Towards interventions to correct sleep problems in patients with a Bipolar Disorder

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ABSTRACT

Bipolar disorders (BDs) are mood disorders defined by recurring episodes of mania and depression, characterized by significant disruptions in rhythmic behaviors such as energy, appetite, attention and sleep. The evidence for chronobiological mechanisms associating with BDs is further reinforced by the effectiveness of multiple treatment chronotherapeutic modalities such as circadian phase advance, bright light therapy and mood-stabilizing drugs such as lithium, all affecting the circadian clock. In order to objectively characterize these problems in BDs especially for clinical use in the primary and psychiatric care, further methodological development is needed to characterize objective features of sleep that capture subjective insomnia. In my work, we found that Athens Insomnia Scale (AIS) and the Sleep Items of the Quick Inventory od Depressive Symptoms (QIDS-SR-16) are suitable for clinical screening of sleep problems among patients with a BD. Subjective insomnia associated with objective actigraphic measures of sleep. For clinical and research purposes, actigraphy and data visualization on inactograms are useful for accurate longitudinal characterization of sleep patterns. Additionally, a systematic review and meta-analysis presented explores the role of antipsychotics (AP) in the regularization of circadian rhythms. We found that especially atypical AP decrease amplitude of cortisol, melatonin and temperature, decrease cortisol secretion, and regulate rhythms.

Les troubles bipolaires (TBs) sont des troubles de l'humeur avec des sous-jacents neurobiologiques définis par des épisodes récurrents de manie et de dépression, accompagné avec des perturbations significatives dans les comportements rythmiques tels que l'énergie, l'appétit, l'attention et le sommeil. Les liens chronobiologiques avec les troubles bipolaires sont renforcés par l'efficacité de multiples modalités de traitement, comme la progression de la phase circadienne, la luminothérapie et les médicaments stabilisateurs de l'humeur, comme le lithium, qui ont des effets sur l'horloge circadienne. Afin de caractériser objectivement ces problèmes liés aux les TBs, il est nécessaire de poursuivre le développement méthodologique pour capturer l'insomnie subjective, en particulier dans le contexte clinique primaire et psychiatrique. Notre recherche a révélé que l'échelle d'insomnie d'Athènes (AIS) et les articles de sommeil de l'inventaire rapide des symptômes dépressifs (QIDS-SR-16) sont appropriés pour le dépistage clinique des problèmes de sommeil chez les patients atteints d'une TB. L'insomnie subjective est associée à des mesures actigraphiques objectives du sommeil. À des fins cliniques et de recherche, l'actigraphie et la visualisation des données sur les inactogrammes sont utiles pour la caractérisation longitudinale précise des modèles de sommeil. En outre, nous présentons une revue systématique et une méta-analyse présentées qui plus loin explorent davantage le rôle des antipsychotiques (AP) dans la régularisation des rythmes circadiens, la découverte que les 'APs, particulièrement du genre atypique diminue l'amplitude du cortisol, de la mélatonine et de la température, et diminuer la sécrétion de cortisol et réguler les rythmes.

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NOTES ON THE AUTHOR AND CONTRIBUTORS

Maria Paola Lavin-Gonzalez, M.D.

I graduated as a M.D. and pursued a specialization in functional imagining and radioactive medical treatments in Mexico. While performing metabolic assessments of the brain of patients with substance abuse, I became interested in researching on innovative, non-invasive and safe ways the brain could be read, measured and understood, that could be useful in routine clinical practice. I started working on research projects focused in delirium and brain injury with Dr. Jacques Lee at Sunnybrook Research Institute - UofT, at Toronto ON, where I became inspired by his work and a group of creative scientist-clinicians aiming at continuously building a bridge that integrates basic sciences, technology and patients' needs. I had the pivotal opportunity of joining Dr. Outi Linnaranta and Dr. Serge Beaulieu's research team in 2019 at The Douglas Mental Health Research Institute at Montreal QC and started my journey as a graduate student in science. I am honored to share my work on circadian dysregulations on rest-activity cycles in patients with a bipolar disorder, as well as the results on the effects of antipsychotics in circadian rhythms. The future lines of research will be in digital psychiatry and interventions, proposing the use of longitudinal studies using actigraphy, mobile applications and biological markers that aid in elucidating the circadian rhythm dysregulations in child and youth psychiatric populations.

Outi Linnaranta M.D., PhD.

Dr. Linnaranta is an Associate Professor in the Department of Psychiatry at McGill University and at the Douglas Mental Health University Institute. She is a MD and Ph.D., with training as a clinical psychiatrist, psychotherapist and as an epidemiologist at the University of Helsinki, in Finland. She works in translational research to describe inflammatory, metabolic, and rhythmic dysregulations in in severe mental illness. Her most cited papers describe how suicidality accumulatively increases according to the time patients have depressive and mixed episodes. She was among the first to describe white matter changes in the brain of mood disorder patients, and recently received a prize for the most cited paper of the year 2018 in the journal Psychiatry Research for her research on gut microbiota and early psychosis. Her most recent work describes a high prevalence and

clinical correlates of dysregulated rest-activity rhythm in bipolar disorders and eating disorders. Dr. Linnaranta is an editor for BMC Psychiatry, has been a reviewer for numerous international journals, and a mentor to numerous students.

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Dr. Beaulieu obtained BSc. in Biochemistry, MSc. in Neurobiology, and Ph.D. in Physiology, as well as an MD, and training as a clinical psychiatrist. He is an Associate Professor at McGill University in the Department of Psychiatry and holds associate membership in the Department of Neurology and Neurosurgery. He has been the Medical Chief of the Bipolar Disorders Clinic at the Douglas Mental Health University Clinic since 2001, and the Executive Chair of the Canadian Network for Mood and Anxiety Treatments workgroup. Dr. Beaulieu was the recipient of the Douglas Utting Prize in 2004, which is awarded annually to one person in Canada who has contributed significantly to promoting awareness of depression and/or its research and treatment. He also, received the Teaching-Clinician Award from the Quebec Medical Association in 2009, which recognizes the exceptional contribution of a physician who also teaches at a faculty of medicine. Dr. Beaulieu is a Distinguished Fellow of the APA (American Psychiatric Association) and served as member of the Board of Councillors of the ISBD and was a member of the Scientific Council of the Canadian Psychiatric Association. He is a Board member of Revivre, a self-help community organization devoted to patients suffering from mood and anxiety disorders.

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Dr. Gruber is a clinical child psychologist and pediatric sleep expert. Her research is focused on the association between sleep and attention deficit hyperactivity disorder, academic performance, and mental health. She has developed a comprehensive framework for sleep promotion and prevention programs for psychologists, pediatricians, and school boards in Quebec since September 2007. In partnership, they have created, implemented, evaluated, and disseminated school-based interventions aiming at promoting sleep health and offering evidence-based tools to treat sleep disorders.

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INTRODUCTION

The National Academy of Medicine has estimated that 50–70 million Americans suffer from a chronic insomnia, which can negatively affect daily functioning as well as physical and mental health. There are around 90 distinct sleep disorders; most are characterised by one of the following symptoms: excessive daytime sleepiness, difficulty initiating or maintaining sleep, and abnormal events occurring during sleep.

Bipolar disorders (BDs) are a group of chronic brain disorders that cause extreme fluctuation in an individual's mood, energy, and ability to function [1]. Research in neurobiology has shown that BDs are multifactorial, thus no single gene, pathway, or brain abnormality is likely to cause the condition, and this is the first step in better articulating an integrated perspective on both its ontological status and pathogenesis[2].

The World Mental Health Survey Initiative reported lifetime prevalence estimates of BDs of 5% across BDI, BDII, and not otherwise specified BD subtypes[3]. In Canada, the Canadian Community Health Survey-Mental Health reported that the lifetime prevalence of BDI was 0.87% and that of BDII was 0.67%.[4]. BDs are disabling illnesses due to their typical early onset, severity and chronicity[5]. The burden of the illness is comprised by cognitive[6], psychosocial, and occupational dysfunction[7], along with increased rates of suicide[8], medical comorbidity[9], and premature mortality[10].

Insomnia has several reasons, one of which is circadian rhythm dysregulation. The information on insomnia and problems with timing of sleep is strongly associated with

BDs. Irregularity of the sleep-wake rhythm[11], eveningness chronotype[12], abnormality of melatonin secretion[13], risk variants of clock genes[14], and the irregularity of social rhythm cues[15] have also been well-documented in this population[16]. Some researchers have proposed that bipolar disorders might be disorders of circadian rhythms [17-22].

In the clinical course of BDs, the circadian rhythm dysfunctions may act as predictors for the first onset of BD and the relapse of mood episodes[16]. Furthermore, sleep disturbance is suggested to be a contributor to symptom severity and functional disability[23], as it exerts negative impacts on treatment outcomes, the overall disease course, quality of life, and functioning[24, 25].

Interventional research in circadian rhythm dysregulations has proposed the use of approaches such as bright light therapy (LT), dark therapy (DT), treatments utilizing sleep deprivation (SD), interpersonal social rhythm therapy (IPSRT), and cognitive behavioral therapy adapted for BDs (CBTI-BP)[26]. Other approaches have been conducted focusing on pharmacological interventions, such as melatoninergic agonists (MA)[27], antipsychotics(Moon et al., under review), and mood stabilizers[28], reporting mixed results.

Despite the high prevalence of sleep problems in bipolar disorders, circadian parameters have not been optimally measured, screening tools for insomnia do not seem reliable and correlation with objective measures is lacking. We know almost nothing about the effect

of other factors on circadian rhythms. There is one study reporting actigraphy and cortisol during different phases, which shows that sleep phase advances in manic phase, while delays in depressive phase[29]. It seems that there is no single pattern of circadian rhythm in BDs. We know that psychoactive medications advance rhythms, but how this relates to individual phasing remains open.

My work contributed to confirm the reliability of a screening tool for insomnia and objective measuring tools for circadian rhythm disorders and fragmented sleep. Polysomnography remains the gold standard for quality of sleep, sleep apnea and restless feet syndrome. Further studies are warranted to clarify the relation between circadian rhythm dysfunction and the pathophysiology of BDs, as well as to characterize individual sleep problems to develop treatment strategies for achieving recovery in this population[16]. Importantly, population growth and aging are leading to an increase in the burden of BDs over time. It is crucial that resources be directed towards improving the coverage of evidence-based intervention strategies for BDs and establishing strategies to prevent new cases of the disorder

LITERATURE REVIEW

I. Normal sleep and basics of chronobiological rhythm regulation

A simplified operational definition of sleep is that it is a natural state defined by a decrease in voluntary motor activity, a decreased response to stimuli (increased arousal threshold), and a stereotypic posture[30]. The DSM-5[1] and the International Classification of Sleep Disorders (ICSD-3)[31] agree with viewing sleep as normal if the following components are present: falling asleep easily, not fully waking up during the night, not waking up too early, and feeling refreshed the next morning. Furthermore, variability in the timing of ±1 hour is considered normal variation. Individuals aged 18 to 64 years old should be getting seven to nine hours of sleep each night, while the population over this age should be getting around one hour less per night[32]. This minimum amount of sleep per night is essential to foster adequate health, however significant inter-individual variability in timing, internal structure of sleep, and sleep needs across the lifespan suggest that there is no single amount that can be defined as optimal duration of sleep.

By the age of five, most individuals have developed the typical circadian pattern of an adult: which is a state of wakefulness during the day and then sleep during nighttime[33]. Later on life, the amount of time spent sleeping gradually decreases until the age of 80 [34]. During aging, changes in sleep patterns may include advanced sleep timing, shortened nighttime sleep duration, increased frequency of daytime naps, increased

number of nighttime awakenings and time spent awake during the night, and decreased slow wave sleep[35].

Biological rhythms of sleep and wake are regulated by both circadian and homeostatic processes which define sleep architecture and include sleep cycles of rapid eye movements (REM) and non-rapid eye movements (NREM) sleep. Arousal as well as sleep -REM and NREM- are active and complex neurophysiologic processes that involve neural pathways of activation and suppression. Normal sleep in adults exhibits a consistent organization. Following sleep onset, sleep progresses to NREM stages N1–N3 in approximately one hour. NREM stage N3 sleep which is typically a slow-wave sleep, presents in the first third of the sleep, and comprises 15–25% of total nighttime sleep in healthy adults. The initial REM sleep episode starts in the second hour of sleep and constitutes 20–25% of total nighttime sleep, while NREM stages N1 and N2 comprise 50–60%[36]. Phases three and four are the deep sleep phases, and when REM sleep and dreams might occur. When this phase ends, sleep becomes lighter again before a new full sleep cycle starts.

There are numerous theories about what normal sleep is and how it is affected by age. For children between the ages of five and twelve, a night's sleep of nine hours is quite normal. The average person sleeps about seven hours a night around the age of 40, and about six and a half hours a night between the ages of 55 and 60. A healthy 80-year-old will usually sleep about six hours a night. However, it is relevant to note that these represent average

durations, and at an individual level, quality and timing of sleep have an impact, and duration of a healthy sleep is variable.

Basics of Chronobiological Rhythms of sleep

The day-night cycle is a fascinating phenomenon in nature. Almost all species exhibit circadian (24-hour) changes in their behavior and physiology[37]. The term "circadian" derives from the Latin words "circa diem," which means "about a day"[38]. These daily cycles are not simply a reaction to the changes in the environment imposed by the earth's rotation but, instead, arise from a clock system, finely developed within the organism throughout evolution[39].

The neural control of circadian rhythms mainly resides in the ventral-anterior region of the hypothalamus, more specifically, in the suprachiasmatic nucleus(SCN)[40]. This biological timekeeping system enables the organism to anticipate and prepare for the changes in the environment that are associated with day and night, therefore ensuring that the organism will act in a suitable way, at the right time of the day[38]. Additionally, the SCN temporally optimizes physiology beyond the level of the molecular clocks, coordinating the timing of cellular activities at the level of multiple organic systems[41].

The synchrony of an individual with external and internal environments is crucial to its survival and well-being, and desynchrony may lead to impairment in a variety of functions,

such as cognition, endocrine, or gastrointestinal homeostasis[38], as seen in jet lag, shift work, and insomnia[42]. The circadian rhythms play a fundamental role in homeostasis as they ensure coordination between the environment and the behavior and physiology of most organisms, including human beings[43]. Therefore, the scientific field of chronobiology emerged to answer questions regarding the mechanisms underpinning the biological timekeeping systems, and the potential consequences of their dysfunction[44]. Recent research has been focusing on various phenomena in this field, such as hormone secretion happening in varying pulses throughout the day, activity and rest cycles, behavior, sleep and eating patterns, reproductive cycles, and associated psychopathology, among others. Almost all vital physiological and metabolic processes are under circadian control[45].

The circadian cycles are programmed by circadian clock and also by external time signals denominated zeitgebers -which include rhythmic locomotor activity, drinking behavior, food consumption, hormone release, and body temperature; the circadian clock can keep functioning to a certain degree without zeitgebers[46]. Together, central and peripheral clocks regulate physiological rhythms and functions[46]. The internal clock consists of an arrangement of genes and their protein products, which regulate specific physiological processes in virtually every tissue across the body[47, 48] and these rhythms adjust us to the world by preparing the brain and other tissues to perform appropriate functions, according to the anticipated day or the anticipated night[47].

The SCN spatiotemporal organization across individuals is a robust feature of the pacemaker important for its function[49]. When this nucleus is isolated in organotypic culture, its autonomous timing mechanism can persist indefinitely, with precision and robustness[40]. The most obvious way in which the circadian pacemaker is observed is by the coordination of the sleep-wake cycle[44]. Other implications of the circadian neural mechanisms are the maintenance of attention and cognitive capacity, which are upregulated in daytime [48], whereas preparation for night involves the activation of pathways that are essential for sleep-dependent memory consolidation (and reconsolidation) and synaptic scaling[50].

The molecular clocks that drive these and many other intrinsic rhythmic changes are based on interlocked transcription and translation feedback loops that integrate with diverse environmental and metabolic stimuli to generate internal 24h timing[51].

