Biological rhythms and chronotherapeutics in depression

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I. INTRODUCTION

Depressive symptoms are frequent and heterogeneous brain conditions affecting up to 20% of the general population (Bakish, 2001; Kessler et al., 2005; Malhi and Mann, 2018). Depression is a major public health problem being one of the three main causes of time spent with disability (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018), and with considerable economic burden (Wang et al., 2003). Until today, diagnostic processes of major depressive disorder (MDD) largely rely on clinical evaluation with validated criteria such as DSM-5 or CIM-11 (American Psychiatric Association, 2013; World Health Organization, 2019). Nevertheless, a tremendous variability in symptoms may occur within a depressive syndrome, which does not allow for relevant treatment recommendations (Geoffroy and Gottlieb, 2020; Malhi and Mann, 2018). In this context some authors proposed a return to fundamental dimensional pillars, approaching the core features and natural presentations of mood disorders (Geoffroy and Gottlieb, 2020; Malhi et al., 2018).

The “sleep” domain should be one of these dimensional pillars to consider, as it is a core symptom of depressive syndromes occupying a primary position in the pathophysiology, phenomenology, historical accounts, and evolution of episodes in mood disorders (Geoffroy, 2018; Geoffroy and Gottlieb, 2020; Lee, 2019a; McClung, 2013; Palagini et al., 2019a; Wirz-Justice and Benedetti, 2019). Indeed, sleep alterations are part of DSM-5 criteria of MDD (American Psychiatric Association, 2013). It has been reported that more than 90% of patients suffering from depression have sleep disturbances (Pierre A. Geoffroy et al., 2018a; Tsuno et al., 2005). Bidirectional associations have been observed between mood episodes and these sleep disturbances (Franzen and Buysse, 2008; Geoffroy, 2018). In

addition, sleep disturbances worsen the severity of depressive symptoms in MDD (O'Brien et al., 2011), are associated with poorer treatment response (Pigeon et al., 2008), and increased the risk of suicidal ideation and suicide attempt (Li et al., 2012; Pigeon et al., 2012). Recently, it has been confirmed that sleep disturbances predicted suicidal behaviors during a 3 years follow-up, independently of all psychopathologies (Geoffroy et al., 2020b). In addition, the persistence of sleep disturbances after treatment of the depressive episode increases the risk of relapses and recurrences (Li et al., 2012). Regarding objective markers, studies using actigraphy reported alterations of sleep-wake cycles during depressive phases with less activity during daytime and longer wake after sleep onset (Tazawa et al., 2019). Studies using polysomnography (PSG) reported that patients may present several alterations including a shortened time spent in slow wave sleep (SWS), increased rapid eye movement (REM) sleep duration, shortened REM sleep latency, a prolongation of the first REM period, and increased REM density (Baglioni et al., 2016; Berger and Riemann, 1993; Berger et al., 1982; Kupfer, 1976; Kupfer et al., 1986; Kupfer and Foster, 1972; Lauer et al., 1991; Riemann et al., 1994). Taken as a whole these PSG findings indicate that a combination of diminished SWS duration and increased REM density may be possible biological markers for MDD (Palagini et al., 2013; Pillai et al., 2011).

In these very heterogeneous populations of patients suffering from depressive syndromes, some subgroups may be more specifically associated with different circadian and sleep disturbances. Indeed, several dysfunctions of circadian, homeostatic and photic regulation of sleep and waking have been reported (Geoffroy, 2018; Lee, 2019b; McClung, 2013; Palagini et al., 2019a; Stephenson et al., 2012; Wirz-Justice and Benedetti, 2019). In this context sleep disturbances appear as promising biomarkers in order to improve early

diagnosis but also medical care of MDD. Indeed, characterizing this “sleep” domain may allow to both better treat acute episodes but also to prevent the manifestation or recurrences of mood disorders with existing chronotherapeutics. This work aims to i) review theoretical and fundamental data of actions in chronotherapeutics, and ii) provide practical recommendations of chronotherapeutics use during depression.

II. METHODS

II.1. Definitions

Sleep disturbances are here synonymous to sleep-wake alterations, which have been defined as a “sleep” domain for characterizing mood disorders being a primary domain impacted by the disorder (Geoffroy and Gottlieb, 2020). Geoffroy and Gottlieb proposed that these primary domains should occupy an integral (primary) position in the pathophysiology, phenomenology, historical accounts, and evolution of episodes in BD (Geoffroy and Gottlieb, 2020). They also proposed to characterize the “sleep” domain with a composite structure with several sub-dimensions : i) sleep physiology (quantity and quality), ii) wake performance and quality (alertness, sleepiness and fatigue), and iii) biological rhythms (circadian, seasonal, and menstrual rhythms) (Geoffroy and Gottlieb, 2020).

Chronotherapeutics are defined as therapeutics exerting their effects on or through the biological timekeeping system (Gottlieb et al., 2019). We focused here on the major chronotherapeutic classes that have emerged over the past 50 years in mood disorsers: bright light therapy (LT), sleep deprivation or wake therapy-based treatments (SD), dark therapy (DT), melatonin and melatonin agonists (MA), interpersonal and social rhythm therapy (IPSRT), and cognitive behavioral therapy for insomnia (CBT-I) (Gottlieb et al., 2019). In this review, we focused only on chronotherapeutics with antidepressant actions. So, we did not review data about DT as no studies exist in depression and is rather contraindicated because clinical and epidemiologic data reported associations between reduced light exposure and depressive episodes (Pierre Alexis Geoffroy et al., 2014a; Gonzalez and Aston-Jones, 2008; Gottlieb et al., 2019; Zhang et al., 2017).

II.2. Literature search and strategy

We aimed to consider papers examining chronotherapeutics in mood disorder including SAD, unipolar and bipolar disorders, with or without seasonal characteristics. We conducted a narrative review using PubMed and Google Scholar databases up to August 2020, using the following keywords combination: ("depression” or “bipolar disorder" or “unipolar disorder” or “seasonal affective disorder”) and (“chronotherapy” or “chronotherapeutic” or "light therapy" or "phototherapy" or “melatonin” or “Sleep

deprivation" or "sleep phase advance" or "dark therapy" or "Cognitive behavioral therapy for insomnia" or "CBT-I" or "Interpersonal and social rhythm therapy" or "IPSRT").

II.3. Study selection

Two authors (PAG, LP) reviewed the title and abstract of identified publications in order to identify eligible studies. PAG and LP independently and then jointly selected studies for detailed extraction of information, mostly based on the full text. The two resulting article lists were compared and, in case of disagreement, the final decision as to inclusion was made by consensus. A key decision was to focus on data with real-world applicability in clinical practice. Only data published in English were included in this review. We decided to divide literature results in five main sections for each antidepressant chronotherapeutics, each of them in turn divided into three main sections: i) Introduction, ii) Physiological and theoretical bases, and iii) Practical recommendations. The sections differ in the information reviewed and proposing practical synthesis about both the scientific rational and practical recommendations.

III. RESULTS

III.1. Light therapy

III.1.1. Introduction

Light therapy (LT) is an efficient antique treatment with new insights both in chronobiology and medicine (Pierre A. Geoffroy et al., 2018b). The very first medical descriptions reported light efficacy on mood, as for instance with Hippocrates who wrote on the interrelation between seasonal climates and mood (melancholia and mania), and Aretaeus of Cappadocia who prescribed, in the second century AD, that “Lethargics are to be laid in the light, and exposed to the rays of the sun[…]”(Choukroun and Geoffroy, 2019). While being reported for millennia, LT was established as an “EBM” treatment for Seasonal Affective Disorder (SAD), which may affect both unipolar and bipolar disorders (BD), only since about 30 years ago (Rosenthal et al., 1984; Wirz-Justice et al., 2004). LT then evolved as a first-line monotherapy not only for treating seasonal depression, but also non-seasonal depression (Al-Karawi and Jubair, 2016; Pierre A. Geoffroy et al., 2019; Perera et al., 2016; Tao et al., 2020), both for unipolar disorders (Al-Karawi and Jubair, 2016; Golden et al., 2005; Humpston et al., 2020; Perera et al., 2016) and BD (Lam et al., 2020; Takeshima et al., 2020; Tseng et al., 2016; Wang et al., 2020). Of note, these recent meta-analyses emphasized the need of further well-designed studies, such as prospective studies with more rigorous design and consistent follow-up, especially in BD (Lam et al., 2020; Takeshima et al., 2020; Wang et al., 2020). In addition, few studies with small samples investigated the efficacy in perinatal depression with non-significant or non-conclusive results (Al-Karawi and Jubair, 2016).

LT can be used as an add-on/augmentation strategy and increases the response to antidepressant drugs (Loving et al., 2002; Penders et al., 2016), but recent findings confirmed also the need to change practices and recommend a first-line combination treatment in order to maximize patients' response rates, as a clear superiority of the combination exist compared with antidepressants alone (Pierre A. Geoffroy et al., 2019). LT is well tolerated in the treatment of adults with moderate to severe depression, with effect sizes equivalent to those observed in trials using selective serotonin reuptake inhibitors (SSRIs) (Al-Karawi and Jubair, 2016; Golden et al., 2005), as in bipolar disorder (Benedetti, 2018). A recent meta-analysis confirmed these observations to some extent, reporting no superiority of LT versus antidepressant as monotherapies in treating depression (Pierre A. Geoffroy et al., 2019). LT is now included in some international therapeutic guidelines for treating depression (Malhi et al., 2015) and an historical step has been made by an international ISBD task force who recently published practice recommendations for LT as a first line treatment in bipolar depression (Gottlieb et al., 2019). Forthcoming therapeutic guidelines should also fully include LT in the therapeutic armamentarium of major depressive episodes (Geoffroy et al., 2020a).

