Determination of Premenstrual Symptom Exacerbations

To the Editor: In the April 2011 issue of the *Journal*, Dias et al. (1) classify bipolar women as having premenstrual exacerbation of symptoms based on retrospective questioning. The poor reliability of self-reported premenstrual mood change has been known for decades (2), and prospective measurement has become the standard (3).

Two unpublished analyses cast doubt on the validity of retrospective reports of premenstrual exacerbation in women with major depressive disorder. Kornstein et al. (4) analyzed data from a large multicenter treatment study of chronic depression in which women were asked, "Are you aware of regularly occurring worsening of your mood related to your menstrual cycle?" A subset of 97 women maintained a daily log of mood symptoms over one menstrual cycle prior to treatment. There was no association between the two types of reports: 27% of women with and 26% of women with no self-reported premenstrual exacerbation had prospectively confirmed premenstrual exacerbation on daily ratings. Harvey et al. (5) examined women in clinical trials of antidepressant efficacy. Premenstrual syndrome was reported by 18 of 27 women. When visit-to-visit changes in HAM-D scores were examined as a function of phase of the menstrual cycle at the time of rating, premenstrual exacerbation was apparent in 26% of the women. There was no association (r^2=–0.002) between self-reported premenstrual syndrome and premenstrual exacerbation score.

It is challenging to collect the daily mood data that are considered the gold standard in studies of premenstrual mood change, leaving self-report as the measure clinicians have tended to use (4). Although retrospectively reported premenstrual exacerbation has been associated with a more symptomatic and relapse-prone phenotype in bipolar women (1) and longer duration of depressive episodes in women with major depression (4), it is not a valid measure of symptom worsening near the onset of menses.

Dias et al. (1) may be able to make an important contribution to the literature if the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study called for the recording of dates of menses throughout the study, as was done in the Sequenced Treatment Alternatives to Relieve Depression study (STAR*D). Only access to dates of menses will permit the placement of observed acute exacerbation of symptoms during the treatment of women with antidepressants (5) into the context of the menstrual cycle.

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Response to Harvey and Kornstein Letter

To the Editor: We thank Drs. Harvey and Kornstein for their comments about the approach to determining the presence of premenstrual mood changes.

We concur that prospective mood charting is the most valid way to establish the occurrence of premenstrual mood symptoms and that, in the absence of this approach, some women with affective disorders will misattribute changes in their mood that are unrelated to the menstrual cycle as premenstrual mood exacerbation. Studies of the validity of retrospective reporting have not been conducted in women with bipolar disorder who endorse premenstrual exacerbation of their underlying mood disorder. However, it is likely that some women with bipolar disorder who retrospectively endorse premenstrual mood exacerbation may not show premenstrual mood exacerbation when their moods are monitored prospectively. This is consistent with what has been observed in women with unipolar depression. Treatments targeting premenstrual mood exacerbation in women with affective illness should utilize prospective mood rating before initiating interventions directed at premenstrual mood exacerbation, especially when the intervention is circumscribed within the luteal phase of the menstrual cycle (e.g., intermittent dosing of a selective serotonin reuptake inhibitor) or involves a hormonal contraceptive therapy.

Data used to support the determination of premenstrual mood exacerbation in our Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) analysis were limited to retrospective reporting of the pattern of mood exacerbation. While prospective mood rating was not available to more definitively establish the premenstrual mood exacerbation pattern, our classification was further supported by other correlative data. These supporting data included a strong association between premenstrual mood exacerbation status and the number of mood and physical symptoms endorsed on a separate itemized list. In addition, women classified as having premenstrual mood exacerbation were not more likely than those without it to be in the luteal phase when they completed the questionnaire describing their symptoms. This latter finding is important because it argues against a bias that

women assessed as having premenstrual mood exacerbation are more likely to report premenstrual mood symptoms simply because they were evaluating their mood when premenstrual. As Drs. Harvey and Kornstein recommend, STEP-BD, like the Sequenced Treatment Alternatives to Relieve Depression study (STAR*D), collected data on the date of the last menstrual period for each woman at each visit. These data are critical for any observational and intervention study in women of premenopausal age.

