Research paper

Sleep and circadian rhythms as possible trait markers of suicide attempt in bipolar disorders: An actigraphy study

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ABSTRACT

Background: The poor prognostic of Bipolar disorders (BD) is closely linked to deaths by suicide. Sleep and circadian abnormalities are observed during all phases of BD and are also associated with suicide attempt (SA). In this context, this study sought to identify specific sleep and circadian rhythms markers associated with suicidal attempt in euthymic patients with BD.
Methods: The sample ($N = 236$) comprised 3 groups: 147 patients with BD including 57 with a history of SA and 90 without (NoSA), and 89 healthy controls (HC). All participants were recorded during 21 days with actigraphy.
Results: SA was associated with women gender ($p = 0.03$), familial history of SA ($p = 0.03$), mixed episodes ($p = 0.001$), and benzodiazepines ($p = 0.019$). SA, compared to noSA, had a morning phase preference ($p = 0.04$), and were more vigorous on the circadian type inventory ($p = 0.04$), and tended to suffer more from insomnia (45% versus 25% respectively, $p = 0.10$). SA was also associated with an earlier onset of daily activity assessed with actigraphy (M10 onset: $p = 0.01$). Backward stepwise linear regression indicated that a combination of four variables (Gender, vigour, insomnia, M10onset) significantly differentiated patients with SA from NoSA ($p = 0.03$).
Limitations: Cross-sectional design, and no examination of suicidal behaviors' subgroups such as first attempters or repeaters, or violent suicide attempt.
Conclusions: Woman gender, vigorous circadian type, insomnia and an earlier daily activity appeared independently associated with SA in BD. If these biomarkers are confirmed in prospective studies, they should be screened and used to prevent suicide, with the development of personal and targeted chronobiological treatments.

1. Introduction

Bipolar disorders (BD) are severe and frequent psychiatric disorders affecting 1–4% of the general population when considering the narrow definition of the disorder (e.g. BD type 1 and 2) (Merikangas et al., 2007). According to the Worldwide Healthcare Organization's data, BD are among the tenth disabling pathologies with a ten years decrease in life expectancy (Collins et al., 2011; Phillips and Kupfer, 2013). The

poor prognosis of BD is closely linked to deaths by suicide (Pompili et al., 2013a,b). Indeed an increased risk of suicide of about 20–30 fold is observed in individuals with BD compared with the general population. Up to 20% patients with BD commit suicide and 25–50% had suicide attempt during lifespan (Schaffer et al., 2015). There is thus an urgent need to identify biomarkers of suicidal behaviors in BD seems essential to better prevent suicide and improve the prognostic of patients suffering from BD.

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A large and growing literature explored sleep and circadian rhythms in BD, highlighting numerous disturbances in BD (Etain et al., 2011; McClung, 2007). Interestingly, these sleep and circadian abnormalities have been observed during all phases of the disorder (Geoffroy et al., 2015). Sleep disturbances are very well documented during depressive episodes and encompass insomnia, night's awakenings, difficulties falling asleep, hypersomnia, sleepiness, and poor sleep efficiency (Kaneita et al., 2006; McCall et al., 2000). Similarly, during manic episodes is observed: insomnia, decreased need of sleep without daytime fatigue, and higher energy (Gold and Sylvia, 2016). Patients with BD in remission also show a more frequent eveningness profile in comparison to healthy people (Boudebesse et al., 2013a; Wood et al., 2009) and persistent sleep disorders (Geoffroy et al., 2015; Ng et al., 2015).

Actigraphy is a medical tool recording continued activity of a person during day and night in natural environment (Morgenthaler et al., 2007). Several recent meta-analyses focusing on actigraphy in normothymic patients with BD show an increased sleep onset latency, a longer sleep duration, an augmentation of sleep arousals, a bigger sleep fragmentation, a increased variability in day to day, and a decreased sleep efficiency (Geoffroy et al., 2015). Interestingly, it has been also demonstrated that euthymic patients with BD suffer also from a higher variability of their sleep/wake patterns (Geoffroy et al., 2015). Other abnormalities in biological rhythms of patients with BD are observed for infradian rhythms with seasonal recurrences (Geoffroy et al., 2013; Geoffroy et al., 2014a; McClung, 2007).

On the other hand, a growing literature also observes associations between suicide attempt or ideations and sleep and circadian rhythms disturbances. In general population, a seasonality of suicide is observed and well known worldwide (Christodoulou et al., 2012). This seasonal rhythm in suicide prevalence show a main peak of during spring and another minor peak of suicides during autumn (Benard et al., 2015; Christodoulou et al., 2012). This later peak of suicides in autumn appears more linked with depressive symptoms, but not the spring one (Anderson et al., 1994). Interestingly, it should be noted that seasonality of patients with BD type 1 seems to be linked with personal history of suicide attempt (Kim et al., 2014). The "photoperiod", is the daily duration of light and dark to which an organism is exposed, considered especially with regard to its effect on growth and development (Watts et al., 2015). Several studies show a positive association between duration of daily sunshine and suicide rates (Petridou et al., 2002; Vyssoki et al., 2014). Moreover, this light/dark cycle seems to influence mortality by suicide with a peak in the morning (Altamura et al., 1999; Gallerani et al., 1996; Maldonado and Kraus, 1991), especially for violent suicides, and in elderly and men population (Maes et al., 1993).