III.1.2. Physiological and theoretical bases

LT acts at different levels that may impact mood. The first observed physiological actions of light were on biological rhythms (LeGates et al., 2014). This was a neuroscientific cumulative demonstration started by Wehr and colleagues in 1979, who observed that phase shifts of circadian rhythms could have an antidepressant effect (Wehr et al., 1979), and continued in 1980 with a report from Lewy and colleagues who observed that light

suppresses melatonin secretion and so may impact circadian rhythms (Lewy et al., 1980). Then Kripke and colleagues in unipolar depression (Kripke, 1981; Kripke et al., 1983) and Lewy and colleagues in seasonal depression (Lewy et al., 1982) confirmed that antidepressant effects of LT administered during early morning may be associated with a phase advance or an alignment of circadian rhythms. In addition, LT was found to be also effective when administered at midday, so presumably independently of any effects on circadian rhythms (Sit et al., 2017). Since actions on biological rhythms may need several days or weeks, these possible more direct effects on monoaminergic pathways may explain the rapid antidepressant effects of LT, which is about 2-3 days (Huang et al., 2019; LeGates et al., 2014; Stephenson et al., 2012). Indeed, light modulates the activation of efferent serotonergic neurons, decreases the serotonin reuptake transporter (5-HTT) levels and increases serotonin (5-HT) levels in mood regulatory areas such as the anterior cingulate and prefrontal Cortex (LeGates et al., 2014; A. E. Tyrer et al., 2016; Andrea E. Tyrer et al., 2016). Another physiological effect of light has been observed on the sleep homeostasis process by increasing the sleep intensity (Tsai et al., 2009). In addition, LT has demonstrated to increase alertness with such direct and rapid effect (Cajochen, 2007), including after a night of sleep deprivation and a morning exposition to LT (Comtet et al., 2019). LT has also demonstrated to improve sleepiness and sustained attention, among other cognitive functions (Comtet et al., 2019; Stephenson et al., 2012). LT may so exerts antidepressant effects thanks to several physiological effects that may combine: phase shifting of biological rhythms, modulation of monoaminergic pathways in mood regulatory areas, action on the sleep homeostasis by increasing sleep pressure (EEG delta activity), and enhancement alertness. All these effects have individual variations and are dependent on the light dose (determined by light irradiance level, duration of exposure, distance and angle from the

light source), the light color spectrum, and on the time of day of light exposure (Bourgin and Hubbard, 2016; Hubbard et al., 2013; Terman and Terman, 2005a; Wirz-Justice and Benedetti, 2019). The Table 1 summarizes the standard protocols and parameters to use for LT in major depressive episode, adapted from previous reviews (Geoffroy, 2020; Maruani and Geoffroy, 2019).

III.1.3. Practical recommendations

LT can be proposed as a first-line antidepressant strategy in monotherapy, or combination, or add-on treatment (Gottlieb et al., 2019; Loving et al., 2002; Maruani and Geoffroy, 2019; Wirz-Justice et al., 2005). As briefly overviewed in previous sections, LT is also effective in improving both sleep, alertness and circadian rhythms, which may be altered in depression (Menculini et al., 2018). Consideration of these symptoms may help guiding the prescription of LT, for which several parameters should be considered (Table 1): light dose, color spectrum, and the time of day of light exposure (Geoffroy, 2020).

LT practical recommendations mostly derived from tests in the seasonal affective disorder. Regarding recommendations in non-seasonal depression, a heterogeneity of study protocols exists with no direct comparisons between them (Pierre Alexis Geoffroy et al., 2018). Nevertheless, key parameters and features are common to all protocols, and standard ones will be summarized here. Also, the BD benefited from a particular attention because of the risk of manic switch with antidepressant strategies. LT is classically delivered through a direct exposure to a light box equipped with fluorescent tubes -mostly replaced now with LED-, a reflector or diffusing screen, and an UV filter (Maruani and Geoffroy, 2019). Other devices also exist such as glasses or visors, which seem as much as efficient but

benefited from less studies (Comtet et al., 2019; Joffe et al., 1993; Meesters et al., 2011). Since the dose is defined both by the Light irradiance level and the exposure duration, LT is traditionally recommended at 10 000 Lux for 30min, or 5000 Lux for 1h, or 2500 Lux for 2h (Eastman et al., 1998; Terman, 2007; Terman and Terman, 2005b). Early morning administration offers greater chances for remission (Eastman et al., 1998; Terman, 2007; Terman and Terman, 2005b). The dose is measured at a distance from the retina, so we recommend to follow the device recommendations that take into account lighting parameters and distance. Good devices usually propose a therapeutic distance at 30–80 cm from the light box. In seasonal depression, it has been observed that low-intensity blue-enriched light (which are new LED devices) has a therapeutic effect comparable to standard bright light (10 000 lux) in treating SAD (Meesters et al., 2011). These results are important, and additional studies are expected, since most LT devices now proposed are equipped with LED. Of note, light sources may have important features such as providing a sufficient level of illumination from a broad visual field and lighting from above to avoid glare and target inferior retinal photoreceptors, which is more effective in suppressing melatonin in humans (Glickman et al., 2003).

First effects are observed during the first week of treatment, and may be faster in seasonal depression and BD, with significant effects reached usually within 4 weeks (Eastman et al., 1998; Humpston et al., 2020; Lam et al., 2016; Rosenthal et al., 1984; Sit et al., 2017; Terman, 2007; Terman and Terman, 2005b). The combination LT and selective serotonin reuptake inhibitors (SSRIs) lead to a faster (within a week) and better remission of patients (Pierre A. Geoffroy et al., 2019; Lam et al., 2016). There is no consensus on the LT duration required to be effective, with duration ranges from 3 days to 8 weeks (Gottlieb et

al., 2019; Knapen et al., 2014; Terman and Terman, 2005b). In seasonal depression, no differences were observed between 1 and 2 weeks of LT in overall therapy outcome, but individuals treated with 1 week LT had a faster decline in depression score (Knapen et al., 2014). Interestingly, a positive effect of the level of expectation on the speed of therapy response was also observed and could account for the faster decrease (Knapen et al., 2014).

Regarding the maintenance treatment, there is a clear need for longer term maintenance and relapse prevention studies. Regarding seasonal depressions, LT is usually recommended to be continued until the time of usual spontaneous remission in the spring or summer to avoid relapses (Wirz-Justice et al., 2013). Discontinuation without tapering can be attempted starting in May, with resumption of LT in case of relapse usually effective within days (Wirz-Justice et al., 2013). In non-seasonal depression, LT is always proposed until full reduction of depressive symptoms and is recommended to be maintained during a full year as for antidepressant strategies (Wirz-Justice et al., 2013).

LT appears to be well tolerated in all patients. Reported adverse effects are usually transient and mild, being headache, glare, sleep disturbance, eyestrain, nausea and agitation, and manic switch in patients with BD (Pierre A. Geoffroy et al., 2019; Takeshima et al., 2020; Terman and Terman, 2005b). The extensive review in BD from the ISBD task force reported in BD that the rate of mood polarity switch from morning light was high (>10%) in 4 studies, moderate (5 to 10%) in 1 study, low (<5%) in 4 studies, and not reported in 4 of the 13 studies. Two studies using LT at midday reported no mood switches. The conclusion was a global low switch rate with LT in patients with BD, and the recommendation to pre-treat patients with BD with a mood stabilizer (anti-manic agent) and monitor closely for hypomanic switches (Gottlieb et al., 2019). Of note, most of these studies recruited patients

who received stable-dosed antimanic mood stabilizers and excluded individuals with current or recent (hypo)manic episodes, mixed symptoms or rapid cycling patterns (Gottlieb et al., 2019). Switch rates may be higher so in less stabilized patients with BD. To reduce mood switching with LT, protocols used in studies proposed a progressive titration of LT, both at midday or morning, with progressive increases every week by 15 min, depending on response and tolerability, to reach a maximum of 60 min daily at 4 weeks for instance (Sit et al., 2017). Slower increases can be also proposed in BD, especially in case of morning exposure, depending on response and tolerability, and may start at 7,5 min or 10 min (Pierre Alexis Geoffroy et al., 2018). In case of treatment-emergent hypomanic symptoms, reducing the number of minutes of daily light exposure appear as a common efficient strategy (Gottlieb et al., 2019).

Main contraindications are ophthalmic disorders such as cataract, macular degeneration, glaucoma, retinitis pigmentosa; and disorders affecting the retina such as retinopathy, diabetes, herpes, etc. Thus patients at risk of retinopathies or ophthalmic disorders should have a pretreatment ophthalmological examination (Gallin et al., 1995; Terman and Terman, 2005b). It is also recommended that patients with preexisting ocular abnormalities and those using photosensitizing drugs undergo treatment only with periodic ophthalmologic examination (Gallin et al., 1995; Terman and Terman, 2005b).

The Table 1 summarizes practical recommendations regarding standard protocols for LT in major depressive episode, and are adapted from Maruani and Geoffroy review (Maruani and Geoffroy, 2019).

III.2. Sleep deprivation/wake therapy

III.2.1. Introduction

The therapeutic potential of sleep deprivation (SD) was discovered by the German psychiatrist Johann Christian August Heinroth in the early 19th who understood the existence of numerous close bidirectional relationships between mental disorders and sleep, and recommended sleep deprivation as a therapy for "melancholia" (for an overview see (Steinberg and Hegerl, 2014). After almost 150 years, this was finally confirmed in later studies who tested SD to treat depression in 1966 and in 1971 (Pflug and Tölle, 1971; Schulte, 1966). This was the beginning of a 20 year period of clinical studies and increasing interest. These early studies have shown a rapid antidepressant effect, typically occurring over 24 to 36 hours with response rates of approximately 60% across a wide range of unipolar and bipolar depressive episodes. The main limitation pointed out in that time was the transient nature of the effect, since the majority of the improved patients experienced a relapse after the next night of sleep with relapse rates of 83% (Benedetti and Colombo, 2011; Wu and Bunney, 1990). Despite the powerful and rapid antidepressant effect, the method has remained for this last reason an “orphan method” for a long period. Nevertheless, some progresses have been made within the last few years allowing to translate this technic in clinical practice. Indeed, firstly thanks an increase in neurobiological insights about the functioning of the biological clock as key factor in relation to SD and mental health. Secondly, numerous studies focused on how to avoid relapses occurring after the next night of sleep and on how to sustain antidepressant response associated with SD. The continuous development of new clinical strategies for the chronotherapeutic treatment

of depression and their combination with antidepressant drugs and mood stabilizers could prolong the effect of SD on mood for weeks to months (Benedetti et al., 2014, 2001; Boland et al., 2017; Colombo et al., 2000; Gottlieb et al., 2019; Ramirez-Mahaluf et al., 2020; Riemann et al., 1999; Sahlem et al., 2014; Smeraldi et al., 1999). Preventing relapse has included combination of SD with LT, with sleep phase advance, repetition of SD at short time intervals (Benedetti and Colombo, 2011; Suzuki et al., 2018). In the last two decades, clinical trials of SD have continued and have provided additional support for its efficacy in the acute treatment of bipolar depression suggesting a role in treatment resistant depression and also in suicide risk (Benedetti et al., 2014; Gottlieb et al., 2019; Sahlem et al., 2014). A recent meta-analysis has been conducted on the efficacy of SD across all depressive disorder subtypes (Boland et al., 2017). It has shown that the overall response rate to sleep deprivation was 45% among studies that utilized a randomized control group and 50% among studies that did not. A recent systematic review in BD has shown that SD-based treatments combined with strategies to prevent relapse have around 60% of response rates, were generally safe, had low rates of manic symptom induction (0 to 5% in over 60% of treated subjects), and were rapid, most yielding response within 7 days (Gottlieb et al., 2019). This literature is characterized by significant variability in administration protocols, length of follow-up, and outcome criteria used.