While prospective mood rating data would have further strengthened our findings, such intensive data collection is often not available in a standard clinical setting when patients retrospectively report that they have a history of premenstrual mood exacerbation. Our results emphasize the importance of inquiring about a pattern of premenstrual worsening of mood and closely monitoring and optimizing therapy for women who report this premenstrual mood exacerbation pattern because of a heightened risk of relapse and greater symptom burden over time.

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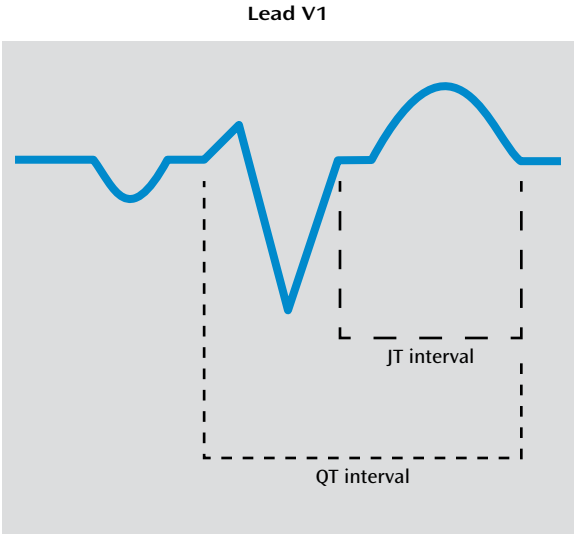
Safety of Antipsychotics in the Setting of QTc Prolongation: The Utility of the JT Index

TO THE EDITOR: Medication that prolongs cardiac repolarization may increase the risk for re-entrant ventricular arrhythmias, notably torsade de pointes, through the increased variability of heart rate corrected QT interval (QTc), or "QT dispersion" (1). The QTc-prolonging properties of antipsychotics are widely studied, but there are no reports on the appropriate treatment for psychiatric patients with baseline QTc prolongation secondary to left bundle branch block. We report the use of the JT interval, which is calculated as QT–QRS duration (Figure 1), and the JT index (JTI), which is calculated as JT(heart rate+100)/518 in this setting (2).

FIGURE 1. QT and JT Interval Measurements With Left Bundle Branch Block



Case Report

"Mrs. R" is a 77-year-old woman with bipolar disorder, hypothyroidism, coronary artery disease, and known left bundle branch block since at least 2003. From 2003 to 2010, her QTc ranged from 436 to 551 msec. Mrs. R's symptoms had been well controlled on haloperidol (1.5 mg), bupropion (200 mg), and mirtazapine (30 mg). Three weeks before admission to the inpatient psychiatry unit, she experienced command auditory hallucinations telling her to not eat or drink, and she became increasingly depressed and withdrawn, possibly indicating a depressive episode with psychotic features. When she was admitted, her QTc was consistently more than 490 msec, and the team discontinued haloperidol and did not add additional antipsychotics for fear of further QTc prolongation and torsade de pointes. In the absence of any antipsychotic drugs (the patient was taking only citalopram, 40 mg/day), her QTc ranged between 458 and 480 msec. As her QTc prolongation occurred with left bundle branch block and a prolonged QRS duration of 152 msec, we consulted cardiology, calculated her JTI to be normal at 102 (prolonged ≥112 msec), and started treatment with aripiprazole (2.5 mg/day). When this was combined with ECT, her auditory hallucinations diminished. Follow-up ECGs showed increased QTc with a JTI in the normal range. Mrs. R resumed eating and drinking, her functioning returned to baseline levels, and she was discharged.

Discussion

The time-tested QTc is of great value for assessing the risk for ventricular arrhythmias when QTc-prolonging agents (e.g., antipsychotics) are considered (1). However, QTc measures both depolarization and repolarization. In ventricular conduction defects such as left bundle branch block and paced ventricular rhythm, depolarization is increased at baseline and QTc has generally diminished utility (2), although knowledge of baseline QRS and QTc duration may allow cautiously proceeding with QTc-prolonging drug therapy. In practice, however, clinicians feel less comfortable with such an approach, and in these conditions, JTI (which excludes QRS and only measures repolarization) may be more useful in determining the safety of medications that prolong repolarization and increase QT dispersion (3). We do not know if JTI is completely independent of QRS duration (4), and more understanding of this metric will allow for its more widespread application. Further elucidation of the relationship among JTI, QTc, and QRS duration is necessary to avoid undertreating patients with bundle branch block who require antipsychotics.

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