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Irritability in a mixed sample of patients with unipolar and bipolar II depression predicts responsiveness to lamotrigine

Evyn M. Peters*, Rudy Bowen

Department of Psychiatry, University of Saskatchewan, Saskatoon, SK, Canada

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ABSTRACT

Lamotrigine may be an effective treatment for depression, although results have been inconsistent. In this exploratory pilot study we analyzed data from a five-month, uncontrolled, open-label trial to determine if participants scoring higher on a measure of pretreatment irritability were more responsive to lamotrigine. Nineteen adults with unipolar or bipolar II depression completed five months of treatment with lamotrigine to an average final dose of 250 mg/day. Depressive symptoms and irritability were measured with the Beck Depression Inventory and the Irritability Questionnaire. Wilcoxon signed-rank tests showed that the treatment effect for the entire sample was not statistically significant. However, there was a significant treatment effect among the subgroup of participants with high pretreatment irritability. Pretreatment irritability and irritability improvement scores were both strongly positively correlated with depression improvement scores. These correlations remained significant after controlling for pretreatment depression severity. Pending replication with a larger sample, the results suggest that irritability may be a useful predictor of responsiveness to lamotrigine for the treatment of depression.

Lamotrigine is typically considered a mood stabilizer, although two literature reviews [1,2] and a small meta-analysis [3] suggest that lamotrigine may be an effective treatment for depression. However, results from these studies have been mixed, and efficacy may be limited to certain subpopulations of patients such as those with severe depression [1,3,4]. These inconsistencies justify further inquiry into lamotrigine for the treatment of depression.

In addition to treating depression, lamotrigine reduces irritability in patients with depression [5], bipolar disorder [6], and borderline personality disorder [6,7]. Irritability is not included in the adult depression diagnostic criteria [8], although it is common among patients [9,10] and may represent a core depressive symptom [11]. It has been suggested that patients with irritable depression may require mood stabilizers, although more research is needed to address these issues [9]. In contrast, SSRI antidepressants may induce or worsen irritability and related symptoms such as agitation and anxiety [12,13].

This was an exploratory pilot study to determine if depressed patients scoring higher on a measure of pretreatment irritability are more responsive to lamotrigine. A previous study using the same data found that lamotrigine significantly decreased affective instability more than depressive symptoms in a mixed sample of patients with unipolar and bipolar II depression [14]. Irritability is considered an aspect of affective instability [15] that was measured concurrently, but because the purpose of the previous study was to test for overall, not subgroup, treatment effects, the current hypothesis was not tested at that time [14]. We reanalyzed this data, which allowed us to safely explore our hypothesis without unnecessarily exposing patients to lamotrigine.

Methods

Data was analyzed from a previous five-month, uncontrolled, open-label trial [14]. Nineteen male and female participants aged 18–65 suffering from a major depressive episode were recruited from two outpatient practices. The study was approved by the university research ethics board and conducted in accordance with the 1983 Declaration of Helsinki. All participants gave informed consent. Participants were excluded if they reported active suicidal ideation, suffered from a medical condition that might affect their mood, abused substances within the last two years, or had a history of manic episodes. Diagnoses and study eligibility were determined with the Mini-International Neuropsychiatric Interview (MINI) [16]. Consecutive eligible patients presenting to the outpatient practices were offered participation regardless of whether they reported significant pretreatment irritability.

The 21-item Beck Depression Inventory-IA (BDI) was used to assess pretreatment (Time 1) and posttreatment (Time 2) depressive symptoms over the previous week [17]. Depression change scores were

* Corresponding author at: Ellis Hall, 103 Hospital Drive, Saskatoon, SK S7N 0W8, Canada.
E-mail address: evyn.peters@usask.ca (E.M. Peters).

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calculated by subtracting Time 2 BDI scores from Time 1 BDI scores. Pretreatment (Time 1) and posttreatment (Time 2) irritability over the past week was measured with the 21-item Irritability Questionnaire (IRQ) [18]. The IRQ was designed to measure irritable moods (e.g., "feeling like a bomb, ready to explode"), cognitive appraisals (e.g., "people make my life difficult on purpose"), and expressions of anger (e.g., "lose my temper and shout") [18]. The IRQ has displayed high internal consistency (0.90) and correlates strongly with similar questionnaires [18]. Irritability change scores were calculated by subtracting Time 2 IRQ scores from Time 1 IRQ scores.

Questionnaires were distributed via stamped envelopes. Forty participants completed the initial questionnaires at Time 1. Twenty-five participants completed the follow-up questionnaires at Time 2 approximately five months later. Twenty participants were still taking lamotrigine at Time 2. The starting dose of lamotrigine was 12.5 mg/day. The mean dose of lamotrigine by Time 2 was 250 mg/day (SD = 79.3). Lamotrigine was added to existing medications at Time 1. All but two participants were on therapeutic antidepressants at Time 1. Additional medications taken during the study that could have improved mood were also recorded (see Results). Nineteen participants had complete data and were included in the analysis. The mean age was 44.5 years (SD = 12.0) and 13 were female. Comorbidity was common, as expected, with histories of generalized anxiety disorder (n = 12), panic disorder (n = 7), social anxiety disorder (n = 3), obsessive-compulsive disorder (n = 3), and post-traumatic stress disorder (n = 1), as determined with the MINI. Fourteen patients had histories of hypomania and were therefore suffering from bipolar II depression.

