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Research report

Randomized, double-blind pilot trial comparing lamotrigine versus citalopram for the treatment of bipolar depression

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Abstract

Background: Uncertainty exists regarding the best approach for treating bipolar depression among patients already receiving a first-line mood stabilizer. The aim of this pilot study was to compare adding a second mood stabilizer or an antidepressant at this treatment decision point.
Methods: Twelve-week, randomized, double-blind pilot trial comparing the addition of lamotrigine or citalopram for bipolar depressed patients on mood stabilizer medication. Change in depressive symptoms and risk of switch were examined.
Results: Twenty subjects were randomized. Each treatment group experienced a significant mean reduction in total MADRS scores (citalopram Δ — 14.2, $p=0.002$; lamotrigine Δ — 13.3, $p= 0.001$), and there was no significant difference between treatment groups ($p=0.78$). Total response rates increased from 31.6% at week 6 to 52.6% at week 12. One out of ten patients in each group experienced a switch to hypomania.
Limitations: Small sample size. Lack of a placebo arm.
Conclusions: Results of this small trial suggest that both lamotrigine and citalopram appear to be reasonable choices as add-on acute treatment for bipolar depression, with response rates continuing to rise considerably past 6 weeks of treatment.

Keywords: Bipolar disorder; Bipolar depression; Lamotrigine; Citalopram; Antidepressant; Mood stabilizer

1. Introduction

The selection of a medication to treat bipolar depression that occurs in patients already taking a mood stabilizer is a common, yet understudied clinical decision point. There is little consensus as to which medication should be added to treat ongoing or emergent depression, and treatment guidelines vary on the degree to which a second mood stabilizer or antidepressant is recommended as the best approach (Yatham et al., 2005; APA, 2002; Goodwin, 2003; Grunze et al., 2002; Calabrese et al., 2004). Direct comparative double-blind data is limited to the report by Young et al. (2000) which found the addition of a second mood stabilizer to be equally as efficacious as the addition of paroxetine, but resulting in a greater number of drop-outs. More recently, lamotrigine has garnered significant attention for its efficacy in bipolar depression (Calabrese et al., 1999; Frye et al., 2000); however we are not aware of any head-to-head comparisons of lamotrigine to an antidepressant as add-on treatment for bipolar depression.

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The purpose of this 12-week pilot study was to provide an estimate of efficacy and risk of switch of add-on treatment with lamotrigine or citalopram for bipolar patients experiencing a depression despite ongoing treatment with a mood stabilizer.

2. Materials and methods

2.1. Study design

Twelve week, prospective, randomized, double-blind, parallel-group pilot study comparing lamotrigine and citalopram as add-on treatment for bipolar depression among patients already receiving mood stabilizer medication(s).

2.2. Patients

All patients enrolled in the study were assessed with the Structured Clinical Interview for DSM-IV (SCID) (Spitzer et al., 1995), and met DSM-IV criteria for bipolar disorder (BD) type I or II, with a current major depressive episode. Recruitment was limited to outpatients, age 18–65, who spoke fluent English, and had a baseline 17-item Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960) score of ≥ 16. Patients must have been treated with a mood stabilizer for at least the past 4 weeks (confirmed by clinical records when available), including one or more of lithium (baseline serum level ≥ 0.6 mmol/L), divalproex sodium (baseline serum level ≥ 50 μg/mL), or carbamazepine (baseline serum level ≥ 4.0 μg/mL).

Exclusion criteria included a current hypomanic, manic, or mixed episode as defined by DSM-IV criteria or by a Young Mania Rating Scale (YMRS) (Young et al., 1978) score of ≥ 12, current psychotic symptoms, substance abuse/dependence during the past 3 months, current antidepressant use, discontinuation of any mood stabilizer, antidepressant, or antipsychotic medication within less than 5 half-lives, past treatment with lamotrigine or citalopram in combination with current mood stabilizer(s), unstable medical condition, history of Stevens–Johnson syndrome, lamotrigine-induced rash, or pregnancy.

Patients were recruited from the Mood Disorders Clinic at Sunnybrook and Women's College Health Sciences Centre, Toronto, Canada, or via advertisements in the local media. The study was approved by the Research Ethics Board at Sunnybrook and Women's College Health Sciences Centre, and each subject provided written informed consent for participation in the study after procedures and possible side effect were explained to them.

2.3. Assessments

Patients were assessed at baseline, and weeks 1, 2, 4, 6, 8, 10 and 12. Study visits included completion of the 17-item HAM-D (Hamilton, 1960), Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), YMRS (Young et al., 1978), Clinical Global Impression (CGI) — Severity and Improvement, and assessment for side effects and adverse events.

2.4. Treatment

For the first 4 weeks, subjects received pre-determined doses of study medication. For lamotrigine, this was done as per guidelines to minimize the risk of Stevens–Johnson syndrome and to manage pharmacokinetic interactions with divalproex. For patients not taking divalproex, lamotrigine was started at 25 mg/day for 2 weeks, then increased to 50 mg/day for another 2 weeks. Patients taking divalproex received lamotrigine 12.5 mg/day for 2 weeks, and then increased to 25 mg/day for 2 weeks. At week 5, the treating physician had the option to increase (or decrease if poorly tolerated) the lamotrigine dose on a weekly basis by 50 mg/day (or 25 mg/day for patients on divalproex) up to a maximum of 200 mg/day by week 7 (or 100 mg/day for patients on divalproex). Patients randomized to citalopram received 10 mg/day for 2 weeks, then increased to 20 mg/day for 2 weeks. At week 5, the treating physician had the option to increase (or decrease if poorly tolerated) the citalopram dose on a weekly basis by 10 mg/day up to a maximum of 50 mg/day by week 7. The dose of citalopram was kept low for the first 2 weeks in order to allow the generally accepted minimum therapeutic doses of either medication to begin at week 3. Dose adjustments of study medication were done blind to the type of medication. Dose adjustments of baseline mood stabilizers were only allowed in order to maintain therapeutic blood levels.

2.5. Statistical analysis

The primary efficacy measure was change in total MADRS score from baseline to endpoint. This was tested using a repeated measures analysis of variance (rANOVA). Response was defined as a $\geq 50\%$ decline in the MADRS score from baseline to endpoint, without a switch to hypomania or mania. Remission was defined as an endpoint MADRS score of ≤ 8. Differences in response and remission rates between treatment groups were tested using chi-squared analyses. All analyses were conducted based on intent-to-treat, last observation carried forward.