconsin Card Sorting Test (WCST) (Heaton et al., 1993), a measure of executive functions (for example, cognitive flexibility, maintenance of a cognitive set, working memory); the Verbal Fluency Task-Controlled Oral Word Association Test (Spreen and Benton, 1977), a test of verbal productivity and intactness of the lexical system; and the Stroop Colour–Word Test (Trenerry et al., 1989). Measures of performance on WCST included the number of completed categories and the number of perseverative errors.

Both clinical ratings and neurocognitive tasks were administered by psychiatrists with at least 5 years of experience in the treatment of anxiety and mood disorders and well versed in the use of neuropsychological instruments.

Patients attended seven visits: initial screening (week -1), randomization (week 0), and five further visits at weeks 2, 4, 8, 12, and 16. Data for clinical and neurocognitive assessments were collected at weeks 0 and 16; the design of inter-test intervals has been chosen with the aim of reducing possible sources of bias that may affect a person's performance on executive and cognitive tasks, such as procedural learning or practice effects. Practice effects are defined as increase in a subject's test score from one administration to the next; common causes of practice-induced score gains are recall effects, procedural learning, reduced anxiety in or growing familiarity with the testing environment (Bartels et al., 2010; Goldberg et al., 2007). Regarding the different cognitive domains, executive functions showed highest score increases over time as a result of a higher repetition rate or the use of less alternate forms (Bartels et al., 2010).

Adverse effects, either observed or spontaneously reported, were recorded at each visit and classified in terms of onset, duration, severity, action taken, and outcome. Electrocardiogram and laboratory tests, including haematology, clinical chemistry, and urine analysis, were performed on admission and at the end of adjunctive treatment. Blood pressure, heart rate, and body weight were measured at all study visits.

Statistical analysis

Prior to the start of the study, sample size was calculated to allow detection of a 30% difference in improvement between lamotrigine and placebo. Under the assumption of a significant level of 0.05 with a power of 0.80, a minimal sample size of 34 with 17 subjects in each group was determined. Estimating a drop-out rate of 20%, we decided to recruit 20 participants for each group.

Data obtained from the study underwent check and quality control and, subsequently, descriptive and inferential statistical analysis. An intention-to-treat analysis with last-observation-carried-forward (LOCF) was performed. Continuous data were expressed as mean ± SD: comparison between the groups at baseline and at end of weeks was performed using the Mann–Whitney *U* test for two independent samples; the within-group differences in efficacy ratings between baseline and final test were analysed by the Wilcoxon rank sum test. To measure the magnitude of a treatment effect, effect size was provided by using Cohen's *d* statistic, which gives a measure of the standardized differences in the mean values of change in scores between medication. Non-continuous data were expressed as percentages, and the comparison between the two groups was performed by using the Chi-Square test. Taking into account that multiple correlations increase the risk of Type 1 errors, a Bonferroni correction was applied, and a significance value of $p < 0.005$ was chosen. The statistical analysis was performed with SPSS 16.0 software (SPSS Inc, Chicago, IL, USA).

Results

In all, 40 outpatients, 16 men and 24 women, aged 22–69 years, fulfilled inclusion criteria and were eligible for the study. The baseline characteristic, the duration of SRIs prior treatment, SRI type and daily dose in lamotrigine and placebo groups are detailed in Table 1. A total of 33 patients completed the study (82.5% completion rate); discontinuation rates were 15% for lamotrigine and 20% for placebo. There were seven premature dropouts, three in the lamotrigine group and four in the placebo group. Of the lamotrigine group, two dropouts were due to non-compliance, and one to the development of a skin rash. Among a total of four dropouts in the placebo group, two were due to non-compliance with the visits and two withdrew due to a subjectively assessed lack of efficacy.

Tables 2 and 3 show the baseline and final values of the different efficacy variables for the lamotrigine and the placebo groups. At the baseline visit (day 0), there were no significant differences between active and control groups on Y-BOCS, HDRS, CGI-S, Stroop test, verbal fluency, and WCST scores. At endpoint (week 16), significant differences between groups emerged at Y-BOCS obsession, compulsion, and total scores, significantly improved in the lamotrigine group but not in the placebo group. Concerning CGI-S scores in completers, a significant improvement was seen in the lamotrigine group ($\chi^2 = 20.065$, $p < 0.0001$) at the end of the study. Regarding cognitive performances, no significant differences between lamotrigine and control groups were found during the study.