Taken as a whole, SD has been recommended for the treatment of acute depressive episodes and has been included in treatment algorithms for BD depression (Gottlieb et al., 2019). Nevertheless, there is insufficient data to evaluate the efficacy of SD as a maintenance treatment for unipolar and bipolar depression (Gottlieb et al., 2019).

III.2.2. Physiological and theoretical bases

A variety of neurobiological effects have pointed toward the potential mechanisms of how SD works. The mechanism of SD can be interpreted in the context of the pathogenic factors of depression, i.e. alterations in sleep/wake regulation, monoaminergic neurotransmissions, neuroplasticity, immune and endocrine systems, the activity of brain structures, as well as circadian rhythms and sleep homeostatic processes. Based on the observations that hyperarousal may predict a favorable SD response, the antidepressant effect was explained using the two-process model of sleep regulation related to the interaction of circadian and homeostatic processes (Borbély et al., 2016). A "two-process model of mood regulation" based on the two-process model well established for sleep regulation has been build up by Wirz-Justice and Van den Hoofdakker (Wirz-Justice and Van den Hoofdakker, 1999). According to this model the therapeutic effect of SD is postulated to be linked to changes in disturbed slow wave sleep (SWS) pressure in depression: depressed patients may have a deficiency in building the slow-wave-sleep pressure while SD transiently leads to an increase in sleep pressure to normal, whereas relapse occurs after “recovery sleep” due to a return to low levels of SWS. SD leads to increase SWS during recovery sleep, suggesting that the deficient production of SWS in many patients with depression may be part of a pathology that can be briefly reversed by the homeostatic processes activated by SD (Vyazovskiy, 2015).

Sleep plays a significant role in the plasticity of the brain. It affects the regulation of many genes within the cortex and other brain structures. Glycogen synthase kinase 3β (GSK3 – β), besides of its role in neuroplasticity processes, plays an important role in the regulation of circadian rhythms. Benedetti et al. 2004 demonstrated a relationship between the polymorphism of GSK3 – β gene and the antidepressant effect of Total SD (TSD) BD

depression (Benedetti et al., 2004). It is suggested that the TSD antidepressant effect is connected to the resetting of malfunctioning “clock” genes, and a later episode of sleep may reactivate these irregularities and that supplemental chronotherapies and medications can block relapse and help stabilize circadian-related improvement (for an overview see (Bunney et al., 2015).

In addition, SD has been shown to enhance noradrenergic, dopaminergic and serotonergic neurotransmission (for an overview see (Dopierała and Rybakowski, 2015). There is also data indicating the effect of SD on the glutamatergic system with studies reporting higher concentration of glutamate and glutamine in the dorsolateral prefrontal cortex after TSD (Dopierała and Rybakowski, 2015).

Moreover, the level of thyroid hormones increases during SD. It is the result of the stimulation of the hypothalamic-pituitary-thyroid axis. In the course of SD, the concentration of cortisol increases considerably as a result of stimulation of the hypothalamic-pituitary-adrenal axis. During the first half of the day after SD, cortisol is above normal, particularly in patients with an antidepressant effect achieved, and then returns to normal (Dopierała and Rybakowski, 2015).

Numerous neuroimaging studies have shown that the antidepressant effect of SD is related to certain metabolic and functional changes in the brain. Patients with a good SD effect had, before the deprivation, significantly higher metabolism within the orbital medial prefrontal cortex and ventral anterior cingulate cortex, while in patients with depression, there is a significant reduction in the activity of the dorsal nexus and in the dorsal medial prefrontal cortex. After SD, the activity of these areas normalized and this normalization was correlated with clinical improvement (Bosch et al., 2013).

III.2.3. Practical recommendations

III.2.3.1 Total and partial sleep deprivation

The recent chronotherapeutic recommendations from the international society for bipolar disorder (ISBD) task force recommended that SD may be considered after more established options fail, or when they are not tolerated, or when rapid antidepressant response is required (Gottlieb et al., 2019). SD is rather contraindicated in the acute treatment of manic episodes but more studies are required to determine if limited SD might play a role in the prevention of manic relapses (Gottlieb et al., 2019). Indeed different protocols exist, and common protocols include total, partial and REM sleep deprivation.

Originally, a complete night of SD was employed resulting in a 36-hours period of wakefulness (named total sleep deprivation, TSD). During one cycle of TSD, patients are told to stay awake for about 36 h, from daytime until next day's evening. Treatment usually consists in one to six cycles. Existing studies suggest that the antidepressant effects of SD do not occur before the end of the night awake and become clinically evident when the patient is exposed to daytime light, after the night awake, or earlier during the night, if the TSD is carried out in bright light. During the prolonged wake, it is suggested that the patients remain awake without napping, in order to avoid the depressive relapse that follows recovery sleep. It is then still debated if a short nap can block the powerful antidepressant effects of TSD (Benedetti and Colombo, 2011).

Later studies explored the use of partial sleep deprivation (PSD) where subjects are allowed to sleep for 4 to 5 hours, with SD either in the first half of the night, from 10PM to 2.30 AM (PSD-early) or the latter half of the night (PSD-late) from 3AM to 8AM (Giedke et

al., 2003; Riemann et al., 1999). The introduction of PSD has led to a marked improvement of SD tolerance because the interval of induced wakefulness is much shorter and so better tolerated by patients. Response to PSD-late appears more evidence-based and probably more powerful than to PSD-early (Hemmeter et al., 2010). Up to date, very few studies have adopted a PSD-early protocol hence a recent meta-analysis pointed out that it was impossible to perform the analysis of comparative efficacy between late and early PSD because of lacking data (Boland et al., 2017). Based on the fact that REM sleep (rapid eye movement sleep) is increased and advanced in the sleep EEG pattern of depressed patients, and based on the observation that most antidepressants suppress REM sleep, it has been suggested that REM sleep reduction is a prerequisite for the achievement of an antidepressant effect. Firstly Vogel and colleagues addressed this question by depriving REM sleep through selective awakenings from REM sleep over a period of 3 weeks with patients with depression (Vogel, 1975). Interestingly they were able to achieve an antidepressant response comparable with the tricyclic substance imipramine, which is also known to suppress REM sleep (Vogel, 1975). By contrast, the selectively deprivation of non-REM sleep did not show any clinical response. But in a later study from the same group (for an overview see Vogel et al 1975), non-REM SD led to an even stronger antidepressant effect than REM sleep deprivation. So Vogel and colleagues observed that, in both conditions (REM and non-REM SD), a prolongation of the duration of non-REM sleep cycles was observed and, therefore, postulated as the common underlying mechanism of action for the antidepressant property of both treatments (Vogel, 1975). Further studies have shown that REM SD is always accompanied by a gradual suppression of non-REM sleep and that REM SD leads to a gradual improvement of mood, leading to suppression of slow wave activities (SWA) observed in stage three of non-REM sleep (i.e. deep sleep). However, the

application of REM SD under clinical conditions is difficult as it requires many nights in the sleep laboratory. Therefore, REM SD may currently be more a matter of research for the further detection of underlying mechanisms of SD (Hemmeter et al., 2010; Palagini et al., 2013).

III.2.3.2 Management and combinations to use with sleep deprivation

Methods to stabilize antidepressant effect of SD and prevent relapse have been developed and applied. These different strategies include concomitant medications, repeated SD, combination with sleep phase advance and/or LT (triple chronotherapy).

Concomitant antidepressant medication have been shown to prevent relapses in 53% of cases (Wu and Bunney, 1990). Total or partial, single or repeated SD has been successfully associated with the selective serotonin reuptake inhibitors (SSRI) fluoxetine, paroxetine and sertraline, the dopaminergic amineptine, the mixed serotonergic-noradrenergic tricyclic antidepressants amitriptyline and clomipramine, and the noradrenergic tricyclic nortriptyline, and with lithium (for an overview see (Benedetti and Colombo, 2011; Gottlieb et al., 2019)). The combined effect has been hypothesized to be synergistic: SD may hastens the antidepressant action of drugs or, conversely, drugs may sustain the transient antidepressant effects of SD over time. Clinical trials consistently show that a stable clinical euthymia is achieved by the majority of patients. A negative interaction has only been reported when SD was combined with trimipramine, which shows in vitro DA antagonistic properties (Benedetti and Colombo, 2011; Dallaspezia and Benedetti, 2015; Gottlieb et al., 2019). Combined SD and antidepressant treatment not only improves the depressive syndrome, it also exerts a beneficial effect on overall quality of life. A recent meta-analysis has been conducted on this topic showing that TSD plus medications such as sertraline or

fluoxetine compared with medications alone showed a significant decrease in depressive symptomatology after one week and confirmed after 10 days (Ramirez-Mahaluf et al., 2020). TSD has shown to sustain antidepressant medication effect with no differences in tolerability or affective switch (Ramirez-Mahaluf et al., 2020).