Circadian rhythms misalignment

Circadian misalignment describes a variety of circumstances both in the laboratory and natural environment. By the Oxford Dictionary, misalignment refers to “the incorrect arrangement or position of something in relation to something else”. One of the most common types of misalignment studied is misalignment of the sleep-wake cycle in relation to the external night. Other types of misalignment include misalignment of feeding rhythms to the sleep-wake or light-dark cycle, or internal misalignment of central and peripheral rhythms[52].

The timing and alignment of circadian rhythms are integral to the health and wellbeing of all organisms, including humans. Misalignment of circadian rhythms can occur when the individual's sleep-wake cycle is inappropriately timed relative to the biological night, when eating is misaligned with other biological rhythms or there can even be misalignment between the central SCN and peripheral rhythms[53]. The consequences of circadian misalignment include changes in dietary behavior, appetite regulation, glucose regulation and mood[52]. The experimental literature suggests that misalignment has profound effects on processes that affect risk for cardiovascular disease, diabetes, obesity and psychiatric conditions.

However, much is still not understood about how misalignment contributes to disease risk, nor how individuals become misaligned. For example, in Delayed Sleep Phase Disorder(DSPD), misalignment between sleep timing and circadian markers has been demonstrated even when participants are sleeping at their preferred sleep-wake schedule, which suggests it is not only due to external factors such as work and social schedules. Treatments to shift and align circadian phase, such as bright light and melatonin have shown promise in the treatment of some conditions, such as depression and seasonal affective disorder[53]The effect of aligning circadian phase in other conditions such as cardiovascular disease, obesity and diabetes has not been well studied. Preliminary data from experimental animal studies suggest that altering meal timing may be a promising intervention for weight regulation[54, 55] Interestingly, a recent randomized clinical trial

showed that restricting the eating window may be an option for treating obesity[55]. They compared time-restricted eating (TRE) with an unrestricted (non-TRE) control and their results suggested that TRE facilitates weight loss, alters body composition, and improves metabolic measures. Further research is needed to understand the mechanisms that contribute to the development of circadian misalignment, the links between misalignment to disease development and finally, the role of improving circadian alignment in the management of chronic illness.

Advanced and Delayed Sleep-Wake Phase Disorders

Diagnostic criteria for circadian rhythm disorders are provided in both the International Classification for Sleep Disorders (ICSD) and the Diagnostic and Statistical Manual of Mental Disorders (DSM). Both the ICSD-3[31] and the DSM-5[1] have 3 major criteria that must be met for any Circadian Rhythm Sleep Disorder. These major criteria include (1) having sleep disruption that can be attributed to disruption of the circadian system or a misalignment between an individual's endogenous rhythm and the sleep-wake schedule needed for work and social activities, which is (2) associated with daytime sleepiness and/or insomnia and (3) causes clinically significant impairment or distress in at least 1 domain of functioning (i.e social, occupational).

The DSM-5 allows the diagnosis to be further classified with a subtype of *delayed sleep phase type* when the sleep-wake schedule is significantly delayed, or *advanced sleep phase type* when the sleep-wake schedule is significantly advanced[1]. Similarly, the ICSD-3

allows for a diagnosis of DSWPD when there is a significant delay in sleep-wake patterns and ASWPD when there is a significant advance in sleep-wake patterns compared with what is desired or required as reported by patient or caregiver. In contrast to the DSM-5, the ICSD-3 provides further requirements for the diagnosis, specifying that the delayed or advanced sleep-wake schedule must be present for at least 3 months, and if an individual is allowed to function on his or her preferred sleep-wake schedule, sleep quality and duration will improve but sleep-wake patterns will still be shifted. The sleep disturbance must also not be better explained by another sleep disorder, medical disorder, or psychiatric disorder.

Assessment Methods

Diagnosis of DSWPD and ASWPD is composed of a thorough assessment including a clinical interview and at least 7 days of prospective, daily sleep diaries that capture both school and/or work nights, as well as free nights[56]. Sleep diaries, such as the Consensus Sleep Diary, have been created to standardize assessment and ensure all appropriate data about perception of sleep are captured[57]. In addition, they allow for the collection of subjective data regarding daytime functioning and factors that may impact sleep such as medication use, alcohol, and caffeine intake.

Wrist actigraphy is recommended to complement the sleep diary data and to gather objective data of rest and activity patterns to confirm the diagnosis[31]. Actigraphy data have been found to correlate with markers of an individual's circadian phase in both

ASWPD and DSWPD[56]. Activity data combined with the timing of morning light exposure showed very high correlation with circadian phase in patients with DSWPD[58]. The use of actigraphy is particularly useful when assessing patients who may have difficulty completing a sleep diary or who's self-report appears to be unreliable. Similarly, assessment of altered sleep-wake timing may be more reliably captured through actigraphy in an individual with cognitive impairment, such as an older adult with mild cognitive impairment and suspected with a circadian rhythm sleep-wake disorder.

In sleep medicine, accumulating research in multidimensional imaging, intersectional genetics, and network theory, are beginning to elucidate the circuit-level mechanisms and emergent properties that make the SCN a uniquely precise and robust clock[59]. However, much remains unknown about the intrinsic properties of SCN cells, their circuit topology and the molecular computations that these circuits support.

II. Sleep in patients with a Bipolar Disorder

Sleep disturbance is increasingly recognized as an important and understudied mechanism in the complex and multi-factorial causation of the symptoms and functional disability associated with psychiatric disorders[23]. Sleep problems are very common in BDs, even in remission phases. About 80 % of patients with a remitted BD have poor sleep quality. Sleep complaints during remission are of particular interest since they are associated with more mood relapses and worse outcomes[60].

In patients with a BD, sleep disturbances and circadian rhythm dysfunctions have been extensively demonstrated, examples being the presence of irregular sleep-wake rhythms, eveningness chronotype, abnormal melatonin secretion, vulnerable clock genes, and irregular social time cues[16]. Circadian rhythm dysfunction is prominent in BDs compared with that in major depressive disorders (MDD), suggesting that circadian rhythm dysfunction is a trait marker of BDs. These dysfunctions may act as predictors for the first onset of the illness and the relapse of mood episodes[61]. Patients with BD suffer from sleep and circadian rhythm abnormalities during major depressive episodes (insomnia or hypersomnia, nightmares, nocturnal and/or early awakenings and/or non-restorative sleep, and delayed rhythm) and manic episodes (insomnia and/or decreased need for sleep without fatigue, advanced rhythm)[29].

Typically, patients with a BD present sleep and circadian rhythms disruptions at every phase of the illness. The remission phases are characterized by a reduced quality of sleep, longer sleep duration, increased sleep latency, a lengthening of the wake time after sleep onset, a decrease of sleep efficiency, and greater variability in sleep/wake rhythms. Patients might also present other sleep comorbidities such as chronic insomnia, sleepiness, sleep phase delay syndrome, obstructive sleep apnea/hypopnea syndrome and restless legs syndrome[60]. The sleep disorders are insufficiently diagnosed and treated whereas they are associated with mood relapses[62], treatment resistance[60], affect cognitive global functioning[63], reduce the quality of life and contribute to weight gain or metabolic

syndrome[64]. Sleep and circadian rhythm abnormalities have been also associated with suicidal behaviors[65]. Therefore, a clinical exploration with the characterization of these abnormalities and disorders is essential.

Optimally, a stepped model of clinical diagnostics can be recommended. Questionnaires are valid as screens to detect a need for further diagnostic evaluation of insomnia, sleepiness, or timing of sleep[66]. This could be followed by on sleep diaries and actimetry objective measures[67] for problems in timing or fragmentation of sleep. For accurate measurement of quality of sleep, sleep apnea or sleep-related breathing disorders, in treatment-resistant insomnia and when substantial sleep state misperception is suspected , examinations such as ventilatory polygraphy, polysomnography or a more comprehensive assessment in a sleep laboratory may be required[68].

Treatment of chronic insomnia is primarily based on non-pharmacological techniques as restructuring behavior and sleep patterns with sleep hygiene measures and psychotherapy techniques as cognitive behavioral therapy for insomnia [CBT-I]; relaxation and interpersonal and social rhythm therapy [IPSRT][26, 69, 70]. When these tools need to be complemented, different pharmacological agents are available and will be discussed in chapter IV

The detection and treatment of sleep alterations in special high-risk populations may help to achieve earlier detection of the illness. Biomarkers of depressive episodes include heightened fragmentation of REM sleep, reduced REM latency, increased REM density,

and a greater percentage of awakenings, while biomarkers of manic episodes include reduced REM latency, greater percentage of stage I sleep, increased REM density, discontinuous sleep patterns, shortened total sleep time, and a greater time awake in bed[17].

III. Implications of dysregulated sleep in health

Current research suggests that the magnitude which sleep has on personal well-being might be similar to the effects of diet and exercise. In Canada, it is estimated that 40% of the population chronically suffers from at least one symptom describing insomnia[71].

The cumulative long-term effects of sleep deprivation and sleep disorders have been associated with a wide range of deleterious health consequences including an increased risk of accidents, hypertension, diabetes, obesity, depression, heart attack, and stroke[72-74] which evidently also increase cost related to health care and lost years at work. Disruption of the brain's circadian system compromises sleep efficiency and cognitive performance as well as associated processes such as synaptogenesis and brain metabolite clearance[75, 76]. Therefore, it is not surprising that disorders of circadian timekeeping have been implicated in multiple psychiatric[77], neurological[78], and metabolic diseases [79].

Sleep disorders have been found to be associated with multiple health problems. Increasingly, sleep disorders such as insomnia are placing individuals at greater risk of car crashes, medical mistakes and industrial accidents. In addition, sleep disorders represent a significant risk to public health, contributing to multiple medical conditions, including cardiovascular problems such as hypertension and stroke, diabetes, obesity, cancer and mental health problems, inclusive of increased suicidality.

- ***Association with cardiovascular problems***: sleep disorders, including sleep-disordered breathing, parasomnias, sleep-related movement disorders, insomnia, and hypersomnia are intimately intertwined with cardiovascular conditions[80]. A recent review found that when insomnia is frequent, chronic, and/or accompanied with short sleep duration or objective markers of arousal, there is a strong association with hypertension[81]. In a study with patients with acute coronary syndrome, sleep problems were associated with neuroendocrine hormones and coagulation activity. More severe insomnia symptoms were associated with higher levels of fibrinogen, driven by difficulties initiating sleep, and with lower levels of norepinephrine, driven by difficulties maintaining sleep[82]. Additionally, current evidence indicates that addressing sleep disorders should be a core part of primary and secondary stroke prevention. Post-stroke sleep disorders also impact stroke rehabilitation, quality of life, and if left untreated can contribute to stroke recurrence[80].

- ***Association with diabetes***: A recent review found that both poor sleep habits and sleep disorders are highly prevalent among individuals with type 2 diabetes. In multiple studies, short sleep duration, obstructive sleep apnea, shift work, and insomnia were associated with higher risk of incident type 2 diabetes and could predict worse outcomes in those with existing diabetes[83]. Some researchers have concluded that the risk of developing diabetes associated with sleep disturbances is comparable to that of traditional risk factors, therefore they should be considered in clinical guidelines for type 2 diabetes screening[84].

- ***Association with Obesity***: Accumulating research suggests that sleep plays an important role in obesity[85], however a recent meta-analysis concludes that the relation of sleep duration and incident obesity so far has insufficient evidence base[86]. One relevant and frequent question is if the results have been conflicting due to the assessment of sleep duration rather than quality indicators.

- ***Association with Cancer***: Emerging data suggest that sleep problems may also impact carcinogenesis. For instance, one animal study found that sleep fragmentation could be associated with increased cancer incidence and mortality[87]. In this study, their findings offered mechanistic insights into how sleep perturbations can accelerate tumor growth and invasiveness through TAM recruitment and TLR4 signaling pathways. A study in humans reported evidence

for a possible protective effect of morning chronotype and for an adverse effect of increased sleep duration on breast cancer risk[88].

- ***Association with memory problems***: Evidence has shown that individuals who experience sleep deprivation tend to experience a range of daytime mental symptoms such as fatigue, impaired and shortened attention span, moodiness, and especially reduced short-term recall and decision-making[89, 90]. A Canadian study reported findings suggesting that insomnia disorder in adults is associated with poorer health outcomes and worse memory performance than adults with occasional insomnia symptoms or without any sleep complaints, even after adjustment for comorbidities[91]. Additionally, there are findings that show that chronic sleep problems, especially when implicate REM sleep mechanisms, can be predictors of clinical dementia[92].

- ***Association with suicidality***: There is a recent increase in clinical and epidemiological studies pointing to a potential relationship between sleep loss or sleep disturbances and suicidality. A meta-analysis supported that sleep disturbances in general, as well as insomnia and nightmares individually, appear to represent a risk factor for suicidal thoughts and behavior. This proposition was further bolstered by the result that depression did not show risk moderation[93].

- ***Associations with bipolar disorders***: A third of patients with a BD suffer from insomnia[94] and 40% report excessive daytime sleepiness, which is contrasted by a prevalence of 18% in the general population[95]. Accumulating evidence suggests a link between a circadian rhythm disruption, and vulnerability for BDs[96]. Sleep problems have been described as a potential factor implicated in the pathophysiology of BDs[11, 16] which are present even during euthymic phases. The main problems of sleep within this population are with sleep latency, duration, wake after sleep onset, and sleep efficiency[97]. An internal dysregulation of chronobiological rhythms as an etiological feature of psychopathology has been further supported by a higher likelihood of having an evening chronotype[98] and abnormal melatonin secretion[99]. Additionally, genetic association studies have provided evidence for the role of clock genes in the etiopathology of BDs[14]. Changes in sleep during major mood episodes have been linked to clinical severity, and vulnerability to suicide in patients with a BD[100]. Furthermore, sleep perturbations may exert negative impacts on treatment outcomes, the overall disease course[17], quality of life[24, 25] and functioning[101].

IV. Summary of potential treatments

It is plausible that relapse prevention can be achieved through treatments focusing on sleep disturbances and circadian rhythm dysfunction, in combination with chronobiological, psychosocial, and pharmacological therapies[16]. Sleep alterations frequently appear long before the onset of a BD and appear to be related specifically to the polarity of the index episode[102].

PSYCHOSOCIAL

Sleep hygiene is a necessary but frequently an insufficient approach for a patient with insomnia[103]. These practices are broadly defined and variable among clinicians, but most recommendations include four core areas: implementing consistent bedtimes and rise times, establishing a comfortable sleep environment, controlling substance use such as alcohol and caffeine and exercising regularly. During clinical interactions, patients should be requested to identify behaviors that they recognize as stimulating versus relaxing and intentionally introduce in their schedule the ones that aid at unwinding in the 30 to 60 minutes before going to sleep. The focus should be on reinforcing the relevance of a consistent sleep-wake schedule and encourage the patients to develop a structured day with regular exercise[104] and consistent mealtimes[105]. Optimizing sleep hygiene may be

particularly helpful for patients who have sleep-onset insomnia. All subsequent treatments for insomnia will be less effective if sleep hygiene issues go unaddressed.

Table 1. Suggested methods to improve sleep hygiene in patients with insomnia [34]

Table 1. Methods to Improve Sleep Hygiene in Insomnia Patients

Helpful behaviors	**Behaviors to avoid**
Use the bed only for sleep and sex If you cannot sleep within 20minutes, get out of bed and read or do other relaxing activity in dim light before returning to bed	Napping, especially after 15:00 Attempting to sleep too early Caffeine after lunchtime
Make quality sleep a priority. Go to bed and get up at regular times daily Ensure a restful environment.	2-3 hours before bedtime avoid heavy eating, smoking or alcohol, or vigorous exercise
Develop a consistent routine before going to bed	When trying to fall asleep avoid solving problems, thinking about issues, review events of the day

Cognitive behavioural therapy for insomnia

Cognitive behavioural therapy for insomnia (CBT-I) is an evidence-based treatment for insomnia[106]. Formats of individual therapy, group therapy, online therapy, and mobile applications have proved efficient[107]. The effects of CBT-I on comorbid psychiatric conditions have received increasing interest as insomnia comorbid with psychiatric disorders has been associated with more severe psychiatric symptoms, and there are studies that indicate simultaneous efficacy of CBT-I on both insomnia and psychiatric symptomology[108]. Interestingly, CBT-I has shown efficacy in improving insomnia

symptoms and sleep parameters among patients with larger effects on psychiatric conditions compared with other medical conditions[109]. Additionally, results from a RCT in patients with a bipolar disorder including insomnia suggested that CBT-I could be a treatment for insomnia in bipolar disorder with possible effects on sleep and on stability of mood[110].