In the active group, the within-group comparison revealed that lamotrigine augmentation of SRIs significantly reduced obsessive, compulsive, and affective symptoms, as evidenced by changes on Y-BOCS (obsessions, $p < 0.0001$; compulsions, $p < 0.0001$; total score, $p < 0.0001$) and HDRS ($p < 0.0001$) scores at the end of the trial (week 16) (Figure 1).

At the end of the study, the decrease in the Y-BOCS score in the lamotrigine patients showed a mean reduction of 32.6% (SD = 18.2). In particular, 17 patients (85%) met response criteria of 25% improvement or greater in Y-BOCS total score versus baseline. Ten of them (50% of the lamotrigine group) had a reduction between 25% and 34%, which could be defined as partial response,

Table 1. Demographic and clinical characteristics of the OCD groups (Lamotrigine vs Placebo).

	Lamotrigine	Placebo
Patients entered (completers)	20 (17)	20 (16)
Sex (M/F)	7/13	9/11
Age (years), mean ± SD[a]	34.2 ± 10.3	38.5 ± 11.3
Duration of illness (years), mean ±SD[a]	6.1 ± 2.3	5.8 ± 2.6
Duration of prior SRIs treatment (weeks), mean ±SD[a]	16.4 ± 3.8	17.5 ± 3.2
Antidepressant (Dose Range – mg/d)	***n***	***n***
Fluvoxamine (200–300 mg/d)	5	4
Fluoxetine (40–80 mg/d)	3	4
Sertraline (100–200 mg/d)	5	4
Citalopram (40–60 mg/d)	3	3
Paroxetine (40–60 mg/d)	4	5

[a]Mann–Whitney *U* test: N.S

Table 2. Clinical changes in patients with OCD receiving Lamotrigine versus placebo at baseline and week 16 (LOCF).

	Lamotrigine (*n*=20)		Placebo (*n*=20)		Mann–Whitney *U* test			
	Baseline Mean (SD)	16 Week Mean (SD)	Baseline Mean (SD)	16 Week Mean (SD)	Difference at Baseline		Difference at 16 Week	
Y-BOCS								
Obsessions*	13.80 (4.1)	9.35 (4.8)	12.20 (3.6)	13.20 (3.4)	144.000	0.134	94.000	0.004
Compulsions**	12.85 (3.8)	8.30 (5.5)	13.35 (2.1)	12.75 (2.3)	178.500	0.565	72.000	<0.0001
Total score***	26.65 (7.5)	17.65 (9.7)	25.65 (5.3)	25.95 (5.1)	179.500	0.583	91.500	0.003
HDRS‡	17.55 (5.8)	11.75 (5.5)	15.70 (7.1)	14.60 (6.8)	153.500	0.211	151.500	0.192
CGI Severity Scale[a]	*n* (%)	*n* (%)	*n* (%)	*n* (%)	Chi-square Test			
Normal	–	–	–	–				
Borderline	–	–	–	–				
Mildly	–	10 (58.8)	–	–	χ^2 = 1.664		χ^2 = 20.065	
Moderately	10 (58.8)	7 (41.2)	6 (37.5)	6 (37.5)	df = 2		df = 3	
Markedly	5 (29.4)	–	8 (50)	8 (50)	*p* = 0.435		*p* = <0.0001	
Severely	2 (11.8)	–	2 (12.5)	2 (12.5)				
Extremely	–	–	–	–				

[a]Observed cases (Lamotrigine group *n* = 17; Placebo group *n* = 16). Wilcoxon rank sum test: **Z* = –3.637 / *p* ≤ 0.0001, ***Z* = –3.663 *p* ≤ 0.0001, ****Z* = –3.655 / *p* ≤ 0.0001, ‡*Z* = –3.645 / *p* ≤ 0.0001.

Table 3. Cognitive functions at baseline (t0) and at week 16 in OCD patients receiving Lamotrigine versus placebo (LOCF).

