Published in final edited form as:

J Geriatr Psychiatry Neurol. 2012 March ; 25(1): 37–42. doi:10.1177/0891988712436685.

Correlates of Treatment Response in Depressed Older Adults With Bipolar Disorder

Ariel Gildengers, MD¹, Curtis Tatsuoaka, PhD², Christopher Bialko, MA³, Kristin A. Cassidy, MA³, Rayan K. Al Jurdi, MD⁴, Laszlo Gyulai, MD⁵, Benoit H. Mulsant, MD⁶, Robert C. Young, MD⁷, and Martha Sajatovic, MD³

¹Department of Psychiatry, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, Pittsburgh, PA, USA

²Department of Neurology, Case Western Reserve University School of Medicine, University Hospitals Case Medical Center, Cleveland, OH, USA

³Department of Psychiatry, Case Western Reserve University School of Medicine, University Hospitals Case Medical Center, Cleveland, OH, USA

⁴Mental Health Care Line, Michael E. DeBakey, VA Medical Center, Baylor College of Medicine, TX, USA

⁵University of Pennsylvania Medical Center and School of Medicine, Pennsylvania, PA, USA

⁶Centre for Addiction and Mental Health, University of Toronto, Toronto, ON, Canada

⁷Department of Psychiatry, Weill Cornell Medical College, New York, NY, USA

Abstract

Aims—To identify baseline clinical factors associated with acute treatment response in depressed older adults with bipolar disorder (BD) receiving lamotrigine.

Methods—Secondary analysis of a multisite, 12-week, open-label, uncontrolled study of add-on lamotrigine in 57 adults 60 years and older with BD I or II depression. Measures included the Montgomery Asberg Depression Rating Scale (MADRS) and Young Mania Rating Scale (YMRS). Cardiometabolic risk was measured with total serum cholesterol and the Cumulative Illness Rating Scale–Geriatric (CIRS-G) item #13 (endocrine/metabolic burden). Neurocognitive (executive) function was evaluated using the Trail Making Test.

Results—Greater reduction in MADRS from baseline was associated with higher baseline cardiometabolic burden at 6 and 9 weeks and lower YMRS scores at 9 weeks. At 12 weeks, improvement in the MADRS from baseline was no longer significantly related to baseline cardiometabolic burden or YMRS scores. A longitudinal mixed model of MADRS scores corroborated these findings with a significant finding of time-by-baseline cholesterol level interaction. In a subset of participants, better baseline executive function was related to greater improvement in the MADRS at 9 weeks but not at 6 or 12 weeks. Among all participants, higher baseline YMRS scores were related to greater likelihood of dropout.

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Corresponding Author: Ariel Gildengers, Department of Psychiatry, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213, USA, gildengersag@upmc.edu.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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All other authors have no conflicts to report.

Conclusions—Lamotrigine appears to work best in depressed elderly patients with BD who have high cardiometabolic risk and low level of mania. Agents like lamotrigine that act primarily on neuroprogressive pathways involving oxidative stress, neurotrophins, and inflammation may be particularly effective in individuals with BD who have significant cardiometabolic burden because of their effects on shared vulnerability factors in BD and medical illness.

Keywords

bipolar disorder; elderly; geriatric; lamotrigine; mood stabilizer; anticonvulsant; depression

Introduction

Depression is a severe and pervasive problem among individuals with bipolar disorder (BD) that is associated with reduced quality of life and functional decline, increased risk for relapse/rehospitalization, and suicide.^{1–3} Across the life span, BD depression causes substantially greater disability than mania.^{1,4–8} Of the 6 million American adults with BD, roughly 1 million are over the age of 60 (NIMH; US Census Bureau, www.census.gov). In older adults, BD depression appears to be particularly malignant, being associated with substantial medical comorbidity, early dementing illness, and premature mortality.^{5,9}

In comparison to younger patients with BD, treatment options for older adults are limited.^{10–12} While lithium is reported to have long-term beneficial effects in BD, such as reduction in suicidality¹³ and neuroprotection,¹⁴ limitations to the use of lithium in elderly individuals include renal toxicity¹⁰ and acute negative cognitive adverse effects.¹⁵ Atypical antipsychotics carry an US Food and Drug Administration (FDA) “black box” warning for patients with dementia and questions remain about more general geriatric applicability.¹⁶ Antidepressants for BD depression are controversial because of efficacy and safety concerns, and practice guidelines generally recommend against using them.^{17–19} Hence, there is a critical need to find effective and tolerable treatments for older adults with bipolar depression.