CHRONOTHERAPEUTICS

In addition to responses to genetic influences or drug administration, the SCN clock network respond to environmental cues, which are core to understanding the human health problems that stem from circadian rhythm disruption[111]. Disturbances of circadian rhythms play an important role in the pathogenesis of affective illnesses, and their treatment with chronotherapy methods might become an essential element. Events, such as feeding timetables, social interactions, and lighting conditions, can all influence the body's daily rhythms and ultimately express as modifications in physiology and behavior[112]. This argument is complemented by data demonstrating that effective pharmacotherapies for BDs show an impact on the timing and amplitude of circadian rhythms[28, 113, 114]. Additionally, the expression and treatment responsiveness of affective illness has been linked to chronotype[115-118]. Light therapy(LT) and sleep deprivation(SD) have been some of the outstanding chronotherapeutic approaches that demonstrate phase advances associated with antidepressant therapy response[119, 120].

- ***Bright Light Therapy(LT)***: Trials conducted on populations experiencing seasonal affective disorder(SAD) showed that bright white light had significant effects on mood compared to placebos[121] and similar effects as fluoxetine[122]. Data on non-SAD depression[123-125] and in bipolar depression[126] demonstrated the efficacy of LT as single or adjuvant therapy with antidepressants. The intensity, duration, timing and color of light [127] are relevant factors of efficacy of LT. It is important to note that the circadian pathways are most responsive to short wavelength, blue light[128]. The Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with depressive disorder recommends using UV–filtered bright white light as there is not data on long-term effects of this therapy[129].

- ***Sleep deprivation(SD)***: A recent meta-analysis on treatments using SD to treat subjects with bipolar depression[130] showed general tolerability and quick response, however, a very short duration of the effect. The major shortcomings among these intervention studies are the variability in administration protocols, length of follow-up, and outcome criteria used. Within the scope of these limitations, the acute, antidepressant response rates from the were approximately 60%[26]. When these parameters were tracked, SD-based treatments were generally safe, had low rates of manic symptom induction (0 to 5%), and were rapid, most yielding response within 7 days[26].

- ***Interpersonal social rhythm therapy (IPSRT)***: IPSRT addresses interpersonal difficulties and disrupted social rhythms with the intent of stabilizing underlying biologic processes[131]. This therapy aims to regulate five daily activities over twenty weeks as an initial intervention, or monthly as treatment for maintenance. The activities include time of out of bed, first contact with another person, start of daily activity, dinner, and time to bed. Patients identify potential causes of rhythm disruption and develop strategies to maintain rhythm consistency, despite disruptors. Focus on the sleep-wake cycle is an essential component of IPSRT, however IPSRT involves a comprehensive approach to standardize activities across the day. Factors that have shown positive impacts are employment with fixed hours, having a partner for fixed exercise appointments, or enrolling into classes at consistent times with their chronotype. There is evidence from RCTs to support efficacy of IPSRT in hastening recovery from a depressive episode[132] and in increasing time to recurrence over two years of maintenance treatment[133].

PHARMACOLOGICAL Currently the Centers of Disease control support the recommendations of pharmacological management of insomnia in adults from Sataeia et al., 2017[31], yet their analysis makes it abundantly clear that the availability and quality of the data which serve as the foundation for such recommendations were limited (Table

2). A more recent systematic review (Moon et al, 2020 under review) analyzed current evidence on the effects of antipsychotics on the circadian rhythm in humans. Most of the studies consistently reported that antipsychotics had a potential effect on circadian parameters such as the sleep-wake cycle, circadian rest-activity rhythm, cortisol rhythm, melatonin rhythm, and temperature. Particularly, the meta-analysis of 16 RCTs related to cortisol rhythm showed that antipsychotics, especially atypical antipsychotics, significantly decreased the area under the curve of cortisol levels and morning cortisol level compared to placebo (refer to the systematic review section). The results showed that antipsychotics have potential as an intervention to correct disrupted circadian rhythms. However, in psychiatric populations, including bipolar disorders, good quality intervention studies testing the effect of antipsychotics on various circadian parameters, comparing also the effects of circadian timing, are needed.

Table 2. Clinical recommendations for treating sleep onset insomnia, based on Jmeson, Fauci, Kasper, Hauser, Loscalzo. Harrison's Principles of Internal Medicine, 20e; 2018[34]

Sleep onset insomnia	Sleep maintenance insomnia	Not recommended for insomnia
Eszopiclone	Doxepin	Diphenhydramine
Ramelton	Eszopiclone	Melatonin(*)
Temazepam	Temazepam	Tiagabine
Triazolam	Suvorexant	Trazodone
Zaleplon	Zolpidem	L-Tryptophan
Zolpidem		Valerian

(*)Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous hormone produced by the pineal gland and released exclusively at night. Exogenous melatonin supplementation is well tolerated and has no obvious short- or long-term adverse effects. Melatonin has been shown to synchronize the circadian rhythms, and improve the onset, duration and quality of sleep[134]. Therefore, melatonin offers an alternative treatment to the currently available pharmaceutical therapies for sleep disorders with lower side effects. In addition to its role in chronobiology, it has been implicated in sleep-promoting, antioxidant, antiapoptotic, immune-enhancing, and oncostatic properties[135]. The discrepancies found in the recommendations of melatonin for sleep problems might be associated to protocol heterogeneity in dosage, the time of administration not fixed, and the follow-up interval not specified.

V. Methods to asses circadian rhythm and sleep in Bipolar Disorders in clinical settings.

Sleep abnormalities should be characterized and diagnosed in order to reduce mood relapses, treatment resistance and improve outcomes[60]. Appropriate measurement of sleep problems is essential for optimal treatment. Table V-1 depicts the most common available options for measuring circadian rhythms in humans, however, due to limitations on masking effects or elevated costs, and the advantages that actigraphy and scales represent, we decided to assess subjective, self-rating questionnaire Athens Insomnia Scale and actigrapgy GeneActiv methods.

Table V-1. Methods to assess circadian rhythms in humans

Circadian Rhythm Measure		**Parameter**
Sleep-wake cycle	Sleep diary, sleep log Self-reported scales Actigraphy Polysomnography	Sleep onset time Sleep offset time Time to bed Wake up time Sleep latency Sleep efficiency Sleep fragmentation CenDI (Sleep mid-point) ConDI (Robustness index Periodogram: tau
Melatonin rhythm	Blood melatonin Salivary melatonin Urinary melatonin aMT6s DLMO	AUC Cosinor analysis acrophase, tau, amplitude
Cortisol Rhythm	Blood cortisol Salivary cortisol, urinary cortisol	AUC Cosinor analysis; acrophase, tau, amplitude
Body temperature	Core body temperature Skin temperature	Cosinor analysis; acrophase, tau, amplitude Wavelet analysis

Subjective measures of insomnia

Advantages. Certain features such as need of sleep, or experience of sleep, can be captured only by asking the patients for their subjective experience. Additionally, sleep

questionnaires are inexpensive and quick tests that pose no risks for the patients, therefore, they are optimal for an initial screening test. The scales can reliably quantify the patients' perceptions about the quality of their sleep in the general population[66].

Limitations. Precisely because they are subjective measures, sleep questionnaires can be influenced by the same sources of bias and inaccuracy as any other self report. However, their subjectivity does not define them as inaccurate, but complementary to objective reports, as it has been evidenced by multiple validation studies[136-141]. A recent review suggests that current subjective methods present a sensitivity between 73% and 97.7%, while their specificity ranges in the interval 50%–96%[142]

Summary subjective scales

For clinical and research purposes, multiple scales are available (Table V-2). A recent meta-analysis[66] showed a comparison of Insomnia Severity Index(ISI)[143], AIS and PSQI(Table V-6), and suggested that the ISI and AIS are probably stronger, appropriate instruments according to the comparisons of scales characteristics for diagnostic properties, sleep domains, and feasibility.

Table V-2 Summary of sleep questionnaires					
Sleep Questionnaire		Reference	Structure	Focus	In Bipolar Disorders
AIS	Athens Insomnia Scale	[144]	8 items (4point scale) One month	Insomnia	[145]
PSQI	Pittsburgh Sleep Quality Index	[146]	9 items (4 point scale) One month	Insomnia	[24, 147, 148]
ISI	Insomnia Severity Index	[149]	7 items (5point scale) Recently	Insomnia	[150, 151]
ESS	Epworth Sleepiness Scale	[152]	8 items (4point scale) Recently	Daytime sleepiness	
BRIAN	Biological Rhythms Interview in Neuropsychiatry	[153]	18 items (4 point scale)	Circadian rhythms (sleep, activity and eating)	[154, 155]
MEQ	Morningness-eveningness questionnaire	[156]	19 items	Chronotype	[98]

The Pittsburgh Sleep Quality Index (PSQI).

Aim and structure. One scale that has commonly been used in studies with psychiatric populations and is among the three best validated scales, is the Pittsburgh Sleep Quality Index (PSQI). This scale is a self-assessment questionnaire that refers to symptoms experienced during the previous month. This scale was derived in 1989 by testing it in three groups, one deemed as "good sleepers" who where healthy subjects, another as "poor sleepers with major depressive disorder(MDD), and the third group of "poor sleepers" referred from a sleep clinic, including patients with a difficulty of initiating and maintaining sleep, or disorders of excessive somnolence.

***Psychometric properties*.** PSQI is integrated by nineteen individual items which generate seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these seven components yields one global score. In the original validation study not including patients with a bipolar disorder, this scale had acceptable measures of internal homogeneity (Cronbach's 0.83), consistency (test-retest reliability scores had coefficients ranging from 0.84 (sleep latency) to 0.65 (medication use) $p < 0.001$, and validity (Hotelling's $TL = 2.62$, $p < 0.001$).

Diagnostic cut-offs, reliability and utility. A global PSQI score greater than 5 yielded a diagnostic sensitivity of 89.6% and specificity of 86.5% (kappa = 0.75, $p \leq 0.001$) in distinguishing "good and poor" sleepers[146]. Despite the fact that PSQI has been a scale of choice to measure subjective sleep problems in psychiatry, the authors reported that the correlations of the PSQI with the polysomnographic measures were not satisfactory[146]. This scale has also been used in studies assessing sleep in BDs, yielding poor correlations with objective measures, such as actigraphy[24, 147, 148]. We propose that a candidate explanation for this might be the patients' challenge in estimating an average of symptoms -possibly associated with fluctuations in symptoms and sleep-, throughout the one-month timeframe of this scale. Other possible explanation might be associated with the scale having two different instructions, and more than double the number of questions than for example, Athens Insomnia Scale(AIS)[144].

The Athens Insomnia Scale (AIS)

The AIS is a self-administered psychometric instrument consisting of eight items. The first five items of the AIS (assessing difficulty with sleep induction, awakenings during the night, early morning awakening, total sleep time, and overall quality of sleep) correspond to criterion A for the diagnosis of insomnia according to ICD-10, while the requirements of a minimum frequency (at least three times a week) and duration (1 month) of any complaint correspond to criterion B of the ICD-10[157]. The ICD-10 requirements of marked distress caused by the sleep problem and/or interference with ordinary activities of daily living (criterion C) are covered through the strictly subjective nature of the response options for every item of the scale as well as through the content of the last three items pertaining to the next day consequences of insomnia (problems with sense of well-being, functioning, and sleepiness during the day). Each item of the AIS can be rated 0 ± 3, (with 0 corresponding to ``no problem at all'' and 3 ``very serious problem''). The responders are requested to rate positive if they had experienced the sleep difficulty described in each item at least three times a week during the last month.

Two versions of the scale can be used. The entire eight-item scale (AIS-8) has a total score ranging from 0 (denoting absence of any sleep-related problem) to 24 (representing the most severe degree of insomnia). The brief five-item version (AIS-5) is limited to the first five items, with a total score ranges from 0 to 15. The AIS-8 is intended for use in a clinical

setting, while the AIS-5 is mainly used when there is a need to focus just on difficulty with sleep quantity and quality. The last three items of the AIS-8 refer to daytime symptoms that often emerge because of nocturnal sleep disturbance in insomniac patients. However, these symptoms are non-specific and may be caused by sleep disorders other than insomnia, such as narcolepsy and obstructive sleep apnea, or other disorders such as depression.

Regarding the sample in which AIS was originally tested, it is relevant to note that the AIS was given to 299 subjects, divided in four groups: 105 primary health care patients presenting with a complaint of insomnia not attributed to any obvious underlying cause (primary insomnia), 100 psychiatric outpatients, 44 psychiatric inpatients, and 50 non-patient controls. The AIS sample characteristics (Table V-3), the high measures of internal consistency (Table V-4), and the test-retest reliability (Table V-5), along with a sensitivity of 91% and specificity of 87% made this subjective scale an excellent candidate tool to be tested within our BDs population.

Table V-3. Sample characteristics of the Athens Insomnia Scale(AIS) [144]

	N	Male gender	Age(mean±S.D)	Range
Primary Insomniacs	105	41%	58.9±10.2	21-79
Psychiatry outpatients	100	41%	43.0±13.3	19-78
Psychiatry inpatients	44	45.5%	32.3±14.2	18-70
Non-patient controls	50	46%	37.2±10.5	22-63
Total sample	299	42%	46.0±15.7	18-79

Table V-4. Internal consistency of the Athens Insomnia Scale(AIS) [144]

	N	AIS-8	AIS-5
All subjects	299	0.89	0.87
Primary insomniac patients	105	0.90	0.85
Psychiatry outpatients	100	0.86	0.81
Psychiatry inpatients	44	0.85	0.86
Controls	50	0.75	0.75

Table V-5. Test-retest reliability of the Athens Insomnia Scale(AIS)[144]

AIS-8 total score	0.89
AIS-5 total score	0.88
Single items	
Sleep induction	0.86
Awakenings during the night	0.80
Final awakening	0.80
Total sleep duration	0.82
Sleep quality	0.70
Well-being during the day	0.85
Functioning capacity during the day	0.79
Sleepiness during the day	0.77
($p<0.001$ for each correlation)	

Table V-6. Comparison of pooled sensitivity and specificity of subjective sleep scales Insomnia [66].

Scales	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)
ISI	0.88(0.79 to 0.93)	0.85(0.68 to 0.94)
AIS	0.91(0.87 to 0.93)	0.87(0.68 to 0.95)
PSQI	0.93(0.86 to 0.96)	0.75(0.64 to 0.84)
P value ISI vs AIS	0.40	0.77
P value ISI vs PSQI	0.31	0.31
P value AIS vs PSQI	0.92	0.92
ISI=Insomnia severity scale; AIS=Athens Insomnia scale; PSQI=Pittsburgh Sleep Quality Index; CI=confidence interval		

AIS was selected as the primary measure of subjective insomnia in our study [145]. While AIS is a gold standard for measuring subjective insomnia, knowledge of the psychometric properties of AIS, and the correlation of this measure with actigraphy-derived sleep variables were lacking for patients with a BD.

Other subjective scales for measuring characteristics of sleep

Among the subjective assessment scales, there are tools that have been used to measure aspects of sleep other than insomnia, such as daytime sleepiness, biological rhythms, and chronotype. We describe here the scales that have been commonly used clinically and in research among patients with a BD.

