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LAMOTRIGINE VERSUS LITHIUM AUGMENTATION OF ANTIDEPRESSANT THERAPY IN TREATMENT-RESISTANT DEPRESSION: EFFICACY AND TOLERABILITY

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SUMMARY

Background: *Mood stabilizer augmentation of standard antidepressant drugs has been shown to be effective in treatment-resistant depression. Despite the reported high overall efficacy, lithium has been relatively underused in recent years. Lamotrigine, a novel anticonvulsant recently recognized as a mood stabilizer, seems to have putative antidepressive properties. The aim of the study was to investigate lamotrigine efficacy and tolerability as antidepressant augmentation for unipolar treatment-resistant depression compared to lithium.*

Subjects and methods: *88 patients suffering from treatment-resistant Major depressive disorder, having acute recurrent depressive episodes according to DSM-IV criteria, were enrolled in the study. This was an open-label trial with a flexible dosing regimen. All patients, received antidepressants in full therapeutic doses. They were divided into two augmentation groups: 46 patients received 50-200 mg/day lamotrigine, and 42 patients received 600-1200 mg/day lithium. The Hamilton Rating Scale for Depression (HAM-D) and The Clinical Global Impression scale (CGI) were used to monitor therapeutic efficacy. Patients were evaluated weekly for an 8 week treatment period.*

Results*: The HAM-D total score was significantly reduced in both treatment groups at the study endpoint, without any difference between the groups. However, significant clinical improvement was reached within the second treatment week in the lamotrigine group compared to the lithium group (p=0.01 vs. lithium). Lamotrigine showed significant efficacy on the HAM-D item 1(depressed mood; p=0.01), item 7 (work and interest; p=0.01) and CGI-Improvement scale (p=0.02). The drop-out rate due to treatment failure was lower in the lamotrigine group (n=1) compared to the lithium (n=4) group. Also, the incidence of side effects did not differ between the groups.*

Conclusions: *Our results suggest that lamotrigine could be useful as augmentation of antidepressants for treatment-resistant unipolar depression. Also, lamotrigine may accelerate the onset of antidepressant action, and therefore might be useful in treatment of major depression in general.*

Key words: *treatment-resistant depression - augmentation strategies – lamotrigine - lithium*

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INTRODUCTION

Treatment-resistant depression (TRD) refers to depression without adequate clinical response to standard antidepressant treatment. Although major depression is reported to be a treatable condition, it is estimated that up to 30% of patients fail to respond to treatment with antidepressants (Amsterdam & Horing-Rohan 1996, Fawcet 1994, Niereneberg & Amsterdam 1990, Roose at al. 1986). The concept of treatment resistance is focused on patients who do not experience at least a 50% reduction of symptoms after two or more adequate trials of different antidepressants, during a treatment duration of at least 6 weeks at a dosage within the recommended range that is expected to produce a therapeutic response (Thase 2003). Because of the chronicity and severity of their condition, these difficult-to-treat patients are more likely to function poorly, to have frequent and

prolonged hospitalizations, and to suffer greater morbidity and mortality from general medical conditions (Thase et al. 2002).

Despite the introduction of a large number of novel antidepressants, the problem of treatment non-response remains a clinical challenge and a substantial public health burden. The major strategies still utilized to deal with TDR are augmentation of ineffective antidepressant medication with another (non-antidepressant) medication, or combining two distinctly different antidepressants. The benefit of mood-stabilizing agents as add-on therapy of TDR has continually been supported in reports (Hantouche et al. 2005, Carvhalho et al. 2007). In particular, lithium augmentation has been reported to be highly effective in this respect (Kantor et al. 1986, Zusky et al. 1988, Schopf et al. 1989, Browne et al. 1990, Stein & Bernadt 1993, Katona et al. 1995, Baumann et al. 1996, Januel et al. 2003, Bauer et al. 2000, Bauer et al. 1999). On the other hand, lamotrigine, introduced initially as an anticonvulsant in 1994, recently has been recognized as a mood-stabilizing agent with potential mood-elevating properties (Sharma et al. 2008, Margolese et al. 2003). Its properties can be helpful during bipolar depressive episodes, but also may prove useful as an adjunctive medication to an existing antidepressant regimen in TDR (Normann et al. 2002, Barbosa & Jamhour 2002, Barbee & Jamhour 2002, Rocha & Hara 2003, Gabriel 2006, Santos et al. 2008, Gutierrez et al. 2005). Since there are no standardized protocols for utilization of mood-stabilizers as augmentation agents in non-responsive depression, we were interested to evaluate the usefulness of different agents. Therefore, the aim of this study was to investigate lamotrigine efficacy and tolerability as antidepressant augmentation for unipolar TRD, in comparison to lithium.