We have previously published an open-label trial of geriatric bipolar depression treatment with lamotrigine.²⁰ We found that lamotrigine was generally well tolerated and was associated with reduction in depressive symptoms as measured by the Montgomery Asberg Depression Rating Scale (MADRS)²¹ over 12 weeks. Lamotrigine, like other mood stabilizers, has been shown to modulate glutamate levels, which is the major excitatory neurotransmitter in the central nervous system (CNS). Glutamate elevation in the anterior cingulate/medial prefrontal cortex has been associated with depression in patients with BD.^{22,23} In particular, impairments in the glutamatergic system appear to play a significant role in the morphometric changes in the CNS observed with severe stress.^{24,25} For example, in hippocampal neurons, it is theorized that excessive glutamatergic throughput leads to high intracellular levels of calcium, which in turn leads to overactivation of calcium-dependent enzymes and the generation of free oxygen radicals, leading to neurotoxicity.²⁶ Although much of the evidence for the potential involvement of the glutamatergic system in depression must be considered indirect,²⁷ an increasing number of reports have suggested that glutamate modulators may exert antidepressant effects in BD depression.²⁵ Further, agents that act primarily on neuroprogressive pathways involving oxidative stress, neurotrophins, and inflammatory cytokines could be particularly efficacious in individuals with BD who have significant medical comorbidities because of their effects on shared vulnerability factors in BD, medical illness, and cognitive loss.

In this secondary analysis, our aim was exploratory, examining whether factors related to medical or cognitive comorbidities would be associated with treatment response over 6, 9,

and 12 weeks. A limited literature in mixed-age BD suggests that there are differences in medication treatment response among subgroups of patients with BD that appear related to clinical and neurobiological abnormalities (particularly cardiometabolic risk factors) that are common among individuals with BD.^{9,25,28} Identifying individuals who might experience early, more robust improvement could be helpful to clinicians and patients due to the requirement of lengthy titration to a therapeutic dose because of the medically significant skin rash (Stevens Johnson Syndrome or Toxic Epidermal Necrolysis; Glaxo-SmithKline, Research Triangle Park, NC 2011). For this exploratory analysis, baseline factors of interest included mood symptom severity, cardiometabolic burden, and executive function. We chose 6 weeks as the starting point of our examination since participants would have titrated to the maximum dose of lamotrigine by that time.

Methods

We conducted a multisite, 12-week, open-label, uncontrolled trial of add-on lamotrigine in 57 adults 60 years and older with BD I or II depression. Detailed methods of the trial are described elsewhere.²⁰ In brief, lamotrigine was added to current maintenance mood-stabilizing medication, initiated at 25 mg/d, and titrated to a target dose of 200 mg/d (100 mg/d in those taking valproate). Mood stabilizers that had been prescribed at stable dose for at least 90 days could be continued unchanged. Antidepressants and antipsychotics prescribed at stable dose for at least 30 days could be continued unchanged. Primary outcome was change from baseline in MADRS scores based on the final dose of lamotrigine. All participants met depressive symptom severity criteria of 18 or more on the GRID version of the 24-item Hamilton Depression Ratings Scale (GRID HAM-D).^{29,30}

Measures

We assessed mood with the MADRS, GRID HAM-D, and Young Mania Rating Scale (YMRS)³¹ scores. We measured cardiometabolic risk with total serum cholesterol and the Cumulative Illness Rating Scale–Geriatric score (CIRS-G) item #13 (endocrine/metabolic burden).³² While other lipid parameters were measured, we focused on total serum cholesterol because low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides are correlated and would introduce the need to correct for multiple testing. We examined blood pressure (systolic and diastolic) and body mass index (BMI). We evaluated executive function with the Trail Making Test (Trails).³³