Furthermore, a daily distribution of suicide by age is observed with subjects >65 years-old committing suicide more frequently in the morning, middle aged people during the mid-day, and youngers in the evening (Benard et al., 2015; Durkheim, 1951; McCleary et al., 1991). Regarding these circadian rhythms, a daily distribution concerning suicide attempts is also observed, with an increase of suicide attempts during evening and an increase severity of suicide attempts in the morning (Altamura et al., 1999; Benard et al., 2015; Caracciolo et al., 1996; Nordentoft, 2007). Subjective sleep disturbances like insomnia, nightmares and poor quality of sleep are well demonstrated to be associated with suicidal ideations, suicide attempts and suicide (Bernert and Nadorff, 2015). Indeed, a study in unipolar depressed patients highlighted associations between sleep disturbances and suicidal risk, particularly an association between global insomnia and suicide within one year (Fawcett et al., 1990). In line with this, a recent meta-analysis in the general population estimate associations between specific sleep disturbances and suicidal ideations or behaviours. The authors show that insomnia and nightmares are associated with suicidal ideations, suicide attempts and suicide with a relative risk between 2 to 3 which independent of depressive symptoms (Pigeon et al., 2012). Another meta-analysis showed that in patients with psychiatric

disorders, including depression, sleep disturbance such as insomnia, nightmares and sleep-related breathing disorders, are associated with suicidal behaviors (Malik et al., 2014). Moreover, sleep disturbances are demonstrated to be associated with impaired neuroplasticity mechanisms, abnormal concentrations of neurotrophic factors, depression and stress-related conditions which could induce brain damage and enhance suicidal risk by hippocampal neurogenesis alteration (Serafini et al., 2014). Finally, numerous studies suggest that sleep and circadian rhythms disturbances could be predictors of suicidal behaviours (Bernert et al., 2015). Indeed, a recent study showed that being awake during night enhances suicidal behaviors in the following days (Perlis et al., 2016). Studies using polysomnography (PSG) observe that alteration of REM-sleep and nocturnal wakefulness are associated with suicidal ideation independently of the depression severity (Bernert et al., 2017). So, sleep disruption observed with PSG can predict suicidal ideation in patients with BD (Ballard et al., 2016).

Taken as a whole, the existing scientific literature suggests that sleep and circadian rhythms disturbances could be associated to suicidal behaviours. In addition, several studies indicate associations between sleep and circadian rhythms disturbances patterns and vulnerability to suicide in patients with BD, which are particularly at-risk of suicide. In this context, we hypothesize that patients with BD and an history of suicide attempt differ during remitted phases from patients without such suicide attempt history regarding sleep and circadian rhythm. Thus, aiming to better understand suicidality in patients with BD, we examined sleep and circadian rhythms disturbances associated with a lifetime history of suicide attempt in patients with BD. The objective of this study was to use questionnaires and actigraphy to identify trait sleep and circadian rhythms markers associated with suicidal attempt in euthymic patients with BD, compared to BD patients without personal history of suicide attempt and a healthy control group.

2. Methods

This is a case-control study that compared two groups of BD I or II patients, in remission phase, with and without a personal history of suicide attempt, and a control healthy group. Sleep and circadian rhythms are evaluated by subjective (self-assessment questionnaires) and objective (actigraphy during 21 days) measures. This study is a part of a research protocol "GAN-Genetic, Actigraphy and Neuropsychology in BD" whose objectives are to evaluate genetic and environmental vulnerability factors of BD. This research project was realized at INSERM UMR-S 1144 and was approved by CPP Ile de France (IDRCB2008_AO1465_50 VI – Pitié Salpêtrière 118–08), by CCTIRS and by CNIL that are the national committees in charge of the ethical approval and the protection of data recorded from persons who participate to biomedical research. The study is registered under the number NCT02627404 (ClinicalTrials.org). Details about the study methods and materials have been previously published (Boudebesse et al., 2015, 2014; Geoffroy et al., 2014; 2014b).

2.1. Sample

With ethical approval from the Institutional review board, written informed consent was obtained from 236 Caucasian adults (BD = 147 and HC = 89). All included cases and HC were recruited from Fernand Widal hospital in Paris and from Albert Chenevier hospital in Créteil. Individuals eligible for the study were included if, during the three preceding months, they had (1) not experienced any periods of severe sleep disruption due to general medical conditions and/or any life event that may have altered their sleep patterns (e.g. shift work, jet-lag, child birth, severe stress or somatic disease known to be associated with sleep disturbances); (2) not been hospitalised or received a treatment that may disrupt sleep (e.g. for cases: electro-convulsivo therapy); (3) not been prescribed medication or taken drugs that may disrupt sleep (e.g. sympathomimetics, stimulants, corticosteroids, thyroid hormones,