SUBJECTS AND METHODS

Patients

The study included 88 subjects aged between 18 and 65 years, consecutively treated as outpatients or inpatients during June 2004 - December 2007 at the Institute for Psychiatry, Clinical Center of Serbia (demographic and clinical data are summarized in Table 1). All the subjects met DSM-IV (American Psychiatric Association 1994) diagnostic criteria for major depressive disorder (MDD), having recurrent depressive episodes, with moderate to severe intensity. They also had a documented history of TRD, i.e. failure to respond to treatment with at least 2 antidepressants of different classes at maximum-tolerated dose for at least 6 weeks.

Patients with psychotic depression and suicidal patients were excluded from the study. Also excluded were patients with a past diagnosis of schizophrenia, schizoaffective disorder, other psychotic disorders, bipolar I or II disorders, or any Axis II disorders. A past history of seizures, other neurological or serious somatic conditions, alcohol and drug related disorders were also exclusion criteria.

Table 1. Demographic and Clinical Characteristics

Characteristics	Lamotrigine (N=46)	Lithium (N=42)	p
Gender, N (%)			
Female	33 (72)	28 (67)	0.94
Male	13 (28)	14 (33)	0.87
Age, mean	45.2±13.7	49.3±12.3	0.91
Age at first depressive episode	29.3±8.6	31.5±7.7	0.78
No. of previous episodes	6.4±6.7	7.1±5.2	0.33
Baseline HAMD score	32.2±7.6	29.3±9.1	0.70
Baseline CGI score	5.0±0.6	5.0±0.9	0.30
Antidepressant in use, N (%)			
Tricyclic	11 (24.0)	9 (21.4)	
SSRI	18 (39.0)	21 (50.0)	
Venlafaxine	10 (21.7)	8 (19.0)	0.84
Mirtazapine	2 (4.3)	1 (2.4)	
Other	5 (11)	3 (7.2)	
Augmentation dose (mg/pd), mean	117.7±54.3	923.3±246.7	

Abbreviation: SSRI = Selective serotonin reuptake inhibitor

Study design

The study was carried out for a period of 8 weeks. All the patients were on antidepressant medication prior to introduction of augmentation therapy, reporting an unsatisfactory response to their current treatment given a duration of treatment of at least 6 weeks at a dosage within the recommended range that is expected to produce a therapeutic response. Medication taken for the time period is shown in Table 1. The patients who agreed to participate in the study were divided into two augmentation groups: 46 patients received 50-200 mg/pd lamotrigine; and 42 patients received 600-1200 mg/pd lithium. The division was made in an open-label manner, meaning first to come received lamotrigine, second received lithium, and so on, with a flexible dosing regimen.

The augmentation agent was added to the existing antidepressant, and the dose was titrated, according to clinical response and tolerability. Lamotrigine was introduced at 50 mg/pd dose, with 50 mg increments every 2 weeks, to a maximum dose of 200 mg/pd. Lithium was administered at dose of 600mg/pd, elevated up to 1200 mg/pd according to its plasma level. Concomitant medication with benzodiazepines and hypnotics was allowed according to clinical need, without differences in utilization between the groups.

Therapeutic efficacy was measured using the Hamilton Rating Scale for Depression (HAM-D) (Hamilton 1960) and the Clinical Global Impression (CGI) scale (National Institute for Mental Health 1970). The CGI-Severity of illness (CGI-S) scale was used to rate illness severity at baseline (the introduction of augmentation), whereas the CGI of Improvement (CGI-I) scale was used to rate the level of improvement throughout the study. Patients were evaluated weekly. A single qualified psychologist carried out the ratings; therefore no interrater reliability measures were required.

Monitoring for skin rashes, headache, dizziness, somnolence, gastrointestinal disturbances, or any other adverse event was carried out weekly to assess the tolerability of the adjunctive treatment. In the lamotrigine group, patients were instructed to stop the drug, and to report rashes immediately should they develop.

Data analysis

Collected data were entered into the Statistical Package for the Social Science database (SPSS 2001). Differences between baseline and each time period were analyzed using paired sample t-test (2-tailed). X^2 was utilized for categorical data analysis. Therapeutic efficacy was compared using 2-way analysis of variance (group x time) with repeated measures of time.

RESULTS

The majority of enrolled patients concluded the study. One patient was prematurely withdrawn because of skin rash in lamotrigine group. Four patients discontinued treatment in lithium group because they were noncompliant. All withdrawn patients were excluded from the statistical analysis.