Statistical Methods

We employed a variety of methods for this secondary analysis. We conducted separate standard regression models with change in MADRS from baseline to the 6-, 9-, or 12-week time point as the dependent variable. Explanatory variables for one set of regression models were baseline YMRS score, CIRS-G item #13, and cholesterol level. Another set of regression models looked at high cardiometabolic risk and low neurocognitive status as explanatory variables. Additionally, we used mixed-effects longitudinal modeling with MADRS scores as the dependent variable. This model included participant-level random effects and the following explanatory variables: time period as a categorical variable and baseline YMRS, total cholesterol, and CIRS-G item #13. Corresponding interactions between time period and total cholesterol were also included. Time was viewed as a categorical variable to allow for flexible, nonlinear modeling of the course of MADRS scores. Last, we used logistic regression to model predictors of treatment termination or dropout that included YMRS score, sex, and cholesterol level. We followed logistic regression with Cox regression to model time until dropout. Explanatory variables included in the model were YMRS score, sex, and CIRS-G item #13.

Results

Demographic and clinical characteristics of the participants are presented in Table 1. Mean lamotrigine dose was 150.9 mg/d, range 25 to 200 mg/d. Concomitant medications included lithium ($n = 6$, 10.5%), divalproex/valproate ($n = 9$, 15.8%), any anticonvulsant ($n = 19$, 33.3%), antipsychotics ($n = 18$, 31.6%), and antidepressants ($n = 34$, 59.7%). There was significant improvement from baseline in MADRS ($df = 8$, $\chi^2 = 43.37$, $P < .0001$). Additionally, there was significant improvement in GRID HAM-D ($df = 8$, $\chi^2 = 46.10$, $P < .0001$).

Baseline Clinical Variables and BD Depression Treatment Outcomes

Significant associations were found between cardiometabolic risk variables and BD depression treatment outcomes. Using a regression model to examine treatment outcome, greater reduction in the MADRS from baseline was associated with higher baseline cholesterol levels and higher baseline endocrine/ metabolic burden (CIRS-G item #13) at weeks 6 and 9, and also lower baseline YMRS scores ($F_{(1, 30)} = 4.28$; $P = .047$) at week 9 (see Table 2 for parameter estimates, standard errors, and P values). However, at 12 weeks, improvement in the MADRS from baseline was no longer significantly related to baseline cholesterol ($F_{(1, 30)} = 2.30$; $P = .140$), CIRS-G item #13 ($F_{(1, 30)} = 1.24$; $P = .275$), or baseline YMRS scores ($F_{(1, 30)} = 3.03$; $P = .092$). We found no relationship between treatment response at 6, 9, or 12 weeks between blood pressure and BMI.

Longitudinal mixed modeling corroborated the regression models with the finding of a significant time-by-baseline cholesterol interaction ($F_{(7, 165)} = 2.16$, $P = .040$). An AR(1) autoregressive correlation structure was estimated, with participant-level random intercept effects, and time and CIRS-G item #13 viewed as categorical variables, and baseline YMRS and total cholesterol as covariates. At 9 weeks, estimated interactions indicated relatively lower expected MADRS scores in individuals with higher baseline cholesterol; while at 12 weeks, relatively higher MADRS scores were expected. For example, in participants with the same YMRS baseline and CIRS-G item #13 scores, but cholesterol level of 100 mg/dL or more, would lead to a lower MADRS score of 2.35 at 9 weeks. At 12 weeks, the same assumptions would lead to a higher MADRS score of 1.22; while at 6 weeks, there would be essentially no expected difference (0.03 MADRS score).

