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Preliminary communication

Lamotrigine and $GABA_A$ receptor modulators interact with menstrual cycle phase and oral contraceptives to regulate mood in women with bipolar disorder

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ABSTRACT

Objectives: To examine the occurrence of menstrually-entrained mood cycling in women with treated bipolar disorder as compared to healthy controls, and to explore whether there is a specific effect of lamotrigine in dampening menstrually-entrained cyclicity of mood.

Methods: Observational comparison study of daily self-ratings of mood, sleep, and insomnia obtained over a mean of four menstrual cycles in 42 women with bipolar disorder taking lamotrigine as part of their treatment, 30 women with bipolar disorder receiving mood stabilizing regimens without lamotrigine, and 13 healthy controls, all with physiological menstrual cycles. Additional exploratory analysis of interactions between psychopharmacological regimen and hormonal contraceptive use in the group of women with bipolar disorder, with the addition of 19 women with bipolar disorder who were using hormonal contraceptives.

Results: Women treated for bipolar disorder manifested lower average mood, longer average nightly sleep duration, and greater fluctuations in mood and sleep across menstrual cycle phases than healthy controls. Women with bipolar disorder who were taking lamotrigine had less fluctuation in mood both within and across menstrual cycle phases, and were more similar to the control group than to women with bipolar disorder who were not taking lamotrigine in this respect. In addition, medications with GABA-A receptor modulating effects were found to result in improved mood ratings when combined with hormonal contraceptives.

Conclusions: Menstrually-entrained mood fluctuation is present in women treated for bipolar disorder to a greater degree than in healthy controls. Lamotrigine may be of use in mitigating this fluctuation. GABA-A receptor modulators in general may act synergistically with hormonal contraceptives to enhance mood in women with bipolar disorder; this hypothesis merits further study.

1. Introduction

Bipolar disorder (BD) is a major cause of social morbidity, accounting for 14.4 million disability-adjusted life years lost worldwide due to uncontrolled mood variations (Collins et al., 2011). Women of reproductive age with BD often find that mood variation can be linked to menstrual cycle phase, termed "menstrually entrained" (Rasgon et al., 2003; Blehar et al., 1998). The nature and degree of this effect, however, vary greatly between individuals (Leibenluft et al., 1999; Shivakumar et al., 2008; Sit et al., 2011; Teatero et al., 2013). BD is often comorbid with premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD), and individuals with BD who experience menstrually-entrained exacerbations exhibit more severe symptoms, more frequent relapses, and impaired therapeutic response (Cirillo et al., 2012).

Although the physiology of menstrual entrainment remains unclear, it has been suggested that hormonally influenced exacerbations of mood symptoms may be affected by cyclic variations of excitatory and inhibitory neurotransmitters across the menstrual cycle. Glutamate levels have been found to be inversely correlated with plasma estrogen and progesterone levels (Zlotnik et al., 2011; Casas et al., 2013), and accordingly glutamate levels vary across the menstrual cycle (Batra et al., 2008). Similarly, several lines of evidence point to changes in GABAergic activity that accompanies alterations in steroid hormone milieu (Bäckström et al., 2003). Both the density and subunit composition of $GABA_A$ receptors in the central nervous system vary over the estrous cycle in response to fluctuations in

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neurosteroid levels (Maguire et al., 2005; Maguire and Mody, 2007, 2009; Porcu and Morrow, 2014).

Lamotrigine, an anticonvulsant used in maintenance treatment of BD, has been implicated in the modulation of glutamatergic (Leach et al., 1986) and potentially of GABAergic (Kuzniecky et al., 2002; Wang et al., 2001) signaling, and could potentially affect menstrual cycle-related alterations in neurotransmitter activity. Hence, it is plausible to speculate that use of lamotrigine might ameliorate cyclic variation in levels of excitatory or inhibitory central neurotransmitters and thereby enhance mood stability across the menstrual cycle for women with BD.

Individual psychiatric case reports (Becker et al., 2004; Sepede et al., 2013; Skokou and Gourzis, 2013) as well as a single controlled study performed in women with epilepsy (Herzog et al., 2011) have supported the utility of lamotrigine as pharmacotherapy for menstrually entrained mood lability. However, to date no controlled study has examined the use of lamotrigine specifically for this purpose.

Mood lability in bipolar disorder is moderated by alterations in sleep, and regular sleep is crucial for maintenance of mood stability (Plante and Winkelman, 2008). Disruptions in sleep rhythms can often precipitate episodes of mood instability (Bauer et al., 2006). Self-perceived sleep quality may vary across the menstrual cycle in healthy women (Baker and Driver, 2004), and disruption in circadian rhythms is associated with disruption in menstrual function (Labyak et al., 2002). Thus it is possible that variations in sleep quality across the menstrual cycle could also have bearing on mood stability in women with bipolar disorder.