- The **Epworth Sleepiness Scale (ESS)**[152]: a simple, self-administered questionnaire which is shown to provide a measurement of the subject's general level of daytime sleepiness. One hundred and eighty adults rated the chances that they would doze off or fall asleep when in eight different situations commonly encountered in daily life.

- The **Hypersomnia Severity Index (HSI)**[158]: a tool designed to measure severity, distress and impairment of hypersomnia in psychiatric populations including euthymic bipolar participants with a range of sleep complaints and unmedicated unipolar depressed participants meeting operational criteria for hypersomnolence disorder. Its validity was established by significant associations

with the Epworth Sleepiness Scale (ESS), the Pittsburgh Sleep Quality Index (PSQI), and two weeks of diary- and actigraphy-determined total sleep time and time in bed.

- The **Biological Rhythms Interview for Assessment in Neuropsychiatry (BRIAN)**[153]: as biological rhythm disturbances are widely associated with the pathophysiology of mood disorders, this self-report indexes rhythm disturbance in sleep, activity, social and eating patterns. The scale was tested with 103 subjects (31 bipolar, 32 major depressive disorder (MDD), and 40 healthy volunteers) who wore an actiwatch for fifteen days and completed a first morning urine sample and the BRIAN on day 15 Item Response Theory (IRT) analyses showed that 11 of 18 BRIAN items displayed a high level of discrimination between item options across a range of BRIAN total scores. Total BRIAN score correlated with wake after sleep onset, total activity count during sleep, and urinary 6-sulphatoxymelatonin.
-

BRIAN Activity domain correlated with the daytime transition probability from rest to activity. A three-factor solution, termed sleep/social rhythm factor, activity factor and feeding factor, provided the best theoretical and most parsimonious account of the data; items essentially loaded in factors as theoretically intended, with the exception of the sleep and social scales, which formed a single factor. Test-retest reliability and internal

consistency were excellent. The study revealed that BRIAN displayed promising external validity compared to objective parameters of circadian rhythmicity. A recent publication confirmed the association of poor functioning and quality of life in patients with major depressive and bipolar disorder using objective and subjective measures of sleep and BRIAN[24]

- The **Morningness-Eveningness questionnaire(MEQ)**: this scale contains 19 items concerning sleep and wake times, preferred times for physical and mental activities, and subjective alertness. It is among the most commonly used scales to measure chronotype. After removing a few items, MEQ is a psychometrically reliable score in BDs[98]; the correlation of mood with chronotype score has shown to be better than using alternative instruments[159].

One shortcoming of the previous work in BDs is that the correlations between subjective measures and actigraphy data have been poor. This might be associated with the limited reliability of the commonly used Pittsburgh Sleep Quality Index (PSQI) in this specific population. The factors affecting the reliability of self-report in BDs include cognitive impairment[160], memory bias, lack of motivation[161], fluctuation in symptom severity[148], or polypharmacy[162, 163]. As a result, sustained attention is compromised.

We observed that Athens insomnia scale has consistent, simple instructions and assess symptoms for an equivalent timeframe as PSQI. We decided to test its properties and association to objective measures and we found good psychometric properties, a moderate

correlation with a later sleep phase (eveningness), higher sleep fragmentation and later timing of sleep offset.

Objective methods to describe sleep

Other category of sleep assessment methods refers to objective measuring tools. Despite the fact that polysomnography (PSG) is deemed the gold standard for sleep quality evaluation, this technology poses some major limitations: constraint to laboratory settings, the high costs, and design to be a cross-sectional assessment, frequently performed over one-night. In laboratory settings, other measures to study sleep might be performed along PSG, such as measure of cortisol in urine or blood samples, dim light melatonin onset and rectal core body temperature. However, the logistics to perform this type of assessments, besides relying on human and material resources, they interrupt the patient's activities, and modify his experience of sleep in ways that might not be controlled enough, such as. increasing his level of anxiety. Therefore, we chose to focus on sleep measuring tools that can be suitable for clinical and in-home settings.

Wrist-based actigraphy is a useful addition to the clinical evaluation of patients with insomnia, sleep-wake rhythm disturbances, and periodic limb movement disorder. Multiple studies highlight actigraphy as a potent objective tool for the ambulatory monitoring of sleep and activity in BDs. However, a recent study found that commercially available sleep parameters (total sleep time, sleep onset/offset) from conventional actigraphy algorithms are sub-optimal for describing sleep-wake cycles in patients with

BDs[164]. This challenge seems to be associated with a high prevalence of fragmented sleep, and daytime inactivity among these patients. Recently, wrist-accelerometry data from general population has demonstrated excellent sensitivity and accuracy to identify periods of sleep using open source algorithms, which are device-independent, and have been validated against polysomnography (PSG). This remained to be validated in populations such as BD, with high prevalence of fragmented sleep.

Additionally, a lack of associations between subjective and objective sleep might have been associated to a limited suitability of the algorithms used to process the actigraphy data. Therefore, the use of a modified algorithm and complement with measures for sleep variability and daytime inactivity that capture chronotype and consolidation of sleep become a useful tool to characterize the sleep of patients with BDs.

Moreover, as mentioned, there are other factors, such as the patient's perception of their sleep, that can be provided only by subjective methods. Therefore, sleep detection methods should be combined to produce a synergy between objective and subjective methods. However, their specificity is low compared to their sensitivity, and the lack of a cut-off point represent limitations of such technology,

STUDY I

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Inactograms and objective sleep measures as means to capture subjective sleep problems in patients with a bipolar disorder.

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Running title: Sleep problems in bipolar disorders

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Abstract

Background: Sleep problems are common in bipolar disorders (BDs). To objectively characterize these problems in BDs, further methodological development is needed to capture subjective insomnia.

Aim: To test psychometric properties of the Athens Insomnia Scale (AIS), and associations with actigraphy-derived measures, applying modifications in actigraphy data processing to capture features of perturbed sleep in patients with a BD.

Methods: Seventy-four patients completed the AIS and the Quick Inventory of Depressive Symptomatology, self-report (QIDS-SR-16). Locomotor activity was continuously recorded by wrist-actigraphy for ≥10 consecutive days. We computed the sleep onset/offset, the center of daily inactivity (CenDI), as a proxy for chronotype, and the degree of consolidation of daily inactivity (ConDI), as a proxy for sleep-wake rhythm strength.

Results: AIS showed good psychometric properties (Cronbach's alpha=0.84; test-retest correlation=0.84, p<.001). Subjective sleep problems correlated moderately with a later sleep phase (CenDI with AIS rho=0.34, p=.003), lower consolidation (ConDI with AIS rho=-0.22, p=.05; with QIDS-SR-16 rho=-0.27, p=.019), later timing of sleep offset (with AIS rho=0.49, p=

≤.001, with QIDS-SR-16 rho=0.36, p=.002), and longer total sleep (with AIS rho=0.29, p=.012, with QIDS-SR-16 rho=0.41, p=≤.001). While AIS was psychometrically more solid, correlations with objective sleep were more consistent across time for QIDS-SR-16.

Conclusions: AIS and QIDS-SR-16 are suitable for clinical screening of sleep problems among patients with a BD. Subjective insomnia associated with objective measures. For

clinical and research purposes, actigraphy and data visualization on inactograms are useful for accurate longitudinal characterization of sleep patterns.

Keywords: insomnia, sleep-wake rhythm, sleep pattern, sleep, bipolar disorders, actigraphy

Background

Measures that accurately capture the subjective and objective features of sleep-wake rhythms have the potential to help advance etiopathological and interventional research in patients with a BD. Sleep problems have been described as one of the factors implicated in the pathophysiology of BDs[1-3] and are present even during euthymic phases[4-7]. Patients with a BD face problems with sleep latency, duration, wake after sleep onset, and sleep efficiency[5]. A third of patients with a BD suffer from insomnia[8], and 40% report excessive daytime sleepiness, which is contrasted by a prevalence of 18% in the general population9. Accumulating evidence suggests a link between a circadian rhythm disruption, and vulnerability for BDs[2, 10]. An internal dysregulation of chronobiological rhythms as an etiological feature of psychopathology has been further supported by a higher likelihood of having an evening chronotype[11], and abnormal melatonin secretion[12, 13]. Additionally, genetic association studies have provided evidence for the role of clock genes in the etiopathology of BDs[14, 15]. Changes in sleep during major mood episodes have been linked

to clinical severity, and vulnerability to suicide in patients with a BD[16]. Furthermore, sleep perturbations may exert negative impacts on treatment outcomes, the overall disease course[17], quality of life[18, 19], and functioning[20].

Wrist-based actigraphy is a useful addition to the clinical evaluation of patients with insomnia, sleep-wake rhythm disturbances, and periodic limb movement disorder[21, 22]. Multiple studies highlight actigraphy as a potent objective tool for the ambulatory monitoring of sleep and activity in BDs[4, 5]. However, a recent study found that commercially available sleep parameters (total sleep time, sleep onset/offset) from conventional actigraphy algorithms are sub-optimal for describing sleep-wake cycles in patients with BDs[23]. This challenge seems to be associated to a high prevalence of fragmented sleep, and daytime inactivity among these patients. Therefore, the authors computed complementary measures for sleep variability and daytime inactivity. Recently, wrist-accelerometry data have demonstrated excellent sensitivity and accuracy to identify periods of sleep using open source algorithms, which are device-independent, and have been validated against polysomnography (PSG)[7, 24]. One shortcoming of the previous work in BDs is that the correlations between subjective measures and actigraphy data have been poor. This might be associated to a limited reliability of the commonly used Pittsburgh Sleep Quality Index (PSQI)[18, 25, 26]. The factors affecting reliability of self-report in BDs include: cognitive impairment, memory bias, lack of motivation[27], fluctuation in symptom severity[26], or polypharmacy[28, 29]. As a result, sustained attention is compromised.

Additionally, a lack of associations between subjective and objective sleep might have been associated to a limited suitability of the algorithms used to process the actigraphy data.

The purpose of this study was to improve the ability of actigraphy to capture perturbations of sleep and/or sleep-wake rhythms among patients with a BD, based on subjective and objective measures. We used the Athens Insomnia Scale (AIS) as the primary measure of subjective insomnia. While AIS is a gold standard for measuring subjective insomnia, knowledge of the psychometric properties of AIS, and the correlation of this measure with actigraphy-derived sleep variables are lacking for patients with a BD. We utilized the sleep detection algorithm developed by Van Hees et al[7] to extract conventional sleep parameters. Additionally, we computed the daily phasing of sleep, the degree of sleep consolidation, and evaluated their correlations with subjective sleep.

Methods

Participants: We recruited 91 consenting patients from the Bipolar Disorders Clinic of the Douglas Mental Health University Institute (DMHUI), Montreal, Canada. The data were collected from April 2016 to June 2018. Patients were eligible for participation if they had clinically been diagnosed with a BD according to DSM-5 criteria30, treated as outpatients at this clinic, capable of consenting, and between the ages of 18 and 70, inclusively. We excluded patients with active substance use disorder, active suicidality, or other symptoms that required hospitalization, or that could have led to compromised adherence to study procedures. The protocol for this study was carried out in accordance with The Code of

Ethics of the World Medical Association (Declaration of Helsinki), and was approved by the Ethics Committee of the DMHUI. All participants provided written informed consent at the first visit. Study data were collected and managed using REDCap electronic data capturing tools[31].

Measures of mood. Mood was evaluated based on interviews, hourly charts, and surveys over a two-week period. In interviews at intake (V1), and two weeks later (V2), researchers asked about mood during the past seven days, and rated mean severity of depressive symptoms using the Montgomery-Åsberg Depression Rating Scale (MADRS)[32], and the peak severity of manic symptoms using the Young Mania Rating Scale (YMRS)[33]. The current mood episode at both visits was investigator-determined (OL) using DSM-5 criteria, taking into account all information in the medical files, symptom scores, and the hourly mood charts. A stable phase was defined as the absence of any DSM-5 episode, and could thus include depressive, hypomanic, or mixed symptoms that did not fulfill the severity or duration criteria of a DSM-5-defined episode.

Subjective sleep. At both visits, the participants completed questionnaires on sleep problems during the past month (AIS)34 and during the past week (the Quick Inventory of Depressive Symptoms (QIDS-SR-1635, items 1 to 4). Although QIDS-SR-16 sleep items were not developed to be a measure of sleep problems, we used them to complement AIS scores.

Descriptors of sleep. Patients were outfitted with GeneActiv wrist-actigraphy devices and were instructed to wear the accelerometer for 14 days36. We used the sleep detection algorithm introduced by Van Hees et al7 to process the actigraphy data as described previously37. Sleep derived from accelerometry data was defined as inactivity associated with a low degree of arm angle changes (≤5° for ≥ 5min). We further excluded any days with more than 1h of non-wear, and, for comparability, 10-day data were used to calculate descriptors of sleep.

The actigraphy-derived sleep scores were converted into inactograms to visualize the temporal sleep pattern across the recording period (Figure 1). A Python script for converting accelerometry data into inactograms is available[145] on Github..

The center of daily inactivity (CenDI) was defined as the mean direction of the 24-hour inactivity in radian, providing information about the daily phasing of sleep, whereas consolidation of daily inactivity (ConDI) was represented by the mean length of the vector describing CenDI, corrected for total sleep. Both values were calculated using the Circular Statistics Toolbox for MATLAB38 (see circular plots in Figure 1 for illustration). We also provide a standard deviation (SD) to reflect diurnal variation of each of these variables.

To calculate sleep, we set a rolling window with a length defined as the minimum value between 2 hours and of 20% of daily total sleep time, divided by ConDI. Total daily time inactive (from here on, total sleep time) across 24 hours was defined as the sum of all 1min bins scored as sleep (inactivity, one) per each daily cycle. The 24hr time span defining one

daily cycle was centered at mean CenDI. The rolling window was moved by 1min increments across the 24-hour cycle as defined above; each period of sleep ended when the moving window started to encompass activity (activity=zero). The longest sleep period per 24-hour cycle calculated in this manner was defined as the nighttime sleep period, and sleep onset and sleep offset were calculated as the beginning and end of nighttime sleep. The calculated onsets/offsets and CenDIs correlated strongly with the patient-reported data (Figure 2), with expectedly longer subjective timing (time in bed), as compared with the actigraphy derived values (closer to actual sleep). Notably, a very similar approach has been recently shown to agree well with PSG-determined sleep onset/offsets24, 39.

Categorization of medication. We consulted the medical files for the current pharmacotherapy, which was also confirmed with the participants. For descriptive purposes, we categorized the medication as described in detail previously40, and then used this classification to describe patients taking/not-taking a given class of medication.

Statistical analysis. Statistical analysis was performed using IBM SPSS Statistics version 24.0 (SPSS Inc.). Normality of distribution for each dimensional variable was tested using the Shapiro- Wilk test. Since most of the dimensional variables were not normally distributed, all correlation coefficients were computed using Spearman's rank order correlation. Despite multiple testing, for descriptive purposes, significant relationships were defined by p-values <.05.

Results

Characteristics of the sample

We offered the study to 130 patients with a BD, of whom 91 gave an informed consent. Both a sufficiently long actigraphy recording (≥10 days) and a complete AIS were available for 74 patients at V1, and 72 at V2. The median age was 49.0 (IQR=19.75), median MADRS score 14.0 (IQR=20.75), and median YMRS score 5.0 (IQR=9.5). The most common episodes were a stable (n=37, 50%), major depressive (n=28, 28%) or hypomanic (n=9, 12%) episode. The current medication included the following: lithium (n=20, 27%), anticonvulsants (n=46, 62%), antipsychotics (n=51, 69%), antidepressants (n=36, 49%), and benzodiazepines (n=13, 18%); the majority of patients had a combination of medication from different categories.

Description of subjective sleep

AIS showed a Cronbach's alpha of 0.84 both at V1 and V2. Each item showed good correlations with AIS total score (all rho≥0.58). The test-retest correlation between V1 and V2 was strong (rho=0.72, p<.001). The median baseline AIS score in the sample was 6.0 (IQR=6.25), which is the cut-off value for insomnia34. At baseline, about half (42/74, 56.8%) of the patients screened positive in AIS (≥6 points), suggestive of insomnia. At V2, the median AIS score was 5.0 (IQR=7.0).