Executive Function and BD Depression Treatment Outcomes

For the following analyses, participants were considered at higher cardiometabolic risk if either their baseline cholesterol level was greater than or equal to 224 mg/dL or their baseline CIRS-G item #13 score was equal to 2 or 3 (32 [56%] out of 57 depressed elders with BD). Participants were considered to have higher or lower neurocognitive status if their ratio of TRAILS B/TRAILS A time was below or above the median of 2.77, respectively. These groups were then fit to a regression model as covariates with reduction in MADRS score from baseline as the dependent variable. Greater reductions from baseline in MADRS scores at week 9 were associated with higher neurocognitive status ($n = 16$, $t = 2.847$, $P = .014$) and higher cardiometabolic risk ($n = 16$; $t = -2.493$, $P = .027$), meaning better executive function was associated with greater improvement in mood (in the context of higher cardiometabolic disease). However, we found no relationship between neurocognitive status and mood at 6 or 12 weeks.

Predictors of Treatment Termination

Dropout at 6, 9, and 12 weeks was 22.8% ($n = 44$ remaining), 31.6% ($n = 39$ remaining), and 33.3% ($n = 38$ remaining), respectively. There was a significant positive relationship between YMRS scores and the likelihood of treatment termination or dropout. A binary

logistic regression model of dropout that included YMRS scores, sex, and cholesterol levels as explanatory variables revealed that higher YMRS scores were a significant predictor of dropout ($df = 1$, $\chi^2 = 5.49$; $P = .019$). Further supporting this finding, a Cox regression model of time until dropout that included YMRS scores, sex, and CIRS-G item #13 as explanatory variables revealed that higher YMRS scores were associated with a higher hazard rate or less time until dropout ($df = 1$, $\chi^2 = 6.57$; $P = .010$). The other explanatory variables in these 2 regression models were not significant predictors of dropout or hazard rate.

Discussion

In this secondary analysis of an uncontrolled, prospective trial of lamotrigine in late-life BD depression, greater cardiometabolic risk was related to early robust response while more manic symptoms related to reduced response. By targeting shared vulnerability factors related to oxidative stress, lamotrigine may work best in depressed elders with BD who have high cardiometabolic risk. These findings are in accord with the growing literature that support the critical need to integrate medical and psychiatric care of depressed elders with BD having high cardiometabolic burden to improve the overall treatment outcomes.³⁴ Additionally, our findings also correspond with published reports that lamotrigine works less optimally in patients presenting with mixed symptoms.¹⁸

While our report did not show a clear effect of cognition on treatment response, studies in mood disorders suggest a relationship between treatment resistance and executive dysfunction or white matter hyperintensity (WMH) burden in the CNS. A recent study demonstrated that pretreatment of WMH and impairment in executive function predicts reduced response to antidepressant treatment at 12 weeks among elderly individuals with unipolar depression.³⁵ Two studies in mixed-aged BD examined WMH as indicators of treatment resistance and poor outcome.³⁶ Moore found that when categorizing patients ($n = 29$; mean age 20–65) by good ($n = 14$) or poor ($n = 15$) outcome, participants with significantly more poor outcome had deep subcortical punctuate but not periventricular WMH burden than good outcome participants or controls ($n = 15$).³⁷ Regenold et al found that treatment resistance was significantly related to WMH volume and CSF concentrations of sorbitol and fructose in individuals with BD ($n = 20$; 44.3 ± 11.8 years) but not in patients with schizophrenia ($n = 15$; 41.1 ± 11.9) or neurologic controls ($n = 15$; 42.5 ± 9.8 years).³⁸ Their findings suggest a relationship between brain polyol pathway activity, WMH, and treatment resistance in BD. Taken together, these findings support the understanding that better executive function may be a marker of more intact frontostriatal neurocircuitry that could be more responsive to pharmacologic intervention.³⁹ If this understanding holds true, then this pharmacologic effect would not be unique to lamotrigine.