The results of repeatedly applied SD on the course of antidepressive therapy are still contradictory. Repetition of treatment is recommended in practice, and can lead to increased effects. Benedetti and colleagues developed a treatment schedule based on repeated total SD, three times a week with each SD cycle composed of a period of 36 h awake, and on the 1st, 3rd and 5th day, patients were totally sleep deprived from 07:00 h until 19.00 h of the following day (Benedetti and Colombo, 2011). Many other schedules for repeated treatment have been proposed: e.g. partial SD repeated once a week for 3 weeks, or 3 times a week, or twice a week for 2 weeks, or 3 times a week for 2 weeks , or 5 times at 5-day intervals , or 6 times at 4- to 5-day intervals; or total SD twice a week , or twice a week for 3 weeks or for a month, or twice a week followed by partial SD twice indeed direct comparisons are very scarce. Repeated total SD once a week has also been proposed as a prophylactic treatment, to sustain response and prevent relapses (for an overview see (Benedetti and Colombo, 2011; Dallaspezia and Benedetti, 2015)). Indeed, repetition of the treatment may lead to a pattern with repeated ameliorations after SD and repeated relapse after recovery sleep, with little net benefit at the end. The trend toward amelioration due to incomplete relapses, when present, is expected to reverse within a few weeks after a regular restoring of the usual 24-hour sleep-wake cycle, and in the absence of combined treatments only a 5–10% of bipolar depressed responders achieve sustained remission from their depressive episode (Benedetti and Colombo, 2011).

Sleep phase advance (sleep from 5 pm to midnight) has been shown to have an antidepressant effect with a latency of 10–14 days (Souêtre et al., 1987). Based on these results, Wehr and Wirz-Justice formulated the 'internal coincidence model for SD and depression', suggesting that the avoidance of sleep during the critical period in the morning hours may be essential for a response to sleep–wake manipulations in depression (Wehr et al., 1979). With this strategy, authors could avoid relapses into depression in 50–75% of the patients who responded to SD. The advantage of this combined treatment is that in more than half of the patients an immediate improvement in depression could be achieved and stabilized, at least over the observation period of the study (Hemmeter et al., 2010). In the last few years sleep phase advance has been used in the context of a "triple chronotherapy" combined with light therapy, sleep deprivation along with concomitant pharmacotherapy (Benedetti et al., 2014; Danilenko et al., 2019; Echizenya et al., 2013; Wu et al., 2009).

Regarding LT, some studies have shown that the application of 2500 lux of bright light in the morning after SD was able to stabilize the antidepressant response of SD and to reduce daytime sleepiness (Dallaspezia and Benedetti, 2015). Benedetti et al. demonstrated that history of drug resistance significantly influenced the pattern of relapses and responses to a combined SD–bright light therapy in bipolar patients (Benedetti et al., 2005). Recently, bright light therapy has been used in the context of triple chronotherapy combined with sleep phase advance and sleep deprivation along with concomitant pharmacotherapy. This combination demonstrated to produce a rapid improvement in depressive symptoms both in unipolar and bipolar disorders (Benedetti et al., 2005; Danilenko et al., 2019; Echizenya et al., 2013; Wu et al., 2009). This triple chronotherapy endured for as long as 9 weeks, in drug-resistant mood disorders and suicidal symptoms in bipolar depression (Benedetti et al., 2014).

Regarding clinical predictive factors of response, the most robust finding concerning the clinical prediction of SD response is the presence of a typical diurnal variation of mood in depressed patients. This has been reported in several controlled studies (Benedetti and Colombo, 2011; Boland et al., 2017; Dallaspezia and Benedetti, 2015; Hemmeter et al., 2010). By contrast, SD in patients with an inverse diurnal variation of mood (evening low) is usually not effective or has negative effects. Besides typical diurnal variation of mood, pre-existing typical sleep disturbance in major depression, including difficulties in falling asleep, frequent awakenings and early morning awakening, appears as a strong predictor of SD response. In contrast, tiredness the day preceding SD is rather associated with SD nonresponse. Among neurobiological predictors of SD response using sleep EEG parameters, they are no clear consensus but patients with PSG markers of typical depression such as short REM latency, increased REM density reduced SWS (Hemmeter et al., 2010). Indeed an "overarousal hypothesis of depression and SD response" has been formulated and it assumed that SD may act by reducing the hyperarousal state associated with depression.

The most common adverse effect of SD is daytime sleepiness, and patients treated with SD should be advised not to engage in dangerous activities which require attention and concentration like driving a car (Benedetti and Colombo, 2011; Boland et al., 2017; Dallaspezia and Benedetti, 2015). The degree of sleepiness shows high individual variability but considering the large literature about sleep loss and the increased risk of accidents, however, patients should be protected from these easily avoidable risks (Bioulac et al., 2017). Carrying out the treatment in an hospital setting, as in most reported trials, can, however, prevent the consequences of this unavoidable adverse effect. In euthymic patients

affected by bipolar disorder, abrupt changes in the sleep-wake rhythm can trigger mania through a self-reinforcing mechanism of sleep loss and progressive mood improvement, which leads to the typical increase in activity, reduced need for sleep, and eventually the full manic syndrome spinning out of control (Geoffroy, 2018). In non-rapid-cycling patients affected by bipolar disorder type I, very low switch rates around 3% have been observed in reported trials. The administration of therapeutic SD in rapid-cycling bipolar patients may causes the same switch rate into mania but switch rates are closely similar to those observed with selective serotonin reuptake inhibitors and placebo and are lower than those reported with tricyclic antidepressants (Benedetti and Colombo, 2011; Dallaspezia and Benedetti, 2015).

The Table 3 and Figure 1 summarize practical recommendations regarding standard protocols for SD in unipolar and bipolar depression.

III.3. Melatonin and melatoninergic agonists

III.3.1. Introduction

Endogenous melatonin, or N-acetyl-5-methoxytryptamine, is a natural mammalian hormone identified in 1958 and secreted in the brain by the pineal gland (Claustrat et al., 2005). Melatonin results from the conversion of serotonin to N-acetyl-serotonin and then to melatonin and its secretion involves two enzymes: the Serotonin-N-Acetyl-Transferase (AANAT) and the Acetyl-Serotonin-Methyl-Transferase (ASMT) (Anderson et al., 2016; Claustrat et al., 2005). Its level of secretion is influenced by the photoperiod (dark-light cycle) via the supra-chiasmatic nuclei and raises in the evening with a peak during the night and is mostly undetectable during the day (Claustrat et al., 2005). The level of melatonin can be measured mainly in the blood and the saliva. Night-time levels of melatonin are at least 10-fold higher than daytime concentrations with high inter-individual variability (Zeitzer et al., 1999). Since the 1980's, it has been suggested that patients with both unipolar and bipolar have abnormalities of secretion of melatonin, both during the depressive phase but also persistent during remission (Boyce and Hopwood, 2013; De Crescenzo et al., 2017; Dolberg et al., 1998; Pierre Alexis Geoffroy et al., 2015; Hartley and Quera-Salva, 2014; Hickie and Rogers, 2011; Lam et al., 1990; Srinivasan et al., 2006). Interestingly, melatonin has also been recommended to treat: i) delayed sleep phase syndrome (van Geijlswijk et al., 2010), ii) to treat chronic insomnia disorder (Baglioni et al., 2020; Buscemi et al., 2005; Ferracioli-Oda et al., 2013; Lemoine et al., 2007; Palagini et al., 2020; Wilson et al., 2019), iii) and to improve sleep quality on a set of objective parameters such as sleep onset latency, the total duration of sleep and sleep efficacy (Baglioni et al., 2020; Ferracioli-Oda et al., 2013). Based on these arguments, it has been proposed that melatonin might help patients with mood disorders in several situations: sleep disturbances or low sleep quality, delayed

sleep phase and for mood stabilization during acute or remitted phases (Pierre Alexis Geoffroy et al., 2015).

III.3.2. Physiological and theoretical bases

Melatonin has many properties and induces circadian-related and sleep-related responses, such as acting as a promoter of sleep and a synchronizer of circadian rhythms (Claustrat et al., 2005; P. A. Geoffroy et al., 2019). As such, the pineal gland and the suprachiasmatic nuclei act together in order to synchronize peripheral clocks and melatonin is involved in signaling the 'time of day' and 'time of year' and then acts as a major chronobiological pacemaker (Pandi-Perumal et al., 2006). Melatonin has also many other actions, such as antioxidant, antiapoptotic, immune-enhancing and oncostatic properties (Anderson et al., 2016; Espino et al., 2011; Pandi-Perumal et al., 2006). Patients with mood disorders have repeatedly been shown to display less stable circadian rhythms when compared to healthy control subjects (Bunney et al., 2015; Pierre Alexis Geoffroy et al., 2014b; Harvey, 2008; Menculini et al., 2018). This has been postulated to be related to altered melatonin kinetics as several studies observed that patients with mood disorders have alterations of melatonin secretion at night (later nocturnal peak secretion and reduced secretion amplitude) and a super-sensitive suppression of the melatonin secretion to light (Boyce and Hopwood, 2013; De Crescenzo et al., 2017; Dolberg et al., 1998; Pierre Alexis Geoffroy et al., 2015; Hartley and Quera-Salva, 2014; Hickie and Rogers, 2011; Lam et al., 1990; Srinivasan et al., 2006). In 1976, the « low melatonin syndrome » was even proposed to define the depressive episode but was not retained because of the high interindividual variability (Wetterberg, 1994). Although the evidence is somewhat inconsistent, these

alterations of melatonin secretions were observed both during acute depressive phase, but also during remitted phases, leading to consider them as trait markers of BD (Milhiet et al., 2011). Interestingly, the increase in melatonin suppression has been shown to be reversible by lithium (K T Hallam et al., 2005) and valproate (Karen T Hallam et al., 2005). In patients with BD, a significant association with a variant of the ASMT enzyme, relevant for melatonin synthesis and conferring reduced enzymatic activity, has been demonstrated (Etain et al., 2012) and associated with a poor sleep quality in carriers of the at-risk allele (P. A. Geoffroy et al., 2014). Melatonin has also been shown to modulate monoaminergic transmission in animal models (Chenu et al., 2013). Other effects of melatonin may also have antidepressant properties, such as its action against lipopolysaccharide (LPS)-induced neuroinflammation and oxidative stress, also implicated in depressive processes (Ali et al., 2020). Indeed, melatonin showed to improve depressive-like behaviors in mice, to reduce cytokines level, to reduce oxidative stress, and to normalize LPS-altered Sirt1, Nrf2, and HO-1 expression (Ali et al., 2020). In this context, the exogeneous administration of melatonin may help to stabilize mood, as well as sleep-wake cycle disorders, and prevent recurrences.