QIDS-SR-16 sleep score showed a Cronbach's alpha 0.17 (V1) or 0.12 (V2), and item 4 had an unacceptable item correlation with total QIDS-SR-16 sleep score (V1 rho=0.30, V2

rho=0.37), as well as negative correlations with items 2 and 3. Removal of item 4 did not improve Cronbach's alpha (V1 0.36, V2 0.28). Test-retest correlation between V1 and V2 was strong (rho=.73, p=<.001). AIS correlated moderately with QIDS-SR16 sleep score (V1 rho=.57, p=<.001, V2 rho=.53, p=<.001).

Description of objective sleep

The accelerometry data analysis showed timing of sleep (sleep onset, offset, and total sleep) as follows: median onset 23:55PM, (25% at 22:15PM, and 75% at 00:40AM), and median offset 08:15AM (25% at 06:40AM, and 75% at 10:10AM). Median total sleep time was 6.3hrs (25% 5hrs, and 75% 7.2hrs). Figure 1 shows examples of actigraphy-derived inactograms, alongside circular plots reporting average CenDI (vector angle) and ConDI (vector length).

Correlations between subjective sleep and actigraphy data

A more severe subjective insomnia, measured by a higher AIS score, correlated moderately with a later CenDI, but also with a later timing of sleep offset, and longer total sleep (Table 1). ConDI negatively correlated with AIS, indicating that insomnia associates with fragmented sleep in patients with BD. QIDS-SR-16 sleep score correlations underscore the findings with AIS: positive correlations were found for sleep offset and total sleep time, and a negative correlation with ConDI (Table 1).

To visualize association between CenDI and insomnia, we sorted the circular plots by increasing CenDI (Figure 3, see also Supplement 1), i.e., from early to late sleep phases. Patients with subjective insomnia (AIS score ≥6) were found enriched among patients with a later CenDI, indicative of an evening-leaning chronotype (Figure 3 and Supplement 1). Notably, patients scoring positive in AIS exhibited a diversity of aberrant sleep patterns, which may indicate different pathological states (Supplement 1).

Discussion

We found that AIS reliably captured the subjective sleep problems among patients with a BD. Variables derived from accelerometry data reporting changes in arm-angle, with a focus on inactivity, proved to capture the characteristics of sleep. We complemented conventional measures with variables reflecting chronotype and fragmentation of sleep. With these methods, subjective sleep problems were reflected in observable characteristics of the inactograms. This was confirmed statistically: a more fragmented sleep, a longer total sleep, and a later timing of sleep offset correlated with severity of insomnia. In clinical work, inactograms can provide a quick and easy way to observe the degree and type of variation in the daily patterns of sleep. Previous research correlating subjective and objective measures of sleep using actigraphy and PSQI in patients with BDs has resulted in discrepant findings18, 25, 26. Here, we report good psychometric properties for AIS, which has the same 1-month time-frame as PSQI, but has more consistent rating instructions across the scale. At the same time, our data suggest that even AIS may not be

perfect in this population: while test-retest showed a moderate correlation with a two- week interval, the associations of AIS with actigraphy measures were not consistent at V1 and V2, despite the overlapping time period covered by the scale and the actigraphy recording. Interestingly, the correlations between QIDS-SR-16 sleep score and actigraphy measures were consistently associated with objective sleep at both V1 and V2. The AIS asks patients to report sleep problems that have been present at least three times per week, during the last month, and it is common that due to fluctuations in their symptoms and sleep, patients find it challenging to estimate an average. On the other hand, QIDS-SR-16 asks for sleep during the past week and includes several options to describe the frequency of symptoms. In conclusion, while AIS can capture sleep problems that are objectively seen, some further development seems necessary to have an optimal scale to screen for insomnia among patients with severe symptoms. A reliable subjective report necessitates clear instructions and a shorter time frame. Fragmented sleep and increased daytime inactivity are typically found along with depressive symptoms, and in our data, they also were the strongest correlates of subjective insomnia. Thus, increasing reliability of actigraphy-derived measures that capture these characteristics is essential. The values from the commercially available actigraphy processing software are unable to alert users about aberrant sleep patterns in a given patient, which may bias conventional sleep parameter calculation. We addressed this gap by converting the actigraphy data into inactograms, and this proved to be useful for quality control of the extracted data. Another limitation of the algorithms used by commercial actigraphy devices is that they have usually been developed in healthy

subjects with regular rhythms. These algorithms are likely to be suboptimal among the patients with severe problems with sleep. We used the algorithm validated with PSG by Van Hees et al7, and further modified this algorithm by adding a rolling window to determine the nighttime sleep bout. This method proved to determine accurate values as demonstrated by the strong correlation between calculated and reported sleep onset/offset and mid-sleep phases.

Reliable objective approaches for the detection and characterization of sleep problems may turn out to be relevant for clinical screening of sleep disorders. Visual inspection of inactograms could support the clinician in conducting effective personalized treatment and follow up. Subjective insomnia scales are feasible in screening and measure subjective need and experience about sleep and functionality, which are not captured by objective measures of sleep. At the same time, the use of questionnaires alone is insufficient to describe the characteristics of sleep. For instance, they might systematically underestimate the sleep duration, compared to healthy controls42. As described in our data, patients scoring positive in AIS showed great diversity in sleep pattern characteristics, including insufficient duration or quality of sleep, excess inactivity, misaligned sleep timing in reference to clock time, or fragmented sleep. Therefore, optimally, both subjective and objective measures should be considered. A combination of a subjective report and the use of inactograms is expected to provide critical guidance on clinical treatment and increase quality of data in research. For instance, the possibility of visualizing inactivity, and

matching pharmacological or chronotherapeutic interventions to the individual chronotype and sleep phasing, might prove useful to increase efficacy. They might also help to reduce side effects and/or risk of complications, such as worsening an already perturbed sleep-wake rhythm. The actigraphy- based variables described here could be used in clinical trials as inclusion and exclusion criteria and, most importantly, to capture pre- and post-intervention characteristics of sleep patterns. However, valid cut-offs for the respective variables need to be determined in future studies. The fragmentation index (FI), which is defined as a measure of sleep continuity, has been recently introduced to complement conventional measures for timing of sleep, and used in cohorts with BDs18, 43. The FI is calculated as the amount of time associated with movement (restlessness) during the sleep period, expressed as percentage. A higher FI indicates more disrupted sleep. FI is sensitive to the (in)accuracy in determining sleep onset/offset. Therefore, we used measures that do not rely on sleep onset/offset determination: CenDI, which is a proxy for chronotype, and ConDI, which reflects the degree of sleep fragmentation, and strength of rhythmicity. Since the daily timing and distribution of sleep is relatively stable in healthy controls44, we also used variation in both CenDI and ConDI to test inter-day variability in sleep parameters in patients with a BD. These measures proved to be useful in describing characteristics of sleep patterns that associated with subjective insomnia.

Some limitations deserve consideration when interpreting the results of our study. The patients were recruited from tertiary care, where the chronic phase of the illness and the

prevalent polypharmacy are expected to have effects on the sleep-wake rhythms, and thus, the severity of sleep problems might not generalize to the bipolar spectrum. We included a relatively large sample of patients with a BD (n=74), with a variety of symptom severity. To increase reliability of subjective report, we used two scales to measure subjective sleep covering different time frames of retrospective assessment (1 month and 7 days). Our main finding, a correlation between subjective and objective measures of sleep, is not dependent on etiology of sleep problems. Fragmented sleep is expected to be more common in this tertiary care sample than in other populations with a BD, and the algorithm is likely to perform more robustly in populations with less severe symptoms. Our actigraphy data were not compared to PSG, which is capable of differentiating sleep from 'inactive' wakefulness. However, we selected actigraphy methods over PSG, since the major limitation of the latter is that it cannot be used as an ambulatory measure to longitudinally assess sleep. Additionally, the accelerometry-based recording of wrist-angle changes to assess sleep has been validated with PSG by Marino et al, showing an excellent sensitivity (0.97) and accuracy (0.86)24. Longer recording periods (7-14 nights) have shown to improve parameter stability45 and to reduce the effect of external confounders on the timing of sleep36. Thus, the participants in our study were instructed to wear the actigraphy device continuously for 14 days, and we implemented an analysis on a minimum of 10 days of recorded data.

Conclusions

We recommend regular screening for insomnia among patients with a BD, using AIS and visual inspection of inactograms to improve diagnostic accuracy. We postulate that actigraphy based sleep assessment, and the use of inactograms will facilitate accurate diagnosis, personalized treatment, and follow-up of various manifestations of aberrant sleep patterns in BDs. We demonstrated that the center of daily inactivity (CenDI) and consolidation of sleep (ConDI) are robust actigraphy-derived variables that perform well in capturing sleep parameters, even in cases of extremely fragmented sleep, which seems particularly prevalent in patients with BDs. Since the robustness of these measures is not affected by even extreme aberrations in sleep timing and distribution, they may be of critical value for the understanding sleep problems, both in clinical and research settings.

Table 1. Correlations of subjective and objective measures of sleep of 74 patients with a bipolar disorder.

Actigraphy measures	V1, n=74								V2, n=72							
	AIS						QIDS-sleep		AIS						QIDS-sleep	
	Sleep		Day		Total				Sleep		Day		Total			
	Rho	p	Rho	p	Rho	p	Rho	p	Rho	p	Rho	P	Rho	p	Rho	p
CenDI	**.26**	**.026**	**.32**	**.005**	**.34**	**.003**	.16	.17	.042	.73	.20	.087	.14	.26	.16	.17
SD of CenDI	.084	.48	.12	.30	.13	.28	.13	.27	.097	.42	.20	.10	.16	.16	**.25**	**.037**
ConDI	-.10	.39	**-.27**	**.019**	**-.22**	**.05**	**-.27**	**.019**	.038	.75	-.18	.13	-.099	.40	**-.28**	**.018**
SD of ConDI	.17	.15	.09	.45	.17	.16	.20	.076	.19	.10	**.26**	**.026**	**.26**	**.031**	.20	.09
Onset	.064	.59	.029	.80	.05	.68	-.20	.093	.094	.43	.014	.91	.022	.85	-.19	.11
SD of onset	.044	.71	.14	.22	.14	.25	.068	.56	-.055	.65	.13	.28	.05	.66	.15	.19
Offset	**.36**	**.002**	**.48**	**<.001**	**.49**	**<.001**	**.36**	**.002**	.006	.95	**.25**	**.039**	.15	.19	**.33**	**.004**
SD of offset	.11	.35	.12	.32	.16	.16	**.29**	**.013**	.028	.81	.21	.07	.15	.20	**.27**	**.02**
Total sleep	.21	.076	**.31**	**.007**	**.29**	**.012**	**.41**	**≤.001**	.064	.59	.16	.19	.10	.40	**.38**	**≤.001**
SD of Total sleep	.17	.15	.10	.39	.18	.11	**.28**	**.015**	-.042	.72	.08	.496	.06	.62	**.25**	**.036**

V1: visit one, V2: visit two; QIDS-sleep: Quick Inventory of Depressive Symptoms, self report (items 1 to 4); AIS: Athens Insomnia Scale;

SD: standard deviation; CenDI: center of daily inactivity; ConDI: consolidation of daily inactivity.

Figure 1. Examples of inactograms alongside circular plots of patients with a bipolar disorder. In the inactograms, black bars indicate times scored as sleep. One line represents 2 successive days of actigraphy recording (double plot). The circular plots to the right of the inactograms represent the same data but now averaged, i.e. the average temporal pattern of sleep is outlined by the area delimited by a thin back line in the plot. The blue bar indicates the midpoint of sleep (=CenDI), whereas its length reports the degree of sleep fragmentation (=ConDI). A shorter vector means more fragmentation and thus, less consolidated sleep. A, a patient showing short sleep that is consolidated, and phased early. B, a patient exhibiting consolidated sleep, which is longer and phased later when compared to A. C, D patients showing late phase, and fragmented sleep (reflected by the reduced vector length in the circular plot). D, a patient who displays a high level of inactivity across the daily cycle.

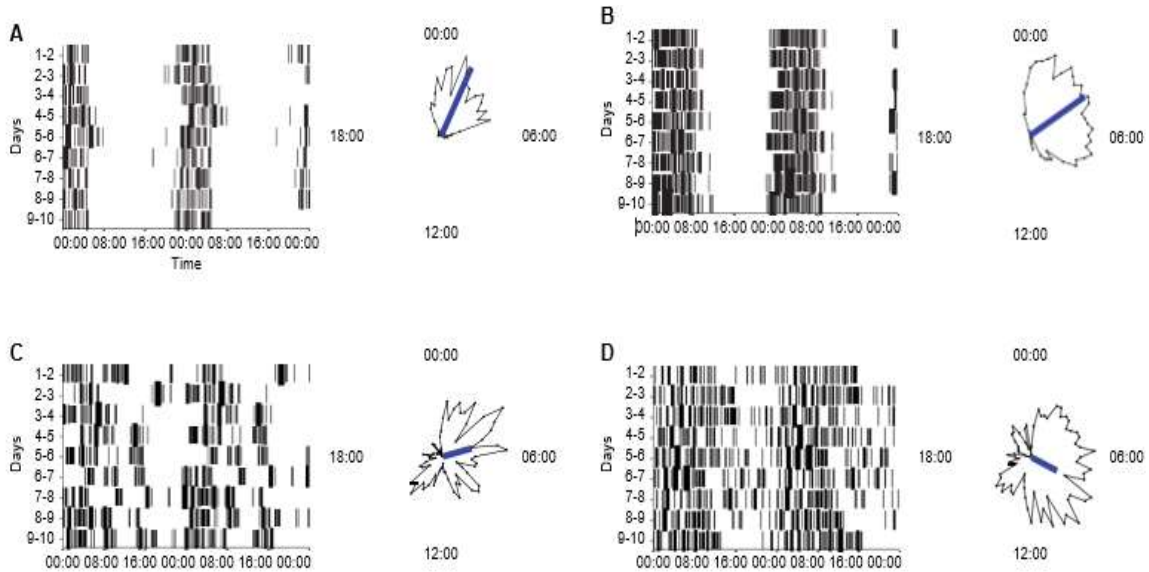
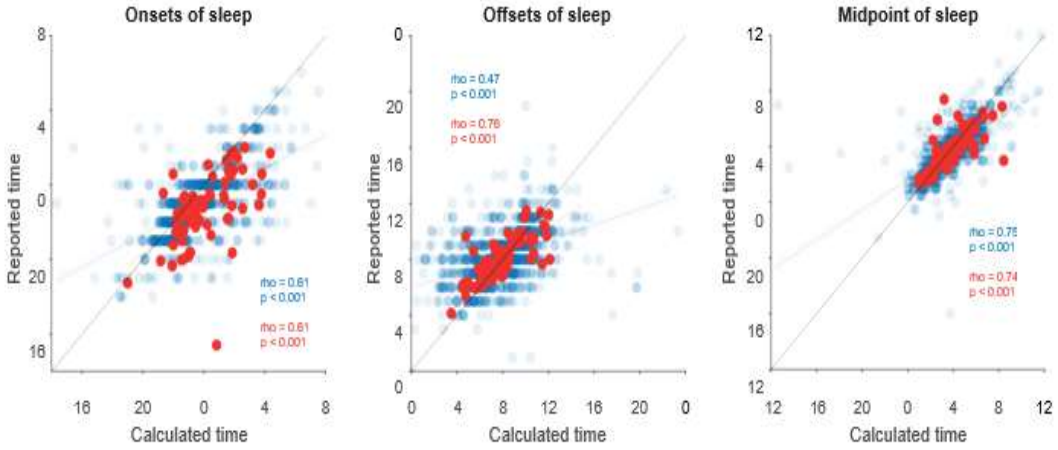


Figure 2. Correlations between patient reported and actigraphy-based sleep onset, offset, and sleep midpoint (CenDI). Blue dots indicate the timing of subjective reports with calculated timing. Red dots indicate the mean values for each patient.