Limitations of the study need to be considered. This is an open-label study, with a small sample size and brief assessment battery, which make the findings *hypothesis-generating rather than confirmatory*. Although the results from the longitudinal mixed modeling are statistically significant, they have less clear clinical significance because the predicted differences in MADRS scores from differences in cholesterol values are not large enough to be *clinically* meaningful. Nonetheless, these results do provide support for the other findings. Additionally, we were unable to employ an overall measure of cardiometabolic burden, such as the Framingham Stroke Risk Profile,⁴⁰ because it was not part of the primary study. That blood pressure and BMI were not significantly related to treatment response, while total cholesterol was, suggests the need to look at the vascular disease in the brain more directly (eg, neuroimaging measures of WMH burden) rather than with peripheral measures. Last, longer term outcome-based cardiometabolic risk factors would be highly informative, given the chronic nature of depressive symptoms in BD.^{1,41}

Initiatives at the NIMH encourage personalization of mental health treatments “to who is most likely to respond to a given intervention”. While the treatment of depressive episodes associated with BD remains a major unmet need, our secondary analysis presents an initial step to identify patients with BD who may respond early and robustly to lamotrigine, based on easily measured clinical variables (eg, serum cholesterol). Having an understanding of which older patients with BD could respond more robustly could help clinicians and patient enhance adherence to lamotrigine through an extended titration period needed for treatment. Additionally, an understanding of trajectories of treatment response might help with treatment planning (eg, identifying additional services to coordinate with pharmacotherapy). Although more work is needed to find better treatment for BD depression across the life span, our approach to older adults with BD may help reduce trial and error in the acute treatment of older adults with BD who are experiencing depression.

Acknowledgments

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by an investigator-initiated research grant from GlaxoSmithKline, Research Triangle Park, North Carolina, USA, and grant UL1RR024989 from Case Western Reserve University Clinical and Translational Science Awards (CTSA). The CTSA is a component of the National Institute of Health (NIH) and NIH Roadmap for Medical Research. The contents are solely the responsibility of the authors and do not necessarily represent the official view of the National Center for Research Resources or the NIH. Ariel Gildengers, Rayan K. Al-Jurdi, Laszlo Gyulai, and Robert C. Young received funding for research from GlaxoSmithKline to conduct this investigator-initiated study. Benoit H. Mulsant has received funding for research from GlaxoSmithKline, the Canadian Institutes of Health Research, NIH, Bristol-Myers Squibb, and Wyeth. Robert C. Young has received funding for research from NIH, GlaxoSmithKline, AstraZeneca, and Janssen. Martha Sajatovic received research grants from AstraZeneca, Pfizer, Merck, and Ortho-McNeil Janssen; is a consultant for Cognition Group and United BioSource Corporation (Bracket); and receives royalties from Springer Press, Johns Hopkins University Press, and Oxford Press.

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Table 1**Baseline Demographic and Clinical Characteristics of 57 Older Adult Participants With Bipolar Depression**

Age, years	66.5 (SD = 6.7, range = 60–90)
Female, %	40% (n = 23)
White, %	86% (n = 49)
Black, %	12% (n = 7)
Asian, %	2% (n = 1)
Total cholesterol	197.9 (SD = 53.8; range = 95–347)
YMRS	5.2 (SD = 4.7; range = 0–21)
CIRS-G total score	9.5 (SD = 4.7; range = 2–21)
CIRS-G item #13 (endocrine/metabolic burden)	0.91 (SD = 0.88; range = 0–2)

Abbreviations: YMRS, Young Mania Rating Scale; CIRS-G, Cumulative Illness Rating Scale–Geriatric; SD, standard deviation.

Table 2

Parameter Estimates for Predictors of Change in Depression (MADRS) Scores at 6 and 9 Weeks in 57 Older Adults Treated With Lamotrigine

Parameter	B	Standard Error	t	P	95% Confidence Interval	
					Lower Bound	Upper Bound
6 Weeks (n = 40)						
Intercept	−0.984	5.547	−0.177	.860	−12.224	10.256
Total cholesterol	−0.060	0.025	−2.395	.022	−0.111	−0.009
CIRS-G Item #13	−3.286	1.574	−2.088	.044	−6.475	−0.097
9 Weeks (n = 34)						
Intercept	2.359	4.835	0.488	.629	−7.516	12.233
Total cholesterol	−0.087	0.022	−4.013	.000	−0.131	−0.043
CIRS-G Item #13 (endocrine/metabolic burden)	−4.729	1.450	−3.262	.003	−7.691	−1.768

Abbreviations: CIRS-G, Cumulative Illness Rating Scale—Geriatric.