III.3.3. Practical recommendations

III.3.3.1 Soporific and/or chronobiotic effects

These two soporific and chronobiotic effects have been summarized and detailed in a previous review from the French sleep society (P. A. Geoffroy et al., 2019). The first action is named “chronobiotic” and exist even at low doses from 0,125mg to 1mg (Claustrat et al., 2005). Exogenous melatonin can be considered as a “chronobiotic substance” since it can change the characteristics of a rhythm (period, amplitude or phase). Indeed, exogeneous

melatonin as endogenous melatonin, according to the time of administration, can advance or delay the functioning of the biological clock (Claustrat et al., 2005). A biological rhythms phase advance occurs when melatonin is administered in the afternoon (beginning and end), with a maximal effect 4 to 5 hours before the start of the endogenous melatonin secretion (Claustrat et al., 2005; P. A. Geoffroy et al., 2019). Guidelines about delay sleep phase disorder recommend that melatonin should be administrated between 1.5 and 6.5 hours prior to the DLMO for four weeks (DLMO is the so-called dim light melatonin onset, in physiological conditions endogenous melatonin starts to rise in dim light i.e. normally between 7:30pm and 9:30pm in adults) (Sack et al., 2007). On the other hand, a biological rhythms phase delay occurs when melatonin is administered in the morning (Claustrat et al., 2005; P. A. Geoffroy et al., 2019).

The second action is a sleep-promoting action, named “soporific”, administered close to bedtime (15-30 min before bedtime) and starting at 2mg for most individuals. Indeed, melatonin has a sleep-promoting effect occurring in a dose-effect relationship, i.e. increasing with the dose, which is not “time-dependent” as the chronobiotic effect (P. A. Geoffroy et al., 2019). It is important to note that similar chronobiotic effects are observed with the increase in dose of melatonin in order to increase the soporific effect (Burgess et al., 2010). Trials with longer duration and using higher doses of melatonin demonstrated greater effects on decreasing sleep latency and increasing total sleep time (Ferracioli-Oda et al., 2013).

In mood disorders, a chronobiotic effect may be useful if the depressive syndrome is associated for instance with a sleep phase delay syndrome, which is frequent (van Geijlswijk et al., 2010). The soporific effect may be more interesting in case of altered sleep quality or

insomnia disorders associated with depression (Baglioni et al., 2020; Buscemi et al., 2005; Ferracioli-Oda et al., 2013; Lemoine et al., 2007). Finally, the cumulate effect of these two actions, chronobiotic and soporific, may also help some patients with several sleep and circadian rhythms disturbances.

III.3.3.2. Management of melatonin in depressive disorders subtypes

Exogenous melatonin exist in many forms such as tablets, capsules, orodispersible, oral solution or spray, and with immediate release (IR) or prolonged release (PR). PR melatonin has been developed to imitate the endogenous secretion of melatonin. No studies directly compared the different forms of melatonin in depression. Studies examining seasonal depressions used IR melatonin, whereas studies in unipolar and bipolar non-seasonal depression used mostly PR melatonin (P. A. Geoffroy et al., 2019).

In patients with BD, Leibenluft and colleagues, in a randomized crossover double-blind study against placebo, assessed the use of 10 mg of IR melatonin administered at 10 pm over a 12-week period to 5 patients with rapid-cycles (Leibenluft et al., 1997). Authors did not observed any efficacy of melatonin on mood or sleep parameters compared to placebo (Leibenluft et al., 1997). Roma-Nava and colleagues carried out a randomized double-blind study against placebo, assessed 5 mg of PR melatonin over an 8-week period of 20 patients with BD and treated with second-generation antipsychotics (Romo-Nava et al., 2014). Of note, the focus of this trial was to examine effects on metabolic parameters, which were improved by melatonin compared to placebo, especially regarding diastolic blood pressure and weight. Whereas this was not the main objective of this study, authors also did not observe any significant effects of melatonin on depressive or manic symptoms (Romo-Nava

et al., 2014). Livianos and colleagues carried out an interesting follow-up study with a cohort of 14 patients with remitted BD and insomnia (Livianos et al., 2012). IR melatonin was administered at bedtime and freely at doses ranging from 3–6 mg in combination with the usual treatment. They observed a significant improvement of the quality and duration of sleep, with a decrease in residual depressive symptoms (Livianos et al., 2012). The melatonin agonist ramelteon was assessed by McElroy and collaborators who studied the effect of 8 mg of ramelteon in 21 patients during manic phases, in combination with an anti-manic treatment, and after 8 weeks observed significant effects in decreasing depressive symptoms but not regarding sleep or manic symptoms against placebo (McElroy et al., 2011). Nevertheless, in a large RCT of patients with BD type I in remission, it has also been reported that ramelteon may induce in rare cases an affective relapse and/or the onset of suicidal ideation (9 of 477 subjects receiving ramelteon) and did not demonstrate preventing relapses as adjunctive maintenance therapy for BD (Mahableshwarkar et al., 2017).

In unipolar disorder, Dolberg et al. conducted a randomized study assessing the effect of 5–10 mg of PR melatonin combined with fluoxetine 20 mg on 10 subjects versus 9 subjects with placebo and fluoxetine at the same dose (Dolberg et al., 1998). These authors observed an efficacy in the treatment of insomnia symptoms but no effects on depressive symptoms. This was confirmed by a later study from Serfaty and collaborators who tested, in a double-blind randomized controlled trial using 6-mg of PR melatonin as an adjuvant to antidepressant treatment in 31 patients with insomnia, showed a decrease in depressive symptoms and sleep disorders, which was not linked to melatonin but rather on its association with antidepressant (Serfaty et al., 2010). The only clear significant study in

unipolar depression was published by Fava and collaborators who carried out a randomized double-blind controlled trial to assess the combined effects of buspirone at low dose of 15 mg and PR melatonin at 3 mg (Fava et al., 2012). Indeed, these authors observed that melatonin combined with buspirone was significantly more effective than the combination with placebo to treat the major depressive episode (Fava et al., 2012).

In seasonal affective disorder (SAD), since LT is the recommended first-line treatment since decades, IR melatonin has been combined with LT in several trials. The first study from Sherer and collaborators use IR melatonin at 200 micrograms administered 30 min before morning LT and then every hour during the day with a total of 2–2.4 mg a day, to obtain an extension of nocturnal melatonin secretion. A week of IR melatonin combined with LT had effects on some cognitive functions but not on depressive symptoms or vigilance (Sherer et al., 1985). Lewy and collaborators, in a double-blind RCT, compared 10 individuals with IR melatonin 0.125 mg twice a day (circardian time (CT) 8 and 12, i.e. 3.18 pm and 7.18 pm) and reported a significant antidepressant effect at 2 weeks (Lewy et al., 1998). SD has been also studied with melatonin or placebo but failed to find any greater effect when combined with melatonin in maintaining the antidepressant effects of SD (Danilenko and Putilov, 2005). The more rigorous study was made by Lewy and collaborators that considered biological rhythms and chronotype while administering melatonin. Indeed, these authors demonstrated that IR melatonin had an antidepressant effect on depressive symptoms if it is administered optimally according to the patients' profiles of delayed or advanced phases (Lewy et al., 2006). This study compared 24 subjects treated with placebo to 44 patients with SAD treated with IR melatonin administered by 7–8 capsules a day (each capsule containing 0.075 or 0.1 mg according to the year of the study, for a total of 0.225 or 0.3

mg/day) for 3 weeks (one every 2 hours as soon as they got up in the morning until 2 to 4 hours before going to bed). Some patients received melatonin capsules optimally in relation to their phase (in order to correct a phase advance or delay) and others at an inappropriate time. In both groups, an improvement in depressive symptoms was observed, but with a greater effect of melatonin when optimally administered according to phase shift (Lewy et al., 2006). This study interestingly highlights the interest to take into account the patients' endogenous biological rhythms and their chronotype to better optimize the exact time of melatonin intake, which could potentially improve its therapeutic effect.

Regarding prevention of relapse, Norris and collaborators studied the efficacy of ramelteon 8mg for 24 weeks on the reduction of relapse rates in 83 patients with remitted BD and insomnia symptoms (Norris et al., 2013). The melatonin agonist showed a significant greater effect than placebo on the prevention of relapse for both depressive or manic episodes (Norris et al., 2013). Despite this interesting trial in BD, long-term effects are mostly unknown with duration of the trials from 6 days to 6 weeks (P. A. Geoffroy et al., 2019).

Regarding tolerance in patients with mood disorders, melatonin is well tolerated. Most frequent adverse events are headache, dizziness, nausea, drowsiness (Buscemi et al., 2006; Gottlieb et al., 2019). No serious adverse events have been reported, except one patient who aggravated mood disorder and committed suicide attempt and another patient who exhibited rapid cycling whilst undergoing withdrawal of melatonin (Leibenluft et al., 1997). Contraindications are those reported in all drug guides and are reported in Table 3.

In conclusion, for unipolar and bipolar depression, IR or PR melatonin may be recommended in the treatment of insomnia symptoms as an adjuvant treatment, with no

clear evidence regarding an anti-depressive effect. IR and LP melatonin have been used with very variable doses from 3 to 10 mg and with unknown long-term effects. It is worth noting that lower doses have not been evaluated in unipolar and bipolar non-seasonal depression. The melatonin agonist ramelteon may help decrease by half relapse after 24 weeks among patients with remitted BD and insomnia symptoms. It may be interesting to take into account the patients' endogenous biological rhythms and their chronotype to better optimize the exact time of melatonin intake. As such, the French recommendations propose for seasonal depression to optimize antidepressant effect by administering non-soporific doses of IR melatonin at 0.1 mg administered in the afternoon/evening or in the morning according to the phase shift (P. A. Geoffroy et al., 2019). According to the advanced or delayed phase profile, it may be easier in clinical practice for treating SAD (associated with LT which is the recommended treatment): i) to administered IR melatonin 2 to 6 hours before bedtime in patients presenting a sleep phase delay (most frequent cases), and ii) to administered IR melatonin in the morning for patients presenting a sleep phase advance (P. A. Geoffroy et al., 2019). The Table 3 summarizes standard protocols for using melatonin in seasonal and non-seasonal depressive episodes in unipolar and bipolar disorders.