Analysis

Wilcoxon signed-rank tests were used to test for overall treatment effects on BDI and IRQ scores. Participants were classified as having high or low baseline irritability based on whether they scored above or at/below the median Time 1 IRQ score. The signed-rank tests were then repeated for each irritability group. BDI scores for participants in each irritability group were also examined at an individual level. Because most of the sample consisted of participants with bipolar II depression, in whom irritability may be more prominent [9] and lamotrigine more effective [1,4], we repeated the subgroup analysis of BDI scores to see if the same results were observed in only participants with bipolar II depression. The sample was too small to test for a subgroup treatment effect in only participants with unipolar depression.

We examined for outliers in BDI and IRQ scores by calculating interquartile ranges (IQR) and creating scatter plots. Our definition of an outlier was any score greater than 1.5× the IQR added to the 75th percentile, or less than 1.5× the IQR subtracted from the 25th percentile. Scatter plots were used to examine the relationships between baseline irritability (Time 1 IRQ scores) and depression improvement (BDI change scores), as well as irritability improvement (IRQ change scores) and depression improvement, in the entire sample. Pearson product-moment correlations were calculated assuming the plots revealed a linear relationship in the absence of overt heteroscedasticity. Given that lamotrigine is more effective for patients with severe depression [2,3], and irritability in depression is associated with increased depression severity [10], we also calculated partial correlations controlling for baseline depression severity (Time 1 BDI scores). All analyses and graphs were completed with Stata 14.

Results

BDI and IRQ scores for the entire sample and each participant group are presented in Table 1. The overall treatment effect on BDI scores was nonsignificant (z = 1.51, p = .13), as was the overall effect on IRQ scores (z = 1.17, p = .24). Among participants with high baseline irritability, the treatment effect on BDI scores was statistically significant (z = 2.38, p = .02); the effect on IRQ scores was marginally nonsignificant (z = 1.90, p = .058). Among participants with low baseline irritability, there was no reduction in BDI scores (z = −0.46, p = .65) or IRQ scores (z = −0.72, p = .47). Among participants with bipolar II depression, there was also a significant reduction in BDI scores for participants with high baseline irritability (n = 7, M BDI change = 13.4, SE = 3.60, z = 2.29, p = .02), but not for participants with low baseline irritability (n = 7, M BDI change = −2.43, SE = 3.60, z = −0.68, p = .50).

Table 1
BDI and IRQ scores before and after treatment.

Scales	Participant group		
	Entire sample (n = 19)	High IRQ (n = 9)	Low IRQ (n = 10)
BDI T1 M (SE)	26.2 (2.24)	28.2 (3.86)	24.4 (2.53)
BDI T2 M (SE)	21.7 (2.44)	17.2 (3.31)	25.8 (3.16)
BDI CS M (SE)	4.47 (2.49)	11.0 (3.37)	-1.40 (2.55)
IRQ T1 M (SE)	33.6 (2.10)	41.4 (2.07)	26.5 (1.28)
IRQ T2 M (SE)	29.7 (2.40)	29.8 (3.98)	29.6 (3.02)
IRQ CS M (SE)	3.89 (3.04)	11.7 (4.56)	-3.10 (2.64)

Note: BDI = Beck Depression Inventory; IRQ = Irritability Questionnaire; T1 = Time 1; T2 = Time 2; CS = change score. Change scores were calculated by subtracting Time 2 from Time 1 scores.

BDI and Time 1 IRQ scores for participants in the high-irritability group are presented in Fig. 1. Seven high-irritability participants displayed a reduction in BDI scores of at least 9 points (range = 9–30). Five high-irritability participants had BDI change scores that were quite similar to each other (range = 9–12), although their Time 1 BDI scores differed by up to about 20 points (e.g., Participants 4 and 5 vs. 8 and 9; see Fig. 1), suggesting BDI score reductions were not only a function of baseline depression severity. Participant 3 had a BDI change score of 30 that was notably larger than most of the participants, although it did not meet our definition of an outlier. A signed-rank test excluding this participant continued to show a significant treatment effect in the high-irritability group (M BDI change = 8.63, SE = 2.71, z = 2.18, p = .03).

Participants 2 and 6 clearly did not benefit from lamotrigine (see Fig. 1), both of whom had very mild Time 1 BDI scores (15 and 13). Participant 2 also had a Time 1 IRQ score of 33, close to the median cut-off of 31 (range for high-irritability group = 33–52). One participant in the low-irritability group had a BDI change score of 12 (the next highest score was 5), which was comparable to several scores in the high-irritability group. This person's Time 1 IRQ score was 29, which was also close to the median cut-off of 31 (range for low-irritability group = 19–31).

The scatter plots (not shown) seemed to depict a linear relationship between Time 1 IRQ and BDI change scores, and between IRQ and BDI change scores, without overt heteroscedasticity. Time 1 IRQ scores were positively correlated with BDI change scores (r = 0.69, p = .002), as were IRQ change scores (r = 0.76, p < .001) and Time 1 BDI scores (r = 0.47, p = .04). With Time 1 BDI scores held constant, BDI change scores continued to be significantly correlated with Time 1 IRQ scores (r = 0.59, p = .01) and IRQ change scores (r = 0.79, p < .001).

None of the BDI and IRQ scores met our definition of an outlier except for an IRQ change score of 30 from a participant in the high-irritability group. As expected, the effect of lamotrigine on IRQ scores in the high-irritability group became less significant when the signed-rank test was repeated without this participant (M IRQ change = 9.38, SE = 4.47, z = 1.61, p = .11), although the treatment effect on BDI scores remained statistically significant (M BDI change = 9.75, SE = 3.54, z = 2.18, p = .03). The correlation between IRQ and BDI change scores also remained significant and largely unchanged (r = 0.73, p < .001).

With regard to additional medications, participants in the low-irritability group were taking SSRI/SNRI antidepressants (n = 10), bupropion (n = 2), mirtazapine (n = 1), atypical antipsychotics (n = 10),