	Lamotrigine (*n*=20)		Placebo (*n*=20)		Mann-Whitney U-test			
	Baseline Mean (SD)	16 Week Mean (SD)	Baseline Mean (SD)	16 Week Mean (SD)	Difference at Baseline		Difference at 16 Week	
Stroop test	46.20 (14.8)	43.10 (13.9)	46.10 (15.4)	44.50 (13.8)	194.500	0.883	173.500	0.478
Phonemic fluency	22.30 (7.8)	24.80 (8.7)	22.05 (10.4)	24.95 (9.1)	198.500	0.968	193.500	0.862
Semantic fluency*	35.30 (8.1)	38.90 (6.6)	40.20 (9.5)	40.55 (6.9)	131.500	0.063	173.000	0.478
WCST								
Perseverative errors	17.40 (11.7)	12.95 (9.1)	22.95 (20.2)	19.45 (19.4)	145.000	0.142	149.000	0.174
Categories	4.55 (1.3)	4.95 (1.1)	4.60 (1.7)	4.90 (1.6)	191.000	0.820	197.500	0.947

Wilcoxon rank sum test: **Z* = -2.918 / *p* = 0.004

whereas seven of them (35% of the lamotrigine group) had a reduction of 35% or greater in Y-BOCS total score, corresponding to a full response, according to the stages of response proposed by Pallanti and Quercioli (2006).

Conversely, in the placebo group, eight patients (40%) worsened on Y-BOCS total score versus baseline, eight patients (40%) remained unchanged, and only four patients (20%) improved on Y-BOCS total score; nevertheless, none of the patients met response criteria of 25% improvement or greater in Y-BOCS total score versus baseline.

With regard to cognitive functioning, as measured by Stroop test, verbal fluency and WCST, lamotrigine augmentation of SRIs significantly improved Semantic Fluency ($p = 0.004$) at week 16.

Table 4 presents the differences in both the symptom improvement and the magnitude of the treatment effect between the lamotrigine treatment and placebo group. Lamotrigine was significantly associated with greater reduction than placebo in Y-BOCS domains 'Obsession' ($p < 0.0001$), 'Compulsion' ($p < 0.0001$) and total score ($p < 0.0001$), and HDRS total score ($p < 0.0001$); on the contrary, no significant difference was observed between the two groups in mean change scores of Stroop test, verbal fluency, and WCST.

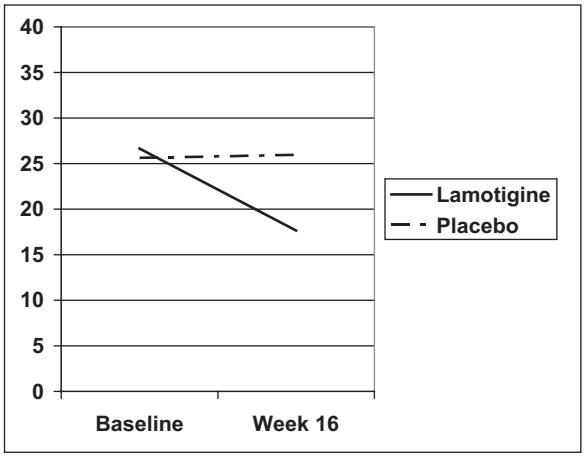

Figure 1. Y-BOCS Total scores from lamotrigine ($n = 20$) and placebo ($n = 20$) groups during the course of the study.

Regarding the augmentation effect of lamotrigine on the different SRIs, due to the small number of subjects, no statistical analyses were conducted to evaluate differences between subgroups.

The combination of lamotrigine–SRIs was generally well tolerated. The most common adverse effects in the lamotrigine group were sedation (four patients, 20%), fatigue (two patients, 10%), headache (two patients, 10%), and skin rash (one patient, 5%). These effects were generally mild and transient; regarding the patient who had the skin rash, this side-effect regressed after lamotrigine suspension. No clinically significant changes in blood pressure, heart rate, respiratory rate, or temperature were recorded, and no acute extrapyramidal effects, seizures, or cardiac events occurred. Seven of 16 patients experienced at least one adverse effect while receiving placebo. These included nausea ($n = 3$), headache ($n = 2$), and sedation ($n = 2$).

Discussion

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. Lamotrigine was significantly more efficacious than placebo in reducing obsessive–compulsive symptoms, as measured by changes on the Y-BOCS total score and subscores. A mean 38.3% reduction in Y-BOCS total score was observed at the end of 16 weeks of adjunctive lamotrigine. The rate of responders in our sample was 100% when the response criterion of 25% improvement or greater in Y-BOCS total score was considered; a full response (> 35% Y-BOCS total score reduction) was observed in 41.2% of the active sample. The rate of full responders is lower than that observed in the 8-week open-label trial by Poyurovsky et al. (2010) in which 200 mg/day final dose of lamotrigine was added to stable ongoing psychotropic drug regimens in patients affected by schizophrenia or schizoaffective disorder with obsessive–compulsive symptoms. The improvement in symptom severity was also evident from changes in CGI-S scores during lamotrigine treatment. On the contrary, in placebo-treated patients no significant changes obsessive–compulsive symptoms were observed. Regarding neurocognitive functions, only Semantic

Table 4. Significance of change during the study period and effect sizes for efficacy measures.

