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Research paper

Influence of lithium on sleep and chronotypes in remitted patients with bipolar disorder

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ABSTRACT

Background: Lithium (Li) is the first-line treatment for bipolar disorder (BD), but its mechanisms of action remain unknown. Although the chronobiological action of Li is well documented in animals, its effects on sleep and chronotypes in remitted BD patients have never been investigated.
Methods: OPTHYMUM is a multicenter, cross-sectional, observational study conducted in France. We compared the sleep (Pittsburgh Sleep Quality Index, PSQI) and chronotypes (Composite Scale of Morningness, CSM) of 525 euthymic adult bipolar outpatients with (n=149) and without (n=376) current Li treatment. We used a general linear mixed-effects Poisson model to correct for age, gender, BD subtype, and mood symptoms.
Results: In patients with BD type I, women taking Li had significantly lower PSQI (−23% [−37; −7]), but men did not (−4% [−20; +16]). Patients with BD I taking Li had better sleep efficiency (−40% [−61; −7]) and tended to better sleep duration scores (−42% [−68; +3]). A Li effect exists in women for both sleep duration and the use of night sedation (resp. −70% [−90; −10] and −37% [−60; +0.01]) but not in men (resp. −12% [−63; +113] and +9% [−31; +72]). No such associations were observed for BD II. No lithium effect was detected in the CSM score.
Limitations: No controls for other medications but no between-group differences for sedative or antidepressant intakes.
Conclusions: Euthymic BD I patients with Li have better sleep efficiency and longer sleep duration than those without Li. Women with Li have better sleep quality, longer sleep duration and less frequent use of night sedation.

1. Introduction

Bipolar disorder (BD) is a severe mental disorder characterized by recurrent manic and depressive episodes; it usually starts in early adulthood and affects1–4% of the general population worldwide (Merikangas et al., 2007). Patients with BD suffer from enduring sleep and circadian rhythm abnormalities, even during remission phases but with milder manifestations (Geoffroy et al., 2015a, 2015b). These sleep and circadian abnormalities may reflect core features related to the underlying neurobiology and genetic susceptibility of BD (Etain et al., 2011; McClung, 2011, 2007; Murray and Harvey, 2010). The severity and poor prognosis of BD are related to the high rate of recurrences despite medications, with a mean recurrence rate of 60–80% within two years of an index episode (Gitlin et al., 1995; Perlis et al., 2006); disruptions in sleep homeostasis and circadian rhythm irregularities have been associated with the risk of subsequent episodes (Jackson et al., 2003; Plante and Winkelman, 2008; Sylvia et al., 2012). In this context, there is an increasing interest in the adjunctive use of chronobiotics (such as melatonin agonists) in BD (Anderson et al., 2015; Geoffroy et al., 2015a, 2015b) and chronotherapeutics (such

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as cognitive behavioural therapies) to specifically target sleep and circadian problems (Frank et al., 2005; Geoffroy et al., 2015a, 2015b; Kaplan and Harvey, 2013).

Lithium salt (Li) is the cornerstone of BD treatment in all international therapeutic guidelines (Goodwin et al., 2016; Grunze et al., 2010, 2009; Yatham et al., 2013). Indeed, Li is the first-line treatment of BD for preventing relapses and recurrences of any episodes of either polarity (Goodwin, 2009; Grunze et al., 2010, 2009; Yatham et al., 2009). Furthermore, it is the only treatment shown to decrease the risk of suicide in BD (Yerevanian and Choi, 2013). Although mechanism of action of Li is not fully understood, its therapeutic benefit has been related to its ability to act on circadian rhythms (Moreira and Geoffroy, 2016). Indeed, a link between the action of Li on both acute and relapsing mood symptoms and its stabilization action of circadian rhythms has long been suggested in humans (Geoffroy et al., 2014a, 2014b; Klemfuss, 1992) and in rodents (Roybal et al., 2007). Li acts at a physiological level on the period, phase, amplitude and coupling of biological rhythms, and at a molecular level on circadian gene expression and protein production (Alda, 2015; Can et al., 2014; Kripke et al., 1979; Kripke and Wyborney, 1980a; Subramanian et al., 1998; Welsh and Moore-Ede, 1990; Yin et al., 2006). Further, Li appears to interact with environmental light through the retinal-hypothalamic pineal pathway to influence circadian rhythms (Hallam et al., 2005a, 2005b; Pablos et al., 1994; Seggie et al., 1987; Werstiuk et al., 1984).