Lamotrigine has been reported in some studies to enhance sleep continuity and promote REM sleep (Placidi et al., 2000; Foldvary et al., 2001), suggesting that it could also have beneficial effects on sleep-related mood instability.

No controlled study to date has specifically compared lamotrigine to other therapies for the management of variability in mood and sleep over the course of the menstrual cycle in women with BD. We report on an investigation of mood and sleep stability across the phases of the menstrual cycle in women with BD taking lamotrigine, compared to mood stabilizing regimens that did not contain lamotrigine.

1.1. Hypotheses

Our first hypothesis was that variability in mood and sleep across phases of the menstrual cycle would be more prevalent and more severe in women with BD compared to women without BD. A second hypothesis was that, in those women with BD whose regimens included lamotrigine, variations in mood and sleep across menstrual cycle phases would be attenuated compared to women with BD whose regimens did not include lamotrigine.

In an additional exploratory analysis, the effects on mood and sleep of combining oral contraceptives (OCP) with lamotrigine and other psychiatric medications commonly used in our study sample were examined.

2. Method

2.1. Participants

Women aged 18–45 years were recruited through the Stanford Women's Wellness and Adult Bipolar Disorder clinics, as well as via community postings, for two concurrent studies taking place at the Stanford University, Department of Psychiatry. Both studies were approved by the University Institutional Review Board, and subjects provided written informed consent prior to participation. Participants were consecutively assigned to alternate study groups based on the order in which they presented to the study coordinators.

Forty-two reproductive-aged women with bipolar disorder (including BD-I, BD-II, or BD not otherwise specified) were recruited for a prospective open-label study of lamotrigine addition to standard treatment. Lamotrigine was added to the existing medication regimens of these participants and continued for six months. Three additional women who were initially included in this group were excluded from the analysis because they did not take lamotrigine for the entire study period.

Thirty control women with BD aged 18–45 who were not taking lamotrigine were recruited for a concurrent study of reproductive functioning in women with BD (Reynolds-May et al., 2014). These women maintained their existing medication regimens and did not receive lamotrigine during the course of the study. Details of the medications taken by study participants are available in Supplementary Table 3.

Finally, 13 healthy controls were recruited through flyer and newspaper advertisements in the surrounding community. These participants had no history of mood disorder (confirmed by structured clinical interview) and had never received any psychotropic medication. (Table 1)

Exclusion criteria for all participants included illicit drug use in the previous six months; uncontrolled medical conditions; being peri- or post-menopause; current pregnancy, breast-feeding, or plans to get pregnant; endocrine disease (e.g., diabetes, hypothyroidism); or a mood disorder secondary to a general medical condition. Women with BD receiving psychotropic medication were required to have stable medications for at least three months prior to baseline evaluation. For the main analysis, women using hormonal contraception were excluded; however in an additional exploratory analysis the effects of combining various medications with oral hormonal contraception were examined. For this work the 72 bipolar patients from the study group described above were used as the no-oral-contraceptive group, together with an additional 19 women with

Table 1
Demographic characteristics of the sample.

	Control ($n=13$)	BD lam− ($n=30$)	BD lam+ ($n=42$)
Age of onset	N/A	14.9 ± 7.4	15.3 ± 10.4
Bipolar subtype			
Bipolar I	N/A	11	12
Bipolar II	N/A	8	16
Bipolar NOS	N/A	11	14
Education[a]			
High school	2 (15.4%)	11 (36.7%)	10 (23.8%)
College	5 (38.5%)	10 (33.3%)	16 (38.1%)
Graduate school	6 (46.2%)	8 (26.7%)	12 (28.6%)
Ethnicity[a]			
Caucasian	8 (61.5%)	23 (76.7%)	30 (71.4%)
Hispanic	3 (23.1%)	3 (10.0%)	4 (9.5%)
Asian/Pacific islander	2 (15.4%)	1 (3.3%)	5 (11.9%)
African American	0	0	0
Other	0	1 (3.3%)	0
Employment status[a]			
Full-time	8 (61.5%)	10 (33.3%)	10 (23.8%)
Part-time	2 (15.4%)	5 (16.7%)	5 (11.9%)
Student	1 (7.7%)	6 (20.0%)	11 (26.2%)
Unemployed	2 (15.4%)	3 (10.0%)	5 (11.9%)
Not in work force (other)	0	5 (16.7%)	7 (16.7%)
Marital status[a]			
Single, never married	7 (53.8%)	9 (30.0%)	11 (26.2%)
Married or partnered	5 (38.4%)	19 (63.3%)	19 (45.2%)
Divorced/separated	0	0	6 (14.3%)
Widowed	0	0	1 (2.4%)

[a] Some columns may not sum to total due to missing data.