The patients' characteristics are shown in Table 1. Demographic and clinical features of the two groups were comparable. Approximately 70% of study participants were females. Age of patients in both groups ranged from 31 to 61 years. The mean age was 45.2 ±13.7 and 49.3±12.3 years in the lamotrigine and the lithium group, respectively (x^2, p=.91). Duration of illness was around 15 years, with multiple depressive episodes in both groups. On the whole, the majority of patients were assessed as "markedly ill" at baseline, with mean HAM-D score of 32 in the lamotrigine, and 29 in the lithium group (x^2, p=.70). More than a half of the patients in both groups had tried at least 3 different antidepressants prior to enrollment. During the study, most of patients in both groups were using selective serotonin reuptake inhibitors (SSRI). Approximately, one quarter were taking tricyclic antidepressants and venlafaxine, respectively. Lamotrigine add-on mean dose was 117.7±54.3, ranging from 50 to 200 mg/pd. The mean dose of lithium was approximately 900 mg, ranging from 600 to 1200 mg/pd.

Efficacy

Table 2. summarizes the efficacy measure findings.

Following the addition of lamotrigine to the antidepressant regimen, the results showed a statistically significant reduction of scores of both HAM-D and CGI-I scales as early as Week 2, compared to lithium addition (t-test, p=0.01 and

p=0.02, respectively). By the study endpoint, outcome measures global scores decreased in both groups and no significant difference was observed between the groups with regard to the final mean scores (t-test, p=0.83 and p=0.92, respectively). The mean reduction of HAM-D score over 8 weeks was 22 points in the lamotrigine group and 18 points in the lithium group. Mean overall clinical impression as measured with CGI declined from "markedly ill" to "borderline ill" in both groups. When the HAM-D scale items were observed separately, in the lamotrigine group significant score reduction was noted for depressed mood (analysis of variance, p=0.01) and work and interest (p=0.001) at Week 2, compared to the lithium group.

Table 2. Hamilton Rating Scale for Depression and Clinical Global Impression of Improvement scale Mean ± SD Values

	HAM-D			CGI-I		
Week	Lamotrigine	Lamotrigine	p	Lamotrigine	Lamotrigine	p
1	27.0±8.4	25.2±7.3	0.89	4.0±2.3	4.0±1.8	0.96
2	16.3±6.1	21.7±4.8	0.01	2.0±1.1	3.0±2.5	0.02
3	11.2±5.6	13.8±7.9	0.79	2.0±1.4	2.0±1.7	0.94
4	11.8±7.1	11.4±8.5	0.82	2.0±1.9	2.0±1.7	0.98
5	10.9±8.2	11.2±9.4	0.84	2.0±1.7	2.0±1.5	0.94
6	10.4±9.6	10.5±7.9	0.76	2.0±1.8	2.0±1.4	0.86
7	10.2±9.2	10.1±8.4	0.74	2.0±1.6	2.0±1.9	0.84
8	10.3±8.3	10.9±7.6	0.83	2.0±1.4	2.0±1.6	0.92

After 8 weeks of treatment, 33% of the lamotrigine group achieved remission, compared to 30% of lithium group (t-test, p=0.60). 24% of the lamotrigine group vs. 28% in the lithium group responded to treatment (t-test, p=0.76), and 13% of the lamotrigine group compared to 10% of the lithium group showed at least a partial response (t-test, p=0.79). According to CGI-I score, two thirds of patients in both groups were "much or very much improved".

Tolerability

Overall tolerability was good in both groups. The occurrence of adverse events resulted in early withdrawal of 1 patient in the lamotrigine group. The most commonly reported adverse event was headache in both groups (Table 3.). Besides headache, most frequent adverse events observed in the lamotrigine group were nausea and somnolence, followed by gastrointestinal disturbances. In the lithium group, patients often reported nausea, dizziness and cardiovascular symptoms. None of the patients presented serious symptoms. More than a half of patients did not experience any kind of adverse event. No significant difference in occurrence and frequency of adverse events was observed between the study groups (t –test, p=0.62).

Table 3. Adverse Events

Adverse Event	Lamotrigine		Lithium		
	N	%	N	%	p
Skin rush	1	2.2	0	0.0	0.23
Headache	8	17.4	7	16.7	0.95
Nausea	4	8.7	6	14.2	0.33
Dizziness	2	4.4	5	11.9	0.39
Somnolence	4	8.7	4	9.5	0.72
Gastrointestinal disturbances	3	6.5	2	4.8	0.68
Dry moth	2	4.4	1	2.4	0.23
Concentration difficulties	1	2.2	0	0.0	0.23
Cardiovascular symptoms	1	2.2	4	9.5	0.14
Other	3	6.5	2	9.5	0.18
Total	29		31		0.62

DISSCUSION

Difficult-to-treat depressive patients make a considerable portion of MDD patients in everyday clinical practice. Add-on strategies are commonly used by clinicians, in order to shorten latency response and sustain improvement in TRD, without the need for tapering down ineffective antidepressants or cross-titration. So far, lithium augmentation has been proved effective in several double-blind controlled trials (Zusky et al. 1988, Schopf et al. 1989, Browne et al. 1990, Stein & Bernadt 1993, Katona et al. 1995, Baumann et al. 1996, Januel et al. 2003, Bauer et al. 2000, Bauer et al. 1999). Our results provide support for at least equal benefits of lamotrigine augmentation.