III.4. Cognitive Behavioral Therapy for Insomnia (CBT-I) adapted for mood disorders

III.4.1. Introduction

The cognitive behavioral therapy for insomnia (CBT-I) is the first line treatment recommended for chronic insomnia or insomnia disorder (Baglioni et al., 2020; Palagini et al., 2020; Riemann et al., 2017). Insomnia symptoms are frequent in unipolar and bipolar depression, affecting 85.2% of patients with a major depressive episode according to a large population-based study (Pierre A. Geoffroy et al., 2018a). In particular, insomnia has been related to depression severity, to emotional hyper-reactivity, greater functional deficits, emotional impulsivity and to increased suicidal risk in patients with mood disorders (Etain et al., 2017; P. A. Geoffroy et al., 2015; Geoffroy et al., 2020b; O'Brien et al., 2011; Palagini et al., 2019a)). Insomnia has been shown to increase the risk of unipolar and bipolar depression relapses and recurrences as it is one of the most frequent residual symptoms (Henry et al., 2015), it is also an independent risk factor for depression and a frequent early sign occurring prior to both depressive and manic episodes (Hertenstein et al., 2019; Palagini et al., 2019a, 2020; Pigeon et al., 2008, 2017). Recently, it has been shown that targeting insomnia may favorably impact on the trajectory of mood disorders (Asarnow and Manber, 2019; Bei et al., 2019; Bellivier et al., 2015; Harvey et al., 2015). It has been also shown that the majority of individuals with mood disorders present alterations in the circadian rhythmicity, which, have been associated with the severity of mood and insomnia symptoms, emotional dysregulation and to increased suicidal risk (Bellivier et al., 2015; Benard et al., 2015; Harvey, 2008; Maruani et al., 2018; Palagini et al., 2019b; Pinho et al., 2015). These data highlighted the complexity and multiple sleep disturbances that are

characteristic of mood disorders including insomnia, hypersomnia, delayed sleep phase, irregular sleep wake schedule and alterations biological rhythms, reduced sleep need and the importance of an intervention to treat sleep problems as a pathway for improving mood and reducing impairment. As part of a program of research into insomnia and psychiatric disorder, Harvey and colleagues have postulated that by treating these sleep disorders such as insomnia and circadian sleep disturbances may favorably impact on the trajectory of BD and have developed a variant of CBT-I modified for BD (CBTI-BP) (Harvey et al., 2015). The CBTI-BP aims to improve sleep, mood and functioning in people with BD, by adding to CBT-I elements of motivational interviewing, interpersonal, and social rhythm therapy, and chronotherapy aiming at regularizing sleep and wake times, named daily timing CBTI-BP (Harvey et al., 2015). The recent international ISBD task force has identified one outcome study of CBTI-BP conducted by the developers in bipolar depression (Gottlieb et al., 2019). Despite behaviorally based chronotherapeutic strategies that have been implemented in most evidence-based approaches to BD, the CBTI-BP has up to date few evidence and is not yet included in evidence-based treatment guidelines of BD. As such, the international task force for instance, because there is some evidence that behavioral therapies targeting sleep and social rhythms have benefits for the maintenance phase of BD, has suggested the use of the CBTI-BP protocol in the treatment of insomnia of patients with BD during euthymic phases (Gottlieb et al., 2019).

III.4.2. Physiological and theoretical bases

CBT-I is a multimodal approach and consists of a combination of i) cognitive therapy, ii) behavioral interventions, such as sleep restriction and stimulus control, and iii)

educational interventions (Morin et al., 2006). It has been proposed that dysfunctional beliefs and attitudes about sleep contribute to disrupt sleep and to sustain the vicious cycle of insomnia by favouring the cognitive, somatic and physiologic "hyperarousal" (Riemann et al., 2015, 2010). CBT-I is an effective treatment for adults with chronic insomnia, with clinically meaningful effect sizes on sleep onset latency, total sleep duration, number of nighttime awakenings, sleep efficiency and sleep quality (Riemann et al., 2015, 2010). CBT-I addresses sleep problems and for interrupting the vicious cycle of insomnia. Hence CBT-I behavioral/educational interventions aim to re-regulate the homeostatic and circadian processes of sleep increasing SWA by re-creating a sleep pressure during the day (Riemann et al., 2015, 2010). The cognitive part works on dysfunctional beliefs and attitude about sleep with the aim to reduce cognitive hyperarousal. Stimulus control is one of the most effective treatment components of CBT-I and focuses on regularizing the sleep-wake cycle and strengthening associations between the bed and sleep (Bootzin and Epstein, 2011). Sleep restriction is also one of the most effective components (Spielman et al., 1987) and is derived from observations that excessive time in bed perpetuates insomnia. Sleep restriction limits the person's time in bed. Both interventions, stimulus control and sleep restriction, aim to restore the homeostatic sleep drive (Riemann et al., 2015). Educational interventions based on principles of sleep hygiene contributes to restore the homeostatic drive to sleep and to re-establish circadian rhythms (Riemann et al., 2015). CBT-I may be a particularly useful intervention to stabilize sleep and circadian rhythms in BD. Indeed, individuals with BD display night-to-night variability in total sleep time, reduced sleep efficiency and increased nighttime wakefulness (P. A. Geoffroy et al., 2015) that may respond well to sleep restriction and stimulus control (Harvey et al., 2015). However CBTI-BP has been modified in certain components such as stimulus control and sleep restriction

to avoid sleep deprivation that is strongly linked to relapse in BD (Riemann et al., 2015).

III.4.3. Practical recommendations

As delivered by Harvey and colleagues, CBTI-BP involves 8 weekly sessions of 50-60 minutes as described by the developers (Harvey et al., 2015). Session 1 is focused on case formulation, goal setting, motivational interviewing, and sleep and circadian education. Case formulation should be conducted by evaluating sleep-related behaviors and their consequences before bedtime, during the night, on waking and during the day. Motivational interviewing (MI) has been used to assess pros and cons of change, recognizing that many sleep-incompatible/interfering behaviors might be rewarding (Miller and Rollnick, 2012). Sleep and circadian education included definitions, environmental influences (particularly light), circadian and social rhythms (following IPSRT) and the tendency toward delayed sleep phase. Sleep inertia should be discussed, defined and normalized (Tassi and Muzet, 2000) while the role of sleep disturbance in mood regulation and as a prodrome of mood episode relapse should be assessed. Subsequent sessions should be dosed on the basis of the case formulation. The behavioral module of CBTI-BP includes five main components.

(a) stimulus control, focuses on regularizing the sleep-wake cycle and strengthening associations between the bed and sleep as well as regularizing daytime rhythms (e.g., setting regular meal and wake-up times).

(b) sleep restriction to improve sleep efficiency and consolidate sleep in order to avoid sleep deprivation for safety, time in bed was never less than 6.5 hours.

(c) Regularizing sleep-wake times. IPSRT principles are utilized to regularize sleep and wake times and avoid naps in CBTI-BP. These techniques promote consistent sleepiness in the evening and enable patients with a tendency toward eveningness to progressively advance their bedtime by 20-30 minutes per week, hence the circadian system can adapt.

(d) Wind-down. Patients need assistance to devise a 'wind-down' of 30-60 minutes in which relaxing, sleep-enhancing activities should be introduced in dim light conditions. This helps the circadian phase advance in patients who are evening-types, and maintains entrainment (Wyatt et al., 2006). A central issue is restricting the use of interactive electronic media (internet, cell phones, etc). MI and behavioral experiments should be used to facilitate voluntarily choosing an electronic curfew.

(e) devising a wake-up routine: individualized wake-up plans draw on IPSRT principles, and include: not hitting snooze, opening the curtains to let sunlight in, and making the bed so the incentive to get back in is reduced.

The cognitive module included (a) altering unhelpful beliefs about sleep and (b) reducing sleep-related anxiety, bedtime worry, rumination, and vigilance.

The module to improve daytime functioning included (a) behavioral experiments to allow the patient to experience the energy-generating effects of activity and (b) identification of energy-sapping and energy-generating activities, with the latter being useful for managing daytime tiredness. Relapse prevention should be the focus for the final session.

The Table 4 summarizes practical recommendations regarding the suggested protocol for CBT-BP that was designed for bipolar disorders, but could be used in practice for both unipolar and bipolar depression.

III.5. Interpersonal and social rhythm therapy- IPSRT

III.5.1. Introduction

The Interpersonal and social rhythm therapy (IPSRT) is a manualized treatment, developed by Ellen Frank (Frank, 2007), that addresses interpersonal problems and disrupted social rhythms with the intent of stabilizing underlying biologic processes (Frank et al., 2005). Patients are educated to identify potential sources of rhythm disruption in their lives and develop strategies to maintain regular rhythms, despite these events. Although focus on the sleep-wake cycle is an essential component of IPSRT, this intervention takes a more global approach to standardizing daily routines. The ISBD chronotherapeutic task force identified 8 studies regarding the use of IPSRT in BD (Gottlieb et al., 2019). Evidence support the efficacy of IPSRT during the recovery from a depressive episode and in increasing time to recurrence over two years of maintenance treatment. Indirect evidence suggests that IPSRT is comparable to active treatments such as quetiapine for acute bipolar depression (Gottlieb et al., 2019). On this basis, Gottlieb and colleagues indicated that IPSRT is a viable therapy for the acute treatment of bipolar depression and for the prevention of bipolar mood episodes. IPSRT can be used as a monotherapy or can be combined with pharmacotherapy when such treatment is indicated.