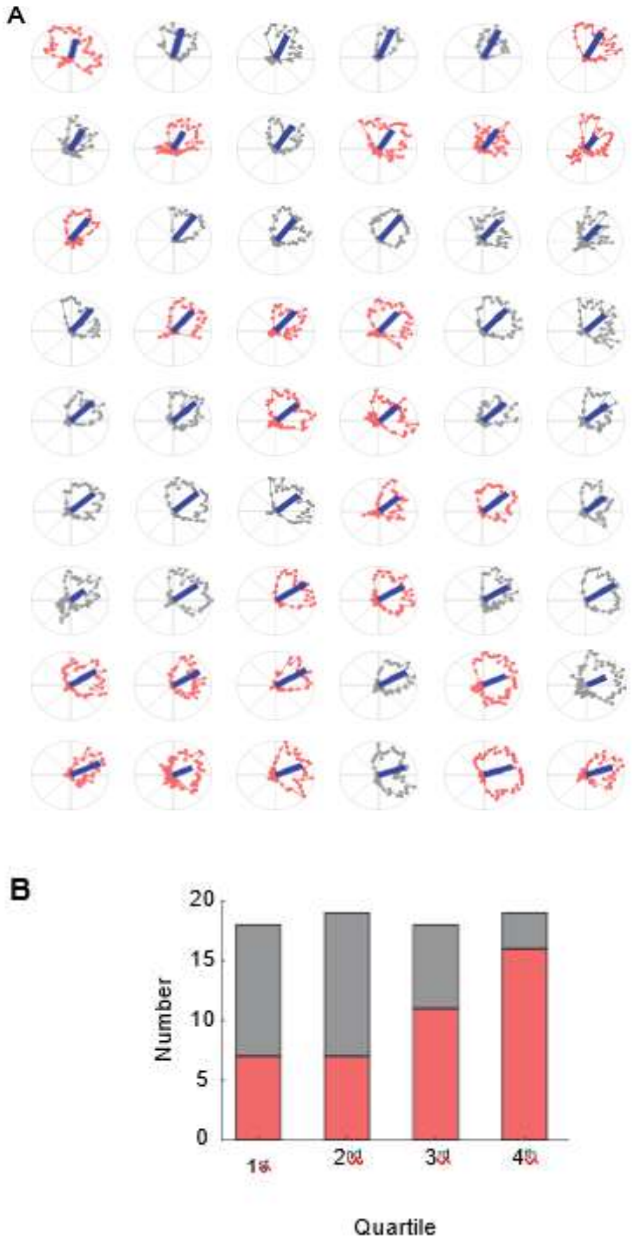


Figure 3. A, Circular plots of 74 patients sorted by ascending CenDI (sleep midpoint). Plots of patients screening positive for insomnia (AIS score ≥6) are highlighted in red. B, distribution of the same patients presented in quartiles (red indicates screen positives, grey negatives). The diagram shows how the proportion of patients that screen positive for insomnia increases towards later timing of sleep (CenDI). The difference between the first and last quartile was 45.2% (confidence interval 13.9% to 66.5%, p=0.0052).

Figure S1. Inactograms and circular plots of the 74 patients, ordered by increasing CenDI, i.e., increasingly later sleep phase.

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STUDY II

Effects of antipsychotics on circadian rhythm in humans: a systematic review and meta-analysis

--Manuscript Draft--

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Abstract

Antipsychotics are widely used in psychiatric treatment. Several studies show that they might modulate circadian rhythm. The purpose of this systematic review is to collect and integrate current knowledge about the effects of antipsychotics on the circadian rhythm in humans, and, where sufficient data is available, to conduct a meta-analysis. The following electronic databases were searched: PubMed, Cochrane Library, EMBASE, Scopus, Web of Science, CI-NAHL, Biosis, clinicaltrials.gov, and LILACS. This systematic review followed the PRIS-MA guideline and included randomized controlled trials, non-

randomized controlled trials, case-control studies, case series, and case reports. Of 7,217 articles, we finally selected 70 articles. The effect of antipsychotics is seen as decreased amplitude of cortisol, melatonin, and temperature. Particularly, a meta-analysis of 16 RCTs related to cortisol rhythm showed that antipsychotics, especially atypical antipsychotics, significantly decreased the area under the curve of cortisol levels and morning cortisol level compared to placebo. Notably, while patients with disrupted sleep showed more regular sleep on atypical antipsychotics, more disrupted rhythm was seen on typical antipsychotics. Overall, gaps in the current knowledge show that there is a need to inform optimal timing of administration of antipsychotics according to individual baseline circadian rhythm. Standardized selection criteria and outcome methods should be agreed on to facilitate good quality intervention studies and evidence-based treatment guidelines. This is essential since there is accumulating evidence about the high prevalence and unfavorable impact of disrupted circadian rhythm in psychiatric disorders.

Keywords*: antipsychotics, circadian rhythm, sleep-wake cycle, rest-activity cycle, cortisol, melatonin, chronotherapeutic*

Introduction

Abnormalities in circadian rhythm are common in psychiatric disorders. Among them, most of the data and thus, the most convincing evidence for alterations of circadian rhythm and chronotype is in bipolar disorders [1]. Disruption of circadian rhythm has also been identified in patients with major depressive disorders, seasonal affective disorders [2], and

schizophrenia [3], and there is recent evidence in eating disorders [4] and attention deficit disorder [5]. While data specifically in psychiatric disorders is not available, it has been well established in different populations that a disrupted circadian rhythm has detrimental effects on both mental and physical wellbeing, as well as prevalence and outcome of disorders such as diabetes or hormonal cancers [6-8]. While the prevalence of these somatic complications is also increased in severe mental illness as compared to the rest of the general population [9, 10], targeting irregular rhythms among patients with psychiatric disorders is likely to be essential to improve not only the primary outcome but also to reduce excess physical illnesses and mortality in this population.

The excess prevalence of disrupted circadian rhythm in severe mental illness can partly be explained by primary sleep disorders such as sleep apnea or restless legs syndrome [11, 12], and then, the guidelines for sleep disorders apply [see references [13, 14] for some recent guide-lines]. However, patients with a severe mental illness also use psychoactive medications, which complicates treatment of disrupted circadian rhythm [11, 12]. Some recent guidelines describe current knowledge about chronobiological treatments in psychiatry [15]. However, the guidelines focus on complementary treatments and do not describe optimal use of psychoactive medications: trials have almost exclusively been done with mood as an outcome measure, and data on individual rhythm before and after intervention is rarely available. Trials with a focus directly on the circadian rhythm parameters are essential to improve success in treatment of the disrupted circadian rhythm

specifically. Equally important is to recognize that, unfortunately, the efficacy vs unbeneficial effects of chronotherapy and psychoactive medication can be dependent on the individual timing of the sleep phase and chronotype as compared to the timing and dosing of the treatment.

Antipsychotics are the treatment of choice in schizophrenia, and commonly used in other psychiatric illnesses, especially in case of insomnia. However, the effect of antipsychotics on circadian rhythm remains contradicting. Several studies have reported that antipsychotics stabilize disrupted circadian rhythm in patients with psychiatric disorders [16-20]. Notably, in some studies, antipsychotics may disrupt the circadian rhythm, and induce circadian rhythm sleep-wake disorder [17, 21, 22]. These results also propose that typical and atypical antipsychotics could have different effects on circadian rhythm [17, 21, 22]. Furthermore, the studies tend to be very heterogenous: their target groups for both cases and controls and compounds in use vary. A lack of consensus criteria for methods and parameters to describe circadian rhythm results is an essential limitation for integration of findings. Importantly, methods to measure circadian rhythms vary, including actigraphy-derived rest-activity rhythm, melatonin rhythm, circadian cortisol rhythm, and core body temperature. Additionally, characteristics of circadian parameters used in the analysis include rhythmicity, phase shifting and cycle lengthening, as well as the change of amplitude. Integrative information on these clinical studies is necessary to guide treatment of patients with major psychiatric disorders.

This study aimed to perform a systematic review and meta-analysis to integrate the knowledge about the effects of antipsychotics on parameters of circadian rhythm based on human studies. We describe the data independent of study designs, and cases and controls could be either patients or healthy subjects. The meta-analysis was limited to RCTs.

Methods

We conducted a systematic review and reported its results according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (Supplementary Table S1). The study protocol was registered at PROSPERO, number CRD42019137288 (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=137288).

Key question

The purpose of this review was to investigate the effect of antipsychotics on the circadian rhythm in human subjects who are healthy or have primary medical conditions to be treated with antipsychotics.

Search strategies

We searched for articles having 'antipsychotics-related keywords' AND 'circadian rhythm-related keywords' in their title and abstract. The search strategies comprised a combination of Medical Subject Headings (MeSH) or their equivalent, keywords, truncations and

Boolean operators. Details of the search strategy are shown in the Supplemental Table S2. An electronic search was performed on PubMed, Cochrane Library, EMBASE, Scopus, and CI-NAHL (Cumulative Index to Nursing and Allied Health Literature), BIOSIS, clinicaltri-als.gov, Web of Science, and LILACS (Latin American and Caribbean Health Sciences Literature). All articles that were published from January 1980 to June 2019 were included. We applied no restrictions for language. Additional manual search was also conducted with using reference lists from retrieved articles (Supplementary Table S2).

Study selection

Duplicated articles were removed electronically. Articles obtained by the search strategies were manually selected with following methods. The inclusion criteria were 1) articles related to the influences of antipsychotics on circadian rhythm in humans, 2) article types such as case report, case series, case-control studies, cohort studies, non-randomized controlled trials, randomized controlled trials (RCTs), 3) clinical studies. The exclusion criteria were 1) articles irrelevant to this topic, 2) article types without new research data such as editorial, comment, and letter, 3) books, 4) work in animals, cell models, or post-mortem. The titles and abstracts of articles in a potential eligible list were independently read by two authors (E. Moon, P. Lavin) in order to evaluate the inclusion and exclusion criteria. Articles that met the exclusion criteria by both raters were removed from the potential eligible list. Full texts of the remaining articles on the potential eligible list were independently read by two authors (E. Moon, P. Lavin) in order to evaluate the eligibility

of articles. If there was any disagreement, we had a consensus meeting with a third review author (O.Linnaranta). References in eligible review articles were additionally evaluated by two authors (EM, OL) in order to find new articles (Figure 1).

Quality assessment

Two authors per article independently completed the quality assessment for each article (EM, PL, OL) (Supplementary Tables S3-8). We used the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for case reports and case series, and the Newcastle-Ottawa scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) in case-control studies [23]. The assessments of risk of bias in RCTs were used by the Cochrane risk of bias tool [24]. We had a consensus meeting on any disagreements with a third review author. All studies are de-scribed in the tables. However, while no reliable cut-off for good quality was found, articles within upper (best quality) 75 percentiles of quality assessment were finally described in the results.

Data extraction

Two authors per article independently extracted data from the included studies (EM, PL, OL) (Table 1-4, Supplementary Tables 9-12). If there was any disagreement, we discussed with a third member of the review team and finalized decisions. Structured forms were be used for data extraction on following contents: authors, publication year, country, type of study, inclusion criteria, exclusion criteria, age range, principal diagnosis of participants,

sample size, drop-out, compound used, dosing and format, duration of intervention, outcome measures, and main findings. If there was any unclear research information, we contacted with study authors by email.

Data synthesis

If there were sufficient numbers of articles and participants in order to perform meta-analysis, after classifying articles based on clinical similarities, the data were pooled together. The measurement data in pairwise meta-analysis used the standardized mean differences (SMD) between comparative groups with 95% confidence interval (95% CI). When synthesizing comparative data in multi-arm trials studies, the methods of splitting the shared group were used in order to maintain the characteristics of each arm in multi-arm [25]. After meta-analysis, secondary subgroup analysis according to the class of antipsychotics, sampling sites, and measurement periods were also performed. In case of continuous variables, meta-regression was also done to evaluate whether clinical variables, such as calculated equivalent dosages, measurement duration, treatment duration, or principal dopamine and serotonin receptor affinities of antipsychotics were significantly associated with standardized mean difference. Dosages of antipsychotics used in included studies were calculated into equivalent doses with three ways of International Consensus (IC), Classical Mean Doses (CMD), and Defined Daily Doses (DDD) methods [26-28]. Dopamine and serotonin receptor affinities were estimated based on previously reported receptor binding profiles [29]. The heterogeneity was assessed with an I2 statistics. We

regarded I2 <25% as a low level, 25~50% as a moderate level, and >50% as a high level [30]. A fixed-effect model was used when I2 ≤50%, while when I2 >50%, a random-effects model was used. Sensitivity analysis was performed to find the source of heterogeneity. Possible publication bias was evaluated with the Linear regression test of funnel plots. A two-tailed p-value <0.05 was considered as a statistical significance. The data analysis was conducted using R statistical software, version 3.6.0 with the meta package for meta-analysis.

Results

Study selection

According to the original search strategy, 7,217 studies were retrieved, and 2,040 duplicate studies were excluded (Figure 1). After screening the titles and abstracts according to the eligibility criteria by two independent reviewers (EM, PL), 4,962 further studies were excluded. A total of 215 studies were further evaluated with reading full-text articles by two independent reviewers (EM, PL), and 146 studies were additionally excluded. References of re-view articles in the article list were screened manually, and we found 1 additional RCTs meeting eligibility criteria. Finally, we identified 70 eligible studies.

Characteristics of included studies

Case reports

Ten case reports described the potential influence of antipsychotics (AP) in patients [16-18, 20, 21, 31-35]. While some studies reported an effect of several AP, the AP covered in the studies included haloperidol (2), bromperidol (1), chlorpromazine (1), and sulpiride (1), and atypical AP, such as aripiprazole (6), clozapine (2), and risperidone (2) (Supplementary Table S11). The duration of use of AP varied from 8 weeks to 3 years, and the measurement of outcome from 31 hours to 3 years. While the studies also could use several methods, the most common methods for measurement were actigraphy (4) and sleep diary (4). Two case reports measured urinary 6-sulphatoxy melatonin (1) and rectal temperature (1), respectively. The median JBI score was 5.5/8 (Interquartile range 4~7, Minimum 3, Maximum 8) (Supplement Tables S3 and S11). The 9 articles within upper 75 percentile were considered for the summary of results.

Case series

There were 16 case series [22, 36-50]. Most of the cohorts included subjects having psychiatric disorders, including schizophrenia (9/16, 56.3%), mood disorders (4/16, 25.0%), delayed sleep phase syndrome (1/16, 6.3%), or a heterogenous diagnostic group (1/16, 6.3%). One cohort included healthy volunteers. These case series examined the effects of typical AP, including haloperidol (5), fluphentixol (1), sultopride (1), sulpiride (1), chlorprotixen (1), and atypical AP, including olanzapine (4), aripiprazole (2), quetiapine (1), and clozapine (1). The duration of medication varied from 120 minutes to 16 weeks, and the duration of outcome measurement from 120 minutes to 16 weeks.

Cortisol rhythm was the most common method used (12); other methods included sleep-wake cycle (2), circadian rest-activity rhythm (2), melatonin (1), and temperature (1). The median JBI score was 7/10 (Interquartile range 4.5~7, Minimum 1, Maximum 9) (Supplement Tables S4). The 12 articles within upper 75 percentile were considered for the summary of results.