In this study, patients who met the criteria for TRD and who received lamotrigine augmentation to their antidepressant regiment were evaluated for their response and safety, compared to lithium augmentation. Although this was an open-label study and must be interpreted with caution, the results showed significant improvement of depressive symptoms in both groups. Moreover, despite the high degree of chronicity and refractoriness, one third of patients in both groups, achieved full remission, and another third responded to treatment. These findings are in line with two open-label studies (Schindler & Anghelescou 2007, Barbee & Jamhour 2002) who reported similar response rates following lamotrigine augmentation. However, two randomized, placebo-controlled, double-blind studies failed to show any efficacy of lamotrigine augmentation in TDR (Barbosa et al. 2003, Santos et al. 2008). Small sample sizes and a high degree of psychiatric comorbidity might explain these negative findings. Our sample included patients with no comorbid condition, which is a highly selected population of depressives. Such a design may rule out any other influence on therapeutic response to augmentation, but, on the other hand, these patients do not represent the majority of a real clinical sample of MDD patients, who often suffer from comorbid anxiety and/or alcohol related disorders. This might be a limitation to our findings. However, recent data also demonstrated that lamotrigine augmentation was, at least numerically, superior to other augmentation strategies in bipolar TDR with respect to recovery rate (Niereneberg et al. 2006).

Perhaps just as noteworthy was the lack of worsening of the depressive symptoms during the initial titration of lamotrigine. This was not an issue with lithium augmentation, which was introduced at 600 mg/pd, the dose proven to be effective as an add-on from the start (Bauer and Dopfmer, 1999). Because we intended to reach a therapeutic dose as fast as possible, we introduced 50 mg/pd lamotrigine, and titrated by 50 mg increments every 2 weeks. Surprisingly, by the second week after initiating lamotrigine, significant improvement was observed, especially with regard to depressive mood and work and interest. The onset of response in the lithium group was not evident until Week 3 of treatment. Lamotrigine's ability not only to potentate, but to accelerate antidepressant effect was evident at approximately the 100 mg/pd dose, which is before a "therapeutic" dose, as it used in epileptology, is reached. These findings are in accordance with results from other studies that included unipolar (Normann et al. 2002, Schindler & Anghelescou 2007) and bipolar (Niereneberg et al. 2006) patients. Our results are in contradiction with the opinion that a lamotrigine slow titration scheme might not be efficient in treatment of acute TRD (Thase 2003). In our study, although lamotrigine was initiated at low doses, a good response was achieved at a mean dose below 120 mg/pd. The only study that compared a low dose (50 mg) with a high dose (200mg) of lamotrigine augmentation showed numerical but not statistical superiority of high doses (Guiterrez et al. 2005). Our patients had no comorbidity whatsoever, unlike the average clinical sample. This might explain the efficacy of relatively low lamotrigine doses. On the other hand, spontaneous recovery as well as positive patients' expectation cannot be ruled out from consideration. Also, the resolution of depressive symptoms might be contributed to by antidepressant treatment itself, without any consequence of lamotrigine or lithium addition. Neither of these assumptions could be tested without the addition of a placebo-arm.

Lamotrigine was well tolerated by most patients in the study. The side effects observed were statistically similar with those reported in the literature – headache, nausea and somnolence (Normann et al. 2002, Santos et al. 2008, Schindler & Anghelescou 2007). One patient reported a skin rash, which resolved completely within a week.

Although there were no statistically significant differences between the lamotrigine and the lithium group, a slightly higher incidence of cardiovascular symptoms was reported in lithium group. The favorable side effect profile might be useful for patients with comorbid somatic conditions, especially metabolic, endocrine, cardiovascular or renal, where other augmentation strategies could be problematic.

The study had several limitations that might have influenced the results. The open design is prone to bias to one of the drugs. Double-blind, placebo-controlled design would rule out this bias, but at the clinical department it was difficult to carry out the technical measures to carry out such study. Furthermore, the diversity of antidepressants used by patients enrolled in the study could make the findings difficult to interpret. Exploring the efficacy of augmentation might have been more informative if different classes of antidepressants were analyzed separately. Obtaining TRD patients that met the inclusion criteria took a substantial amount of time, and separate analysis would further reduce sample size. Although the plasma levels of antidepressants and lamotrigine were not measured, lamotrigine proved a safe add-on therapy to a variety of antidepressants.

CONCLUSION

Our results support lamotrigine as a promising and safe augmentation strategy in TRD unipolar depression. The onset of treatment response was observed as early as the second treatment week. This hypothesized accelerating effect might be useful in treatment of major depression in general, which needs to be tested in future larger controlled studies.

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