III.5.2. Physiological and theoretical bases

Goodwin and Jamison postulated the “instability model of BD” and hypothesized a role for psychosocial stressors and for the disrupted social circadian rhythms in impairing sleep regulation and in turn in favoring mood episodes (Goodwin and Jamison, 2007). Subsequently it has been shown that psychosocial stressors may determine not only a change in the circadian sleep regulation but also in other biological rhythms such as meals,

energy, social life, activities and alertness, leading to affective episodes in predisposed individuals. On the other hand, alterations in such biological rhythms can cause significant psychosocial stress favoring mood episodes (Ehlers et al., 1993; Frank et al., 2015, 2000; Harvey, 2011). The Social Zeitgebers Theory of mood disorders (Ehlers et al., 1993) offers an explanation of Goodwin and Jamison model and of the relationship between life events, circadian rhythms alterations and mood disorders. According to this theory, life stress leads to mood episodes by causing disruptions in individuals' interpersonal relationship and social role, causing a change in the stability of social circadian rhythms and in turn in biological circadian rhythms. In particular, alterations in social cues may modify the exposure to light and changing in light exposure can disrupt the timing of circadian rhythms then contributing to the disruption of sleep (Ehlers et al., 1993). The IPSRT is a manualized psychotherapy focused on the instability model of BD and on the Social Zeitgebers Theory of mood disorders (Frank, 2007). Frank and colleagues hypothesized that at least one aspect of the biological diathesis for BD may be related to a vulnerability of the circadian system. Accordingly the IPSRT targets four different levels: i) the link between mood and life events, ii) the importance of maintaining regular daily rhythms, iii) identification and management of potential factors which may alter circadian rhythms, with particular attention to interpersonal ones, iv) the identification and management of affective symptoms. IPSRT was adapted for bipolar depression based on the interpersonal psychotherapy (IPT). In fact IPSRT incorporates social rhythm theories into the framework of IPT. Authors hypothesized that in individuals with BD and mood-stabilizing medications, recurrences might occur via three main pathways: (i) nonadherence to medication; (ii) presence of a stressful life event; and (iii) disruptions in social rhythms. IPSRT was so designed to target each of these potential vulnerability factors. IPT treatment strategies focus on four specific interpersonal problem

areas: grief (symptoms deriving from unresolved feelings about the death of an important person of the patient), interpersonal role disputes (symptoms related to nonreciprocal expectations in any close relationship), role transitions (symptoms are related to major life role changes), and interpersonal deficits (symptoms deriving from important social problems or recurrent pattern of conflicts) (Klerman and Weissman, 1994). The IPSRT added a fifth problem area, the "loss of healthy self", to describe the symbolic loss that patients experience as a consequence of the illness. Patients with BD often grieves with their potentiality and role lost with the BD onset . Specifically, IPSRT aims stabilizing patients' routines while improving the quality of their interpersonal relationships, their performance of social roles, current mood and level of functioning and to provide them with the skills necessary to shield them from new mood episodes. As a result, IPSRT makes patients accept the life-long nature of their illness, increases the patient's awareness of how easily these rhythms can be disrupted and reduces the denial commonly associated with the disorder (Frank, 2007).

III.5.3. Practical recommendations

IPSRT from Ellen Frank manual is divided in 4 phases: initial, intermediate, preventive and termination (Frank, 2007). All these phases aimed to address i) nonadherence to medication ii) presence of a stressful life event and (iii) disruptions in social rhythms. During the initial phase, beside the collection of detailed history of illness an interpersonal approach using the Interpersonal Inventory (II) is the main point. The rationale is to identify an interpersonal problem related to the most recent mood episode with special attention devoted to the detailed daily routine and to its alteration in relation to the interpersonal problem identified. IPSRT therapists utilize the Social Rhythm Metric (SRM) to monitor and

improve the regularity of five daily activities over 20 weeks (as an acute intervention) or monthly (as a maintenance treatment): time of out of bed, first contact with another person, start of daily activity, meals and time to bed (Frank, 2007). It should be useful during the intermediate phase to identify rhythms that need to be resynchronized and will become a rhythm stabilization form. The intermediate phase aims to develop strategies to manage the affective disorder, to stabilize daily rhythms, to identify specific targets, recognize sources of rhythms disruption, to manage changes in social routine, and to select and resolve interpersonal problems. The objective is for the patient to be able to maintain regular social rhythms despite the probable occurrence of stressors such as job changes, vacations, and other unexpected life events. The patient should be encouraged to keep the level of interpersonal distress at a minimum. He should also have the opportunity to discuss how they feel about the disorder itself and express their grief and/or anger or discuss the sense of "lost healthy self". Techniques that are suggested for accomplishing these interpersonal goals include the communication analysis, which allows to identify problem areas in communication and to help the patient interact more effectively with significant others. Role-playing allows the patient to practice in expressing emotions and self-assertion and decision analysis helps patients to reflect on the potential risks and benefits of alternate choices and options on specific problems (Klerman and Weissman, 1994). During this phase, patients should be provided with guidance and training on how to maintain a consistent medication schedule. The third "Preventive phase" should reinforce confidence in the patient's capability to use the skills learned in the acute phase of treatment to maintain their current euthymic mood, level of functioning, and new social rhythms. This phase should also help learning strategies to maintain regular social rhythms despite the probable occurrence of stressors. The last "termination phase" aims to consolidate and

review gains during the treatment and might last months with three to five monthly sessions.

The Table 5 summarizes practical recommendations regarding standard protocols for IRSPT in bipolar depression adapted from Ellen Frank manual (Frank, 2007).

IV. Discussion

Among current chronotherapeutic options, LT ad SD showed the strongest level of evidence in the acute treatment of unipolar and bipolar depressions. Nevertheless, data are still lacking about their role in the prevention of depressive relapses. Melatonin could not be recommended for acute depressive episodes without insomnia symptoms or circadian rhythm alterations (such as the sleep phase delay syndrome). During remitted phases, melatonin is a credible treatment option to treat residual sleep and rhythm symptoms, and to possibly prevent mood relapses. In addition, IPSRT and CBTI-BP are very interesting behavioral chronotherapeutics to use during remitted phases as preventive strategies for both depressive and manic episodes. IPSRT is also recommended in acute depressive bipolar depression.

Moreover, this review highlighted the interest to combine these chronotherapeutics both to increase and maintain efficacy. The triple chronotherapy for instance, combining the repetition of SD cycles (TSD or PSD) with sleep phase advance and augmented with LT in the morning, showed interesting synergistic properties with a better maintenance of antidepressant effects. In line with this, a recent meta-analysis, assessing any combinations of SD followed by sleep phase manipulation and/or additional LT, confirmed after 5-7 days that chronotherapeutics combined had greater efficacy than other antidepressant strategies such as psychotherapy, antidepressants, exercise or LT alone (Humpston et al., 2020). They also confirmed that chronotherapeutics combined are well-tolerated in addition of acting rapidly against depressive symptoms (Humpston et al., 2020). An additional recent systematic review and meta-analysis, about the triple chronotherapy (SD - Sleep Phase Advance - Bright LT) in unipolar and bipolar depression, found 50% to 84% of response rates

when associated with conventional treatment, with remission rates varying from 33,3% to 77% (D'Agostino et al., 2020). Nevertheless, there is a clear need for further studies with more rigorous designs, as well as studies comparing different protocols.

Another important challenge for future studies would be to better consider individual biological rhythms and so personalize the chronotherapy (Lewy et al., 2006). Precision of this kind would enable a more accurate assessment of LT and melatonin's actions in mood disorders. In addition, all summarized chronotherapeutics have side actions from their common chronobiological properties that should be better assessed to accurately evaluate the antidepressant action. For instance, LT is also acting on the homeostasis sleep process and has monoaminergic direct effects (Stephenson et al., 2012) and melatonin has immune-inflammatory and antioxidant effects (Claustrat et al., 2005), which all may impact depressive symptoms or the course of the disorder and its comorbidities.

The existing literature has several flaws that limit results interpretation. The main one is the small number of large randomized trials, which reduces statistical power and interpretations, as well as conclusions in subgroups of patients. The issue of the control condition is also an important one, and it might be challenging to compare to an "inactive" and credible control condition (Geoffroy et al., 2019). For instance in LT, the blinding of light treatment has been subject to several different placebos, including the use of a deactivated negative ion generator, red light and different light intensities (Benedetti, 2018; Geoffroy et al., 2019; Lam et al., 2016). Whereas the blinding of the investigators is possible, as well as the blinding of participants to the study hypothesis, patients benefit from recognizably different treatments that can produce different expectations since participants cannot be masked to all chronotherapeutics to the same degree that is possible with a drug trial and a

placebo pill. Another important issue is the need for future studies to compare different protocols to identify the most efficient one in different populations (Geoffroy et al., 2018). In addition, the use of very different protocols for some chronotherapeutics limits the comparison between studies and so the production of meta-analyses, which provide the accepted basis for task-force recommendations by the professional societies (Gottlieb et al., 2019; Wirz-Justice and Benedetti, 2019). Nevertheless this research agenda is possible and very expected only because chronotherapeutics appear as efficient antidepressant strategies that deserve their place in the first-line therapeutic armamentarium of depression. The ISBD task force on chronotherapy and chronobiology recently published the first practice chronotherapeutic recommendations in BD (Gottlieb et al., 2019), which is an historical international initiative and a major step for their integration in other forthcoming mood disorders therapeutic guidelines (Geoffroy et al., 2020a). Finally, regarding the literature search strategy, we decided to focus on PubMed and Google Scholar databases and did not examine other databases, so we may have missed some grey literature even if all key publications are indexed in these databases.

This review synthetizes the knowledge about chronotherapeutics and their physiological rationale in depressive symptoms, as well as practical recommendations drawn from evidence-based scientific literature. Chronotherapeutics are efficient and well-tolerated antidepressant strategies that warrant longer term maintenance and relapse prevention studies. Finally, these chronotherapeutics in monotherapy or combination should always be administered in association with behavioral measures for healthy sleep. A better training of psychiatric residents and psychology graduate students about chronobiology and chronotherapeutics may help spreading the use of these treatments.

Finally, a simple but important take home message for the everyday clinical practice should be to recognize the essential role for mental health of a good entrainment of the circadian sleep-wake cycle.

Conflicts of interest

The authors declare no conflicts of interest.

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None

FIGURES CAPTIONS

Figure 1. Protocols for sleep deprivation in unipolar and bipolar depression

PSD: partial sleep deprivation; TSD: total sleep deprivation

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Standard protocols

TSD-36 hours awake-TSD

TSD repeat 2 times in a week

PSD-2 days interval-PSD

PSD repeat 3 times in a week

Other protocols

PSD-1 week interval-PSD

Repeat for 3 weeks

PSD-2 days interval-PSD

Repeat for 1 or 2 weeks

PSD-3/4 days interval-PSD

Repeat for 2 weeks

PSD-5 days interval -PSD

Repeat for 5 or 6 times

We recommend to use TSD or "PSD-late" (=SD from 3AM to 8AM) rather than "PSD-early" (= SD from 10PM to 2.30 AM)

Table 1. Standard protocols for Light Therapy in seasonal and non-seasonal depressive episode for unipolar and bipolar disorders.