Case-control studies

We identified 25 case-control studies [3, 40, 51-73]. Eight studies included patients taking specific AP (8/25, 32.0%), while most studies reported overall effects regardless of the type of antipsychotic (17/25, 69.0%). The controls were drug-free. The cases included patients with schizophrenia (20/25, 80.0%), psychosis (1/25, 4.0%), bipolar disorder (1/25, 4.0%) or heterogenous patient groups (3/25, 12.0%). One study examined the participants in a children camp [55]. The controls were mostly healthy controls (24/25, 96.0%) except one study comparing two AP in two patient groups. Case-control studies measured circadian rhythms with cortisol (19/25, 76.0%), actigraphy (4/25, 16.0%), and melatonin (2/25, 8%). While cortisol was the most frequent outcome measure, it was measured from blood (14/19, 73.7%), saliva (3/19, 15.8%), CSF (1/19, 5.3%), or this remained unclear (1/19, 5.3%). While some reports described patients who had used AP for years, the prospective data collection varied between 4 days and 3 months. The median NOS score was 4.0/9 (Interquartile range 3~4, Minimum 2, Maximum 8) (Supplement Tables S5). The 22 articles within upper 75 percentile were considered for the summary of results.

Randomized controlled trials

RCTs included subjects having psychiatric disorders (10/21, 47.6%) or healthy volunteers (11/21, 52.4%) [19, 51, 74-92]. The trials with psychiatric disorders included patients with schizophrenia (6/10, 60%), bipolar disorder (1/10, 10%), major depression (1/10, 10%), Alzheimer's disease (1/10, 10%), or generalized anxiety disorder (1/10, 10%). These RCTs examined the effect of AP, including haloperidol (8), fluphenazine (2), sulpiride (2), quetiapine (8), olanzapine (4), risperidone (2), aripiprazole (1), ziprasidone (1), amisulpride (1), and clozapine (1), on circadian rhythms. In studies with healthy volunteers, two RCTs used a protocol with a duration of medication around 1 week, while most of RCTs used single administration of medication. The duration of outcome measurement varied from 2 to 16 hours. In studies with patients, most RCTs showed the duration of medication and prospective outcome measurement were the same, and their durations varied from 4 to 22 weeks. One RCT used the single administration protocol with a duration of outcome measurement from 50 to 60 minutes. Most of studies measured the cortisol rhythm (17/21, 81.0%), using blood cortisol (14), urine cortisol (3), or salivary cortisol (1). Others included actigraphy (4), melatonin (1), and temperature (1). The overall quality of RCTs was good with one exception. The median risk of bias score was 4.0/14 (Interquartile range 4~5, Minimum 1, Maximum 10) (Supplement Tables S6-7).

Do patients differ from controls before treatment?

Nine case-control studies compared at baseline the cortisol levels between drug-free patients and healthy subjects (Supplementary Table S12). In the largest case-control study including 162 drug-free patients with schizophrenia and 138 healthy controls, patients showed higher serum morning cortisol level than healthy controls [65]. Four case-control studies including 5 to 89 patients and 5 to 34 controls showed no difference between these two groups in plasma morning cortisol level, or other serum cortisol-derived parameters [61, 68, 70, 73]. In contrast, one case-control study reported a lower CSF morning concentration in patients [57], and an-other study lower serum cortisol concentration during insulin-induced hypoglycemia [56].

What are the effects of Antipsychotics?

Effect of AP on sleep-wake cycle and circadian rest-activity rhythm

A) Rest-activity rhythm - Among healthy subjects

One RCT examined the effect of quetiapine on sleep-wake cycle and circadian rest-activity rhythm in 20 patients and 20 healthy controls within a relatively short time, one week (Table 2) [85]. After intervention, quetiapine group showed later final wake time, longer total sleep duration, and greater sleep efficiency than placebo group. However, there were no significant differences in Fragmentation index, Sleep onset latency, M10 activity (the activity during a most active 10-hour window), L5 activity (the activity during a least active 5-hour window), Relative amplitude (the degree reflecting the difference between M10

activity and L5 activity, RA = (M10-L5)/(M10+L5)), Inter-daily stability (the degree of consistency of activity pat-terns form one day to the next), and Within-in-variability (the fragmentation of periods of activity from periods of rest within a 24-hour period) between quetiapine and placebo groups.

B) Rest-activity rhythm - Among patients

Case reports (Supplementary Table S11) and case series (Table 3) with patients consistently suggest that typical AP such as haloperidol and fluphentixol tend to disrupt circadian rhythm, and atypical AP such as clozapine, aripiprazole, risperidone reinstate circadian rhythm [16-18, 21, 22, 34]. Meanwhile, the treatment of aripiprazole in delayed sleep phase syndrome consistently showed earlier sleep-wake cycle compared to pre-treatment in three case reports [20, 32, 33] and one case series [47]. One case series in patients with bipolar disorder or major depressive disorder showed that quetiapine increased the M10 activity, did not change the L5 activity [37]. Two case-control studies with an adequate follow-up compared the sleep-wake cycle and circadian rest-activity rhythm using actigraphy between the pre-treatment and post-treatment in psychiatric patients [62, 69]. Post-treatment, patients showed a decrease of daytime alertness and circadian rhythm robustness and an increase of sleep peri-od and total sleep time.

C) Rest-activity rhythm - Patients vs controls

Two case-control studies compared in total 40 patients taking AP and 41 healthy controls with no medication (Table 4) [3, 51]. One case-control study showed consistently that patients taking AP show lower daytime activity than both patients without AP and healthy controls [51]. The other case-control study with unclear duration reported that 17 patients among schizophrenia group (N=20) showed abnormal sleep-wake activity during AP, and 16 subjects among control group with no history of psychiatric illness (N=21) showed delayed sleep onset or less consolidated and fragmented sleep phases [3].

Effect of AP on Cortisol rhythm

A) Cortisol - Among healthy subjects

Eleven RCTs examined the effect of AP on cortisol rhythm in healthy subjects (Table 2, Supplementary Table S12 B2). Among them, six RCTs with in total 130 individuals on AP and 88 individuals without AP showed that the group with AP had consistently low morning serum cortisol level compared to no AP group [75-77, 80, 83, 88]. All of five studies used atypical AP. In contrast, other five RCTs with 112 individuals on AP and 69 with no AP re-ported no difference in cortisol levels as measured from plasma, saliva or urine between individuals on AP and placebo [76, 78, 81, 89, 91]. Among these five articles, only two RCTs used atypical AP [81, 91]. Another one RCT reported that haloperidol increased cortisol level compared to placebo [84]. Meanwhile, two RCTs comparing the AUC of cortisol secretion between atypical AP and typical AP showed conflicting results [76, 81]. Thus, after RCTs were reclassified according to clinical

similarities, the meta-analysis of some of these data were performed subsequently (Figure 1).

B) Cortisol - Among patients

More than half of articles reported decreasing effects of AP on cortisol level (Table 3, Supplementary Table S12 C1-3). Four case series including total 100 patients showed a de-creased plasma or serum cortisol level after post-intervention [36, 38, 44, 50]. Six case-control studies including 302 cases and 312 controls also reported a decrease of morning serum or plasma cortisol level in patients treated with AP compared to controls [53, 56, 59, 61, 65, 73]. Furthermore, one RCT including 41 cases and 41 controls indicated that atypical AP significantly decreased serum cortisol levels compared to placebo [90]. Meanwhile, two case series, one including 196 cases, clozapine and salivary cortisol [39]. and the other 5 cases on sultopride with serum cortisol level [45] reported no difference of cortisol level between pre-intervention and post-intervention [39, 45]. Among case-control studies, six articles including 164 cases and 230 controls reported no difference of cortisol derived parameters between cases and controls [53, 56, 61, 68, 70, 72]. Among them, three case-control studies used typical AP [56, 61, 68], and two case-control studies used atypical AP [70, 72]. On the other hand, two case series showed a higher cortisol level after the treatment of typical AP [40, 43]. Meanwhile, among three RCTs comparing atypical and typical AP, two RCTs reported that individuals with atypical AP showed lower morning cortisol level than typical AP [82, 92], but one RCT did not show significant difference

between two groups [74]. Thus, the meta-analysis of three RCTs were subsequently performed (Figure 1).

C) Cortisol - Patients vs healthy controls

A large majority of studies comparing patients with AP and drug-free healthy subjects, reported no significant differences of cortisol levels between the two groups (Table 4, Supplementary Table S12 D) [40, 60, 61, 63, 66-68, 70, 72]. Only two studies reported a lower cortisol level in patients than in healthy subjects [59, 73].

Effect of Antipsychotics on Melatonin rhythm

A) Melatonin rhythm - Among healthy subjects

One RCT observed the effect of single administration of quetiapine on melatonin rhythm in 18+18 healthy subjects (Table 2) [75]. This study showed that quetiapine did not significantly change the urinary melatonin secretion compared to placebo. Furthermore, there was no difference of the urinary melatonin secretion between quetiapine 25mg and 100mg.

B) Melatonin rhythm - Among patients

One case report in a patient with schizophrenia examined urinary melatonin secretion for 2 days (Supplementary Table S11) [21]. The peak of melatonin secretion in this patient was 2:29 AM. One case series reported that olanzapine administration for 4 weeks in

patients with schizophrenia did not significantly change the area under the curve (AUC) of nocturnal blood melatonin levels compared to the baseline in drug-naïve condition (Table 3) [44]. However, the melatonin secretion during the first half of the night after olanzapine treatment seemed to be earlier than one of drug-naïve condition. Even though, unfortunately, this study did not compare statistically the change of melatonin secretion phase, this finding implies that olanzapine might have an advancing effect on the phase of melatonin secretion [44].

C) Melatonin rhythm - Patients vs controls

One case-control study [64] cross-sectionally compared the melatonin AUC between drug-naïve schizophrenia and healthy control, and drug-naïve schizophrenic patients showed significantly lower melatonin AUC than healthy controls (Table 4). The subsequent follow-up study with 10-week AP treatment including clozapine, haloperidol, or pimozide, did not significantly change melatonin secretion compared to the drug-naïve condition. Also, they found no evidence of phase shifting despite a trend of decrease of melatonin levels [64].

Effect of antipsychotics on core body temperature

A) Core body temperature - Among healthy subjects

One RCT showed the effect of single oral administration of haloperidol or sulpiride on body temperature in healthy individuals (Table 2) [78]. This study measured the oral body tempera-ture for 6 hours after taking medications in a room that was carefully controlled

and kept con-stant at 22℃. Both haloperidol and sulpiride significantly attenuated the increase of oral tem-perature AUC compared to placebo.

B) Core body temperature - Among patients

One case report suggests that core body temperature measured by rectal temperature was phase advanced in a patient with schizophrenia and treated with haloperidol (Supplementary Table S11) [21]. One case series found that haloperidol administration in depressed patients significantly decreased overall body temperature measured at regular interval (Table 3) [43].

The results of the pooled meta-analysis

There were 17 RCTs related to cortisol rhythm among the included 21 RCTs. After classifying these articles based on clinical similarities, articles of three categories were pooled together using meta-analysis (Supplementary Figure S1).

The comparison of cortisol secretion AUC in healthy subjects with AP and placebo

There were 11 comparative data in 6 articles related to this group. We adjusted data using combined groups and splitting one shared group in order to minimize unit-of-analysis errors. The standardized mean difference (SMD) of 11 comparative data was synthesized. The pooled SMD in healthy subjects showed that AP significantly decrease the cortisol

secretion AUC compared to placebo (Heterogeneity I2=46%, τ2=0.226, p=0.05, fixed effect model SMD [95% CI] = -0.608[-0.911 ~ -0.304]) (Figure 2). The sensitivity analysis showed that the significant result was not changed after removing any one of the analyzed data (Supplementary Figure S2). Linear regression test of funnel plot asymmetry did not indicate asymmetry thus excluding publication bias (Egger's regression test t = -1.003, df = 9, p = 0.342) (Figure 3).

In a subgroup analysis according to the class of AP, there was significant difference of pooled SMD in atypical AP between two groups, but not in typical AP (Atypical AP, heterogeneity I2=55%, τ2=0.333, p=0.02, random effect model SMD [95% CI] = -0.672[-1.185 ~ -0.159]); Typical AP, heterogeneity I2=0%, τ2=0, p=0.49, fixed effect model SMD [95% CI] = -0.646[-1.370 ~ 0.077]) (Supplementary Figure S3). In a subgroup analysis according to sampling site, there were significant differences of pooled SMD in urine, but not in blood and salivary samplings (Urine, heterogeneity I2=43%, τ2=0.219, p=0.17, fixed effect model SMD [95% CI] = -1.481[-2.091 ~ -0.870]); Blood, heterogeneity I2=0%, τ2=0, p=0.85, fixed effect model SMD [95% CI] = -0.331[-0.764 ~ 0.102]); Saliva, heterogeneity I2=60%, τ2=0.277, p=0.11, random effect model SMD [95% CI] = -0.324[-1.265~0.617]) (Supplementary Figure S4). In a subgroup analysis according to sampling time, there were significant differences of pooled SMD in nighttime, but not in daytime (Nighttime, heterogeneity I2=43%, τ2=0.219, p=0.17, fixed effect model SMD [95% CI]

= -1.481[-2.091 ~ -0.870]); Daytime, heterogeneity I2=0%, τ2=0, p=0.72, fixed effect model SMD [95% CI] = -0.321[-0.671 ~ 0.029]) (Supplementary Figure S5).

In meta-regression, the measurement duration of cortisol AUC (Estimate -0.154, SE 0.046, 95% CI = -0.244 ~ -0.064, p = 0.001) and D2/5-HT2A receptor affinity ratio (Estimate -0.067, SE 0.020, 95% CI = -0.106 ~ -0.028, p = 0.001) were significantly associated with SMD. There was no significant association between three equivalent dosages and SMD (IC, Estimate 0.052, SE 0.045, 95% CI = -0.037 ~ 0.140, p = 0.251;CMD, Estimate 0.044, SE 0.113, 95% CI = -0.179 ~ 0.266, p = 0.701; DDD, Estimate 0.100, SE 0.086, 95% CI = -0.069 ~ 0.268, p = 0.247)

The comparison of cortisol secretion AUC in healthy subjects with atypical and typical AP

Three comparative trials from 2 articles related to this group. After correction of multiplicity by splitting the shared group, the SMD of 3 comparative data was synthesized. The pooled SMD showed no difference of cortisol secretion AUC between subjects with atypical and typical AP (Heterogeneity I2=71%, τ2=0.529, p=0.03, random effect model SMD [95% CI] = 0.007[-0.976~0.990]) (Supplementary Figure S6). Meanwhile, in meta-regression, the measurement duration of cortisol AUC (Estimate -0.274, SE 0.106, 95% CI = -0.483~-0.066, p = 0.010) was significantly associated with SMD.

Comparison of morning cortisol level in psychiatric patients with atypical and typical AP

The SMD of three comparative data in three articles related to this group were synthesized. The result of meta-analysis did not show significant difference of cortisol secretion AUC be-tween subjects with atypical and typical AP (Heterogeneity I2=76%, τ2=0.4271, p=0.02, random effect model SMD [95% CI] = -0.701[-1.561~0.158]) (Supplementary Figure S7). However, in meta-regression, the treatment duration of AP was significantly associated with SMD (Estimate -0.104, SE 0.042, 95% CI = -0.186~-0.022, p = 0.013).

Discussion

This systematic review searched and integrated the extensive but heterogeneous literature related to the effects of AP on human circadian rhythm. Studies described circadian rhythm as measured by sleep-wake rhythm, rest-activity cycle, cortisol, melatonin, or temperature. The results suggest that AP have an influence on the rhythmicity, but due to limitations of study design, we cannot definitively conclude whether this is an impact on the amplitude and/or a phase-shifting effect. Given the high prevalence of disrupted circadian rhythms in psychiatric disorders, a comprehensive understanding about the dynamics of circadian regulation on AP as compared to no AP is necessary, as is knowledge about individualized timing of dosing of AP.