Although a number of studies have demonstrated the functions of lithium on circadian rhythms (Geoffroy et al., 2014a, 2014b), its actions in remitted patients with BD have not been studied to date. The *OPTHYMUM* study is an observational study that aimed to examine residual symptoms in patients with BD who were recruited in the euthymic phase. In this large sample, we compared sleep and circadian phase preferences (i.e., chronotype) in Li-treated patients and patients effectively treated with other mood stabilizer medications (including second-generation antipsychotics). The objective was to test the hypothesis that Li treatment is associated with better sleep quality and a more stable chronotype.

2. Methods

2.1. Study design

The *OPTHYMUM* study is a multicenter, cross-sectional, non-interventional research study conducted in France in adult outpatients diagnosed with BD who were enrolled by active psychiatrists in hospital and office-based settings between April and October 2012. The study design was published in detail in a previous work (Samalin et al., 2014). The examination of sleep and circadian rhythms as residual symptoms was one of the primary objectives of *OPTHYMUM*; these were measured in real-life conditions in patients with BD in the euthymic phase. The procedures followed in the study were approved by an independent national ethics committee (Comité de Protection des Personnes Sud-Méditerranée IV, CPP) and were conducted in accordance with the Helsinki Declaration as revised in 1989.

During an initial two-month period, the participating psychiatrists included their first six adult patients diagnosed with BD type I or type II according to the DSM-IV criteria (American Psychiatric Association, 2000) at least 6 months after the last acute episode and in the euthymic phase defined by the symptomatic remission criteria for a mood episode proposed by the International Society for Bipolar Disorders (ISBD) (Tohen et al., 2009). Euthymia was strictly defined as a Young Mania Rating Scale (YMRS) score <8 (Young et al., 1978) and a Bipolar Depression Rating Scale (BDRS) score ≤ 8 (Berk et al., 2004). There were no exclusion criteria other than participation in a clinical trial because of the conditions of the study (non-interventional research, conducted under the usual conditions of medical practice). For this study we only considered the subset of patients who had information available regarding lithium treatment.

2.2. Assessments

As described previously (Samalin et al., 2014), a study monitor distributed case report forms and patients' self-report questionnaires to the participating psychiatrists. Patients completed the questionnaire either in the waiting room or at home. To maintain confidentiality, the completed questionnaire was returned to the psychiatrists in a sealed envelope. Hetero-assessments were conducted during the same week as the self-rated questionnaires.

This study included the following information:

- *Clinical characteristics* of patients with BD treated with or without Li: age (years), gender, BD subtype I or II, illness duration (defined as time since first mood episode), body mass index (BMI) and residual mood symptoms assessed by YMRS and BDRS scores.
- *Sleep* was measured for each participant using the French version of the 19-item Pittsburgh Sleep Quality Index (PSQI) (Blais et al., 1997). Here, we report the mean total score of the PSQI (Minimum Score=0; Maximum Score=21, indicating the worst global sleep quality) and 7 sub-scales with specific measures of sleep (with higher scores indicating lower quality or worse outcome): sleep efficiency (based on questions 1 and 3), sleep latency (based on questions 2 and 5a), duration of sleep (based on question 4), sleep disturbance (based on questions 5b to 5j), overall sleep quality during the past month (based on question 6), need for medication to sleep (based on question 7), and day dysfunction due to sleepiness (based on questions 8 and 9).
- *Chronotype* was measured for each participant using the French version of the 13-item Composite Scale of Morningness (CSM) evaluating the circadian typology (Caci et al., 2000; Smith et al., 1989). Here, we report the mean total score of the CSM, ranging from 13 to 55 (higher scores indicating a higher degree of morningness); and 4 sub-scales (higher scores indicating a higher degree of morningness): time of rising (total score of items 1, 6 and 10), time of retiring (total score of items 2 and 7), activity planning (total score of items 8, 9 and 13) and morning affect (total score of items 3, 4, 5, 11 and 12) (Caci et al., 2000; Smith et al., 1989).

2.3. Statistics

All analyses were performed using R 3.2.0 with additional packages lme4 (Bates et al., 2014), car (Fox et al., 2016) and coin (Hothorn et al., 2015).

PSQI and CSM score were modelled using a Poisson model (general linear mixed-effects model, GLMM; package lme4), using centre as a random effects and lithium treatment as a fixed effect, including potential confounding factors (based on the significant results of univariate analysis and when considered clinically relevant); BDRS, YMRS, age, gender, BMI, BD subtype (I or II) and illness duration were considered. Briefly, after removal of strongly correlated predictors, quantitative predictors (BDRS, age, YMRS, BMI, illness duration) were used centred on the global mean and scaled by the global standard deviation, up to quadratic terms; dichotomous predictors (gender, lithium, BD subtype) were included up to first-order interactions. The significance of each term or variable was obtained using the likelihood ratio test (LRT) for