	Lamotrigine (n=20)	Placebo (n=20)		
Efficacy Measures	Change, Mean (SD)	Change, Mean (SD)	p-value[a]	Cohen's d
Y-BOCS				
Obsessions	−4.5 (3.2)	1.0 (1.3)	< 0.0001	2.2
Compulsions	−4.3 (2.9)	−0.6 (1.5)	< 0.0001	1.6
Total score	−8.0 (4.1)	0.3 (2.5)	< 0.0001	2.4
HDRS	−5.8 (4.6)	−1.2 (2.2)	< 0.0001	1.3
Stroop test	−3.1 (12.6)	−1.6 (6.6)	1.000	0.1
Phonemic fluency	2.1 (6.6)	2.9 (3.9)	1.000	0.1
Semantic fluency	3.6 (4.9)	0.3 (6.8)	0.121	0.5
WCST				
Perseverative errors	−4.4 (12.2)	−4.5 (6.8)	0.925	0
Categories	0.4 (1.4)	0.4 (0.7)	0.862	0

[a]Mann–Whitney U test

Fluency, a subtest of the Verbal Fluency Task, significantly improved after lamotrigine treatment, at week 16. To the best of our knowledge, there are no clinical studies addressing the effects of lamotrigine on cognitive functions in obsessive–compulsive patients, whereas cognitive-enhancing effects of lamotrigine were observed in epileptic and bipolar patients (Chung et al., 2009; Pavuluri et al., 2010). Lamotrigine was well tolerated, causing only mild and transient side-effects; one patient dropped out for the development of a benign rash. The risk of developing a benign rash was estimated to be 8% (Calabrese et al., 2002), but it can be limited by adhering to the recommended low-dose titration (Labiner, 2002). Nevertheless, lamotrigine treatment is associated with the risk of exfoliative dermatitis which can affect on average 1 in 500 patients during long-term use (Hurley, 2002).

This is the first double-blind placebo-controlled study of lamotrigine augmentation in OCD; nevertheless, our findings are not congruent with the results of the only open-label trial of lamotrigine addition in eight OCD patients refractory to SRI, in which the Y-BOCS improvement was marginal (Kumar and Khanna, 2000).

The implication that glutamate dysregulation may contribute to the pathophysiology of OCD is relatively recent. The observation that drugs acting on glutamatergic pathways may be useful in patients with refractory OCD is consistent with previous evidence showing the efficacy of riluzole, an anti-glutamatergic agent used in amyotrophic lateral sclerosis, in patients with OCD (Coric et al., 2005).

Moreover, it has been proposed that SRIs may indirectly attenuate glutamatergic activity through inhibitory effect of serotonin on corticostriatal glutamate release (Pittenger et al., 2006). This hypothesis is supported by the finding that elevation in Glx, a MRS index reflecting levels of glutamate, glutamine, homocarnosine, and GABA, has been shown to normalize in subjects with OCD who respond to treatment with SRIs (Rosenberg et al., 2000).

Our findings provide evidence that the addition of lamotrigine to ongoing treatment with SRIs may be a valid strategy for patients with OCD unresponsive to SRI monotherapy. The mechanism by which lamotrigine might enhance SRI-mediated anti-obessional activity remains speculative; however, it appears possible that this association may exert a synergistic action on the multiple receptor subtypes and on the neurotransmitter systems involved in the pathophysiology of obsessive–compulsive symptoms.

Our results should be interpreted with caution due to the small sample size, which limits the extent to which our findings may be extended to the OCD population; another limitation is the short duration of the trial. Double-blind, placebo-controlled trials in a larger number of patients are required to evaluate the therapeutic potential of lamotrigine augmentation of SRI-refractory OCD, including determination of optimal dosage and a better definition of possible predictors of response to this combination. Furthermore, a better understanding of the causal role of glutamate abnormalities in the development of OCD might improve the development of the next generation of therapeutics with a more beneficial effect on obsessive–compulsive symptoms.

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Conflict of interest

The authors declare that they have no conflict of interest.

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