Effect of AP on the amplitude and phasing

Most of the evidence seems to support a decrease in the amplitude of hormonal regulators of the circadian rhythm. Especially atypical AP seem to decrease cortisol secretion. Most

of the studies in this systematic review were done using cortisol, one of the most important hormones related to circadian rhythm. Before the intervention, patients had a higher serum cortisol level and lower cerebrospinal fluid (CSF) cortisol level than controls and were similar in other parameters. After the intervention, atypical AP decreased the cortisol secretion AUC and morning level of cortisol. However, the effect size of typical AP was smaller, and this was confirmed in the meta-analysis. While disrupted rest-activity rhythms are highly prevalent in psychiatric disorders, typical and atypical AP seem to differ in their effect on the rhythm. As such, typical AP tended to disrupt the rest-activity circadian rhythm, but atypical AP corrected a disrupted rest-activity circadian rhythm. Interestingly, in one RCT comparing the effect between risperidone and haloperidol, risperidone showed an increase of daytime activity and decreased nighttime activity [51]. In one RCT with healthy volunteers having low risk of circadian rhythm abnormality, quetiapine did not change within-day-variability of rest-activity rhythm compared to placebo [85]. The findings indirectly suggest that AP might be mainly associated with the entrainment of rest-activity rhythm. The healthy circadian pattern of temperature tends to decrease during night and increase during day. One case series re-ported that haloperidol decreased body temperature during the day [43]. Also, one RCT showed that AP significantly attenuated the increase of temperature during the day [78]. These findings might suggest the deceasing or dampening effect on the temperature amplitude. Meanwhile, one case report found that clozapine advanced rectal temperature [21]. Regarding phase, there seems to be the advancing effect.

However, due to methodological limitations of the original studies, we cannot exclude that what seems to be a change in amplitude currently reflects a change in the timing of phasing. While some of our findings indicate that the effect of AP could be a phase shifting, the number of studies examining circadian parameters, such as phase shift and period length, were small, and the duration of measurement of hormonal markers insufficient to inform about a potential phase shift. Considering roles of the suprachiasmatic nucleus clock on modulating circadian cortisol rhythm [93], the abnormalities of the AUC of cortisol secretion or morning cortisol levels might reflect partly the abnormalities of circadian cortisol rhythm [94, 95].

One meta-analysis showed increased morning cortisol levels in schizophrenia and bipolar disorder that were highly related to circadian abnormalities [96]. Even though melatonin is the representative hormone of circadian rhythm, only one RCT measured the change of melatonin secretion. This RCT reported that there were no effects of quetiapine on total amount of urinary melatonin secretion [75]. Additionally, one case series and one case-control study also report-ed that AP did not significantly change nocturnal melatonin secretion [44, 64]. Only one case report describes that schizophrenic patients taking clozapine 300mg/day showed earlier phase of melatonin secretion, compared to the results of the peak time of melatonin secretion in other studies with healthy people [21, 97, 98]. Even though a case series reported no effect of AP on melatonin, this article also implies the possibility of an advanced phase of melatonin in the pattern of melatonin secretion [44].

Heterogeneity of original work

This is the first systematic review integrating the current knowledge on the effects of AP on circadian rhythm. To be able to separate the effect of the medication from the illness, we included information from a heterogenous selection of study designs, including several but not only RCTs. The studies were variable in terms of the target group, compound, duration of treatment, and outcome used. Despite the methodological variability, the results in healthy subjects were similar to those in psychiatric patients. Thus, we conclude that the medication has a certain impact independent of the condition causing the disrupted circadian rhythm. The most commonly used outcome measure was cortisol, which had been measured from urine, blood or saliva. The clearest effect of AP was detected in urine cortisol. Interestingly, three different equivalent dosages had similar effects on cortisol secretion in the two available RCTs comparing effect of dosing.

Reliability and utility of outcome measures

Our findings propose use of urine cortisol when measuring outcome of AP intervention: the meta-analysis for urine cortisol samples showed the largest effect size. Furthermore, urine and saliva cortisol reflect only unbound cortisol, in contrast, serum cortisol measures unbound and bound cortisol together [99]. Saliva cortisol is the most sensitive to the sampling conditions [99], and the AUC of cortisol in serum and saliva sampling were calculated through the data measured at regular intervals, making them sensitive to the frequency of measurement. Meanwhile, the AUC of cortisol in Urine sampling can be

measured through total unbound cortisol released in urine. In general, a sufficient duration of measurement for hormonal markers of the rhythm is needed to increase the effect size. Based on this review, we recommend a duration more than 8 hours for hormonal markers. Measurement of melatonin should be minimum 24 hours to show the acrophase. If the measurement duration can include the peak time of circadian parameters like recommended by Vidarsdottir et al. (2009), the acrophase of circadian parameters can be compared between agents [88]. The measurement of core body temperature necessitates further development of methods to increase feasibility. Wrist-based actigraphy is the method of choice for the diagnosis of circadian rhythm sleep disorders, and optimal for longer-term monitoring of rest: activity patterns and phasing of sleep [100].

Clinical implications

Given the profile of metabolic side effects, the utility of AP in correcting circadian rhythms is likely limited to severe mental illness, where the prevalence of disrupted circadian rhythms is high. However, we need better knowledge about beneficial and detrimental effects of AP among this population. Morning cortisol increase has been associated with unfavorable clinical factors, such as cognitive impairment, childhood trauma, stress reactivity, and emotional regulation [101-104]. AP would be potential agents to correct disrupted cortisol rhythm since they have decreasing effects on cortisol secretion. Additionally, the cortisol lowering effect of AP in patients who show an excess stress response might be especially beneficial. However, more knowledge about the dynamics of

the AP effect across the dark: light cycle, especially in patients, is needed to know whether and how the cortisol lowering effect of AP in patients is dependent of the timing of administration. Probably, individual circadian rhythm should be considered to maximize the beneficial therapeutic effects. Finally, clinicians should be aware of peripheral circadian clocks that are likely included in the complications caused by peripheral receptor effects of AP.

Future lines of research

Some recommendations for future studies can be given based on our findings. Patients and healthy controls do not differ in circadian effects of AP, despite relatively constant baseline rhythms in controls. Thus, studies on less vulnerable populations are meaningful to examine the effects of AP. The overall effect for novel compounds on circadian rhythms can be firstly tested in healthy subjects, and then RCTs should be performed in patients with misaligned or disrupted circadian rhythm. Also, clear cut-offs for reliable measures to describe misaligned or disrupted circadian rhythm compared to healthy condition are needed. While findings were robust transdiagnostically, we need instructions for inclusion and exclusion criteria that lead to more uniform pre-treatment circadian parameter characteristics. Consensus criteria for measuring circadian rhythms as the primary outcome in trials are needed to efficiently in-crease knowledge about efficacy of chronobiological interventions, and to provide evidence-based treatment guidelines.

Limitations

Firstly, quality of sleep might be one aspect of circadian rhythm in the extended concept and warrants future review. Secondly, despite the reasonable number of original studies, the methodological variability reduced the number of comparable studies for meta-analysis. Our main findings concern results from the meta-analysis; the studies with specific outcome measures showed low heterogeneity in results based on I2 and low risk of publication bias except lack of large-sample studies. Larger sample sizes and well-designed RCTs controlling for confounding factors are warranted. Thirdly, there are no consensus criteria for quality of studies. While all studies were presented in the tables, we decided to include only studies rated among 75% of the best quality studies in the results section; this still does not indicate necessarily good quality.

Conclusion

The effect of AP was seen as decreased amplitude of cortisol, melatonin, and temperature. Especially, meta-analysis of RCTs related to cortisol rhythms implies that AP might decrease cortisol secretion. Typical AP seem to disrupt rest: activity rhythms, while atypical AP regulate rhythms. Urine cortisol, 24-h melatonin to describe acrophase, and actigraphy to show rest: activity patterns/phasing and consolidation of sleep seem to be the best tools to describe outcome in trials. Methodological guidelines are necessary to improve comparability of trials and thus, evidence-based guidelines for optimal treatment of disrupted circadian rhythms.

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DISCUSSION

The objective in this research to provide tools to reliably assess sleep and circadian rhythm in Bipolar Disorders in clinical settings, was met. We found that AIS, QIDS-SR-16 and actigraphy measures are appropriate for clinical screening of sleep problems among patients with a BD. Subjective experience of insomnia associated with objective measures. For clinical and research purposes, actigraphy and data visualization on inactograms are useful for accurate longitudinal characterization of sleep patterns. As sleep disturbances in bipolar disorder are present during all stages of the illness and exert a negative impact on overall course, quality of life, and treatment outcomes, the availability of measuring tools that incorporate the symptoms and subjective experience as well as the objective measures of sleep across time opens possibilities for conducting public health interventions in the psychiatric population.

One limitation of the results however, is the lack of secondary analysis by DB type, which is an interesting exploration for future studies. Additionally we offer the proposal of conducting more research, optimally RCTs on the strong evidence about the circadian effect of antipsychotics with a longitudinal, real-time monitoring of circadian markers to differentiate a change in amplitude from a shift in phasing, and for knowledge about optimal timing of administration of antipsychotics, according to individual circadian

rhythm. Standardizing selection criteria and outcome methods could facilitate good quality intervention studies and evidence-based treatment guidelines. This is relevant considering the accumulating evidence of the high prevalence and unfavorable impact of disrupted circadian rhythm in psychiatric disorders.

The analysis performed on the existing data on antipsychotics and circadian rhythms allowed us to suggest the utility of AP in correcting circadian rhythms is likely, and especially relevant in the psychiatric population due to the elevated prevalence of disrupted circadian rhythms. As morning cortisol increase has been associated with unfavorable clinical factors, such as cognitive impairment, childhood trauma, stress reactivity, and emotional regulation, AP could represent potential agents to correct disrupted cortisol rhythm since they have decreasing effects on cortisol secretion. Additionally, the cortisol lowering effect of AP in patients who show an excess stress response might be especially beneficial.

However, future lines of research about the dynamics of the AP effect across the dark: light cycle, especially in patients, is needed to know whether and how the cortisol lowering effect of AP in patients is dependent of the timing of administration. Optimally, individual circadian rhythm should be considered to maximize the beneficial therapeutic effects. Finally, clinicians should be aware of peripheral circadian clocks that are likely included in the complications caused by peripheral receptor effects of AP

CONCLUSION

We propose a stepped model of evaluation In BD, where screening with AIS detects patients with subjective sleep problems. Accurate diagnostics with actigraphy for timing and fragmentation of sleep rhythms leaves only those with a suspected sleep apnea or restless feet to be investigated with polysomnography. This model helps in resourceful but accurate diagnostics and personalized treatment of sleep problems. Methodological improvements and future trials with a focus on circadian rhythm parameters are necessary to guide evidence-based treatment of sleep problems among patients with a BD are necessary.

GLOSSARY

Chronobiology: A subdiscipline of biology concerned with the timing of biological events, especially repetitive or cyclical phenomena, in individual organisms.

Circadian: A term derived from the Latin phrase “circa diem,” meaning “about a day”; refers to biological variations or rhythms with a cycle of approximately 24 hours. Circadian rhythms are self-sustaining (i.e., free running), meaning that they will persist when the

organism is placed in an environment devoid of time cues, such as constant light or constant darkness. For comparison, see diurnal, infradian, and ultradian.

Circadian time (CT): A standardized 24-hour notation of the phase in a circadian cycle that represents an estimation of the organism's subjective time. CT 0 indicates the beginning of a subjective day, and CT 12 is the beginning of a subjective night. For example, for a nocturnal rodent, the beginning of a subjective night (i.e., CT 12) begins with the onset of activity, whereas for a diurnal species, CT 0 would be the beginning of activity. For comparison, see Zeitgeber time.

DD: A conventional notation for an environment kept in continuous darkness (as opposed to a light-dark cycle). For comparison, see LD.

Diurnal: Varying with time of day. Diurnal rhythms may persist when the organism is placed in an environment devoid of time cues, such as constant light or constant darkness. Therefore, diurnal variations can be either light driven or clock driven. For comparison, see circadian.

Entrainment: The process of synchronization of a timekeeping mechanism to the environment, such as to a light-dark cycle, or LD. For comparison, see free running.

Free running: The state of an organism (or rhythm) in the absence of any entraining stimuli. Typically, subjects are kept in constant dim light or constant darkness to assess their free-running rhythms. For comparison, see entrainment.

Infradian: A term derived from the Latin phrase "infra diem," meaning "less than a day"; refers to biological cycles that last more than 1 day and, therefore, have a frequency of less than one per day. For comparison, see circadian and ultradian.

LD: Conventional notation for a light-dark environmental cycle; the numbers of hours of light and dark are typically presented separated by a colon. For example, LD 16:8 denotes a cycle consisting of 16 hours of light and 8 hours of dark. For comparison, see DD.

Masking: The obscuring of the "true" state of a rhythm by conditions that prevent its usual expression. Usually, the phase of an entrained rhythm or the absence of entrainment (e.g., in an animal that is unable to entrain because of some defect) is said to be masked by a light cycle. For example, the aversion of a nocturnal rodent to bright light results in its activity onset appearing to coincide with the absence of light, or "lights off," when the animal actually has been awake for hours. For comparison, see *entrainment.*

Nonrapid eye movement (NREM) sleep: Sleep stages that include the "deeper" stages of sleep in which dreaming typically does not occur. Also referred to as slow-wave sleep. For comparison, see rapid eye movement sleep.

Phase shift: A change in the phase of a rhythm. This change can be measured by observing a change in the timing of a phase reference point (e.g., activity onset or the nocturnal rise in the release of the hormone melatonin) from the timing expected based on previous, *free-*

running cycles. Phase shifts may be either advances (i.e., the phase reference point occurs earlier than normal) or delays (i.e., the phase reference point occurs later than normal).

Phase-response curve (PRC): A graphical summary of the *phase shifts* produced by a particular manipulation, such as a light pulse or a pharmacological treatment, as a function of the phase (i.e., *circadian time*) at which the manipulation occurs. Defining the PRC to light has enabled researchers to understand and predict how *entrainment* to light cycles is accomplished.

Rapid eye movement (REM) sleep: A stage of light sleep characterized by rapid eye movements and associated with dreaming. Also called paradoxical sleep. For comparison, see *nonrapid eye movement sleep.*

Suprachiasmatic nucleus or nuclei (SCN): A cluster of nerve cells located in the brain region called the hypothalamus that is responsible for generating and coordinating circadian rhythmicity in mammals.

Ultradian: A term derived from the Latin phrase "ultra diem," meaning "more than a day"; refers to biological cycles that last less than 1 day and, therefore, have a frequency of more than one per day. For comparison, see *circadian* and *infradian*.

Zeitgeber: A German word literally meaning "time-giver." A time cue capable of entraining *circadian* rhythms. Light represents the most important Zeitgeber.

Zeitgeber time (ZT): A standardized 24-hour notation of the phase in an

entrained *circadian* cycle in which ZT 0 indicates the beginning of day, or the light phase, and ZT 12 is the beginning of night, or the dark phase. For comparison, see *circadian time.*

APPENDIX

Appendix A.
Athens Insomnia Scale

ID:_____ Age:_____ Sex:_____ Date:_____

Instructions: This scale is intended to record your own assessment of any sleep difficulty you might have experienced. Please, check (by circling the appropriate number) the items below to indicate your estimate of any difficulty, provided that it occurred at least three times per week during the last month[a]

Sleep induction (time it takes you to fall asleep after turning-off the lights)
0: No problem 1: Slightly delayed 2: Markedly delayed 3: Very delayed or did not sleep at all

Awakenings during the night
0: No problem 1: Minor problem 2: Considerable problem 3: Serious problem or did not sleep at all

Final awakening earlier than desired
0: Not earlier 1: A little earlier 2: Markedly earlier 3: Much earlier or did not sleep at all

Total sleep duration
0: Sufficient 1: Slightly insufficient 2: Markedly insufficient 3: Very insufficient or did not sleep at all

Overall quality of sleep (no matter how long you slept)
0: Satisfactory 1: Slightly unsatisfactory 2: Markedly unsatisfactory 3: Very unsatisfactory or did not sleep at all

Sense of well-being during the day
0: Normal 1: Slightly decreased 2: Markedly decreased 3: Very decreased

Functioning (physical and mental) during the day
0: Normal 1: Slightly decreased 2: Markedly decreased 3: Very decreased

Sleepiness during the day
0: None 1: Mild 2: Considerable 3: Intense

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