		Unipolar depression	**Bipolar depression**
Dose	**Light irradiance level** depends on **Exposure duration**	10 000 Lux for 30 min/day or 5000 Lux for 1h/day or 2500 Lux for 2h/day In case of partial response with good tolerance, consider an increase of the exposure duration and/or irradiance level	Slower increase Titration with for instance 5000 Lux with increase of 15min per week until 60min at one month (depending on response and tolerance) Or 10 000 Lux for 7,5 min/day With increase then to 15 min and of additional 15min per week until 45/60 min (depending on response and tolerance)
	Distance and angle from light source	Lamp at eye level Distance of 40-80 cm (depending on the device recommendations) Direct exposition	
Light color spectrum		Full light color spectrum (white) has the higher level of evidence Blue enriched light also demonstrated efficacy in seasonal depression	
Timing		Early morning (for instance: 8am, chronotype may be considered) Daily Regular schedules	Early morning Or Midday *(especially in case of an history of manic switch)* Daily, with regular schedules Chronotype should be consider
Onset of response		~1-4 weeks *(Effects may appear in 3-4 days, especially in seasonal depression and bipolar disorder)*	
Treatment duration		Until reduction of depressive symptoms Maintained during 1 year (to avoid risk of rapid relapse) or In case of seasonal patterns : Until the period of usual spontaneous remission in the spring or summer	

Prevention	Possibility to treat by light therapy a few weeks before the usual seasonal depressive relapse period	
Manic switch prevention	None	Only with a mood stabilizer with antimanic properties and correct dosage
Adverse effects	Mild side effects : headache, glare, sleep disturbance, eyestrain, nausea, agitation	Manic switch Mild side effects : headache, glare, sleep disturbance, eyestrain, nausea, agitation
Contraindications	Ophthalmic disorders (cataract, macular degeneration, glaucoma, retinitis pigmentosa) and disorders affecting the retina (retinopathy, diabetes, herpes, etc.) Photosensitizing drugs In case of preexisting ocular abnormalities or using photosensitizing drugs : LT only with periodic ophthalmologic examinations	

Table 2. Standard protocols for sleep deprivation/wake therapy in depressive episode for unipolar and bipolar disorders

		Unipolar depression **Bipolar depression**
Protocols	**Total Sleep Deprivation (TSD)**	36-hours period of wakefulness From morning until next day's evening
	Partial Sleep Deprivation (PSD)	Patients are allowed to sleep for 4- 5 hours with: (a) PSD in the latter half of the night from 3AM to 8AM (PSD-late) Good level of evidence-based efficacy or (b) PSD in the first half of the night from 10PM to 2.30 AM (PSD-early) Low level of evidence-based efficacy
Onset of response		~24-36 hours and within 7 days
Treatment duration		Repeated TSD 2 times or PSD 3 times at 2-days interval are recommended for a stable and long term effect Other protocols have been proposed (lower levels of evidence): (a) TSD twice a week for 3 weeks or for a month, (b) TSD twice a week followed by PSD twice a week (c) PSD repeated once a week for 3 weeks, or 2-3 times a week for 2 weeks, or 5 times at 5-day intervals , or 6 times at 5-day intervals
Relapse Prevention		(a) Repeated TSD once a week (b) Combined with sleep phase advance (c) Combined with antidepressant medications/mood stabilizers such as lithium (d) Combined with light therapy (e) Combined with light therapy and sleep phase advance (triple chronotherapy)
Manic switch prevention		with a mood stabilizer with antimanic properties and correct dosage for patients with bipolar disorder
Adverse effects		Sleepiness (advise patients not to engage in dangerous activities which require attention and concentration such as driving) Hypo-manic switch

Contraindications	History of seizure

PSD: partial sleep deprivation; TSD: total sleep deprivation

Table 3. Standard protocols for using melatonin in seasonal and non-seasonal depressive episode in unipolar and bipolar disorders.

	Unipolar depression	**Bipolar depression**
Effects	<u>Chronobiotic effect</u> (In case of comorbid irregular rhythms or delayed sleep phase) : melatonin ≤ 1 mg 2–6 hours before bedtime IR form *in association with behavioral measures for healthy sleep and morning light therapy* <u>Soporific effect</u> (In case of insomnia symptoms or poor quality sleep) Melatonin ≥2mg 15-30 min before bedtime IR or PR forms *in association with behavioral measures for healthy sleep*	
Dose during acute phase	Combined with antidepressant : melatonin 3-10 mg (Indicated if insomnia symptoms are associated) Could be combined with buspirone 15mg for increased efficacy on depressive symptoms (more efficient than buspirone alone)	Combined with mood stabilizer : melatonin 3-10 mg (Indicated if insomnia symptoms are associated) 8 mg of ramelteon
Forms	IR or PR melatonin for non-seasonal disorders Only IR melatonin was tested in seasonal depression (IR form mainly use for chronobiotic effects)	
Timing	During acute phase of non-seasonal depression: at bedtime (Consider chronotype) During remitted phases: according to the chronobiotic or soporific effect For seasonal depression: antidepressant effect could be optimized when associated with a significant phase shift if it is administered according to the advanced or delayed phase profile : - most patients present a clinical phase delay and respond to IR melatonin administered 2 to 6 hours before bedtime,	

	- a minority of patients present an advanced phase and respond to IR melatonin administered in the morning, - it is recommended to use chronobiotic doses of IR melatonin at 0.1 mg administered in the afternoon/evening or in the morning according to the phase shift
Onset of response	~1-4 weeks
Treatment duration	At least 4-6 weeks
Manic switch prevention	No increased risk of manic switch
Adverse effects	Most frequent mild side effects : Headache, dizziness, nausea, drowsiness
Contraindications	Contraindications : Hypersensitivity Pregnancy and lactation Use Cautiously when: History of seizure Diabetes Hypertension Use Cautiously with: Fluvoxamine Immunosuppressants Anticoagulants and anti-platelet drugs Cytochrome P450 1A2 (CYP1A2) and cytochrome P450 2C19 (CPY2C19) substrates

IR: immediate release; PR: prolonged realease.

Table 4. Suggested protocol for Cognitive Behavioral Therapy for Insomnia adapted to bipolar disorders: CBTI-BP

		Bipolar depression
Protocol	**Session 1** First week	First session includes: (a) case formulation (b) definition of goal setting (c) administration of Motivational Interviewing (MI): to assess pros and cons of change, recognizing that many sleep incompatible/interfering behaviors might be rewarding (d) Educational session about sleep and circadian rhythms including: definitions, environmental influences (particularly light), circadian and social rhythms (following IPSRT), the tendency toward delayed sleep phase, assessing sleep inertia and the role of sleep disturbance in mood regulation as a prodrome of mood episode relapse
	Session 2-6 Week 2-6	Application of behavioral modules includes: (a) stimulus control, for regularizing the sleep-wake cycle and strengthening associations between the bed and sleep (b) sleep restriction to improve sleep efficiency and consolidate sleep in order to avoid sleep deprivation for safety, time in bed never less than 6.5 hours (c) Regularizing sleep-wake times: following IPSRT principles to regularize sleep and wake times and avoid naps. (d) Wind-down*:* 30-60 minutes in which relaxing, sleep-enhancing activities should be introduced in dim light conditions. (restricting the use of interactive electronic media by also using MI and behavioral experiments) (e) programming a wake-up routine: individualized wake-up plans draw on IPSRT principles, and include not hitting snooze, opening the curtains to let sunlight in the bedroom
	Session 7 Week 7	Application of cognitive module includes: (a) addressing unhelpful beliefs about sleep (b) reducing sleep-related anxiety, bedtime worry, rumination, and vigilance and c) improve daytime functioning with behavioral experiments to allow the patient managing daytime tiredness
	Session 8	Concluding session and Relapse prevention

	Week 8	
Onset of response		~2-3 weeks within 8 weeks
Treatment duration		8 weeks: 8 weekly sessions each lasting about 50-60 minutes
Prevention		CBTI-BP protocol in the treatment of insomnia of bipolar subjects during euthymic phases potential relapse prevention
Manic switch prevention		Sleep restriction and stimulus control should be correctly used to avoid sleep loss which might favor manic switch
Adverse effects		Sleepiness Tiredness
Contraindications		History of seizure

Table 5. Standard protocol for Interpersonal and social rhythm therapy- IPSRT for bipolar depression

		Bipolar depression
Protocol	**Phase 1** Initial 3-5 sessions	Initial phase includes: (a) collection of detailed history of illness (b) utilization of Interpersonal Inventory (II) to identify an interpersonal problem related to the most recent mood disorder and to daily routine, this will be the initial focus therapy (c) utilization of Social Rhythm Metric (SRM) to monitor and improve the regularity of five daily activities over 20 weeks (as an acute intervention) or monthly (as a maintenance treatment): time of out of bed, first contact with another person, start of daily activity, meals and time to bed
	Phase 2 Intermediate 10-12 sessions	Intermediate phase includes: (a) identify and focus on one rhythm that need to be resynchronized and fill out the rhythm stabilization form (b) develop strategies to stabilize daily rhythms, identify specific target, manage changes in social routine. This often needs to be done quite gradually over the course of weeks. The main focus is on regularizing the patient's social rhythms and intervening in the selected interpersonal problem

		(c) recognize sources of rhythms disruption, select and resolve interpersonal problems address with IPT technique grief and/or anger or the sense of "lost healthy self"
	Phase 3 Preventive 3-5 sessions	Preventive phase includes: (a) reinforce confidence in the patients capability to use the skills learned in the acute phase of treatment to maintain their current euthymic mood, level of functioning, and new social rhythms (b) learn strategies to maintain regular social rhythms despite the probable occurrence of stressors
	Phase 4 Termination 3-5 sessions	Concluding sessions consolidating and reviewing gains during the treatment
Onset of response		During Phase 2 within 12-16 weeks
Treatment duration		Initial and intermediate phases could require 14-18 weekly sessions, in particular the intermediate phase could require 10-12 sessions. During Phase 3 treatment frequency might decrease to biweekly and eventually to monthly sessions as the patient moves from acute to maintenance therapy; during Phase 4 within three to five monthly sessions are generally required. Total = 16-24 weeks
Prevention		Monthly administration to prevent bipolar mood episodes
Manic switch prevention		No increased risk of manic switch IPSRT prevents both depressive and manic episodes
Adverse effects		Not reported
Contraindications		Not reported