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Some implications of melatonin use in chronopharmacology of insomnia.

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Contents

Abstract

The last decade has witnessed the emergence of new chronopharmacological perspectives. In the case of sleep, accumulating evidence suggests that even a minor dysfunction in the biological clock can impact upon body physiology causing increases in sleep onset latency, phase delays or advances in sleep initiation, frequent nocturnal awakenings, reduced sleep efficiency, delayed and shortened rapid eye movement sleep and increased periodic leg movements. Thus, restoration of the adequate circadian pattern of by proper sleep hygiene, targeted exposure to light and the use of chronobiotic drugs, such as melatonin, which affect the output phase of clock-controlled circadian rhythms, can help to recover the sleep-wake cycle. The optimization of drug effects and/or minimization of toxicity by timing medications with regard to biological rhythms is known as chronotherapeutics. While chronotherapeutical approaches have been particularly successful in the treatment of hypertension, allergies and some forms of cancer, a time-dependent pharmacological approach can be also effective when dealing with sleep disruptions like insomnia. A large proportion of patients under benzodiazepine (BZD)/Z drug treatment fail to achieve a complete and sustained recovery and are left with residual symptoms, like tolerance or dependency, that make relapse or recurrence more likely, and poorer quality of life a reality. Thus the chronic and extensive use of BZD/Z drugs has become a public health issue and has led to multiple campaigns to reduce both prescription and consumption of BZD/Z-drugs. This short review discusses available data on the efficacy of melatonin to reduce chronic BZD use in insomnia patients.

Keywords: circadian rhythms; chronobiotics; melatonin; insomnia; benzodiazepines; chronopharmacology

1. Introduction

While the study of circadian rhythms has flourished in recent decades, including the discovery of the mammalian master biological clock in the hypothalamic suprachiasmatic nuclei (SCN) (Moore, 2013; Welsh et al., 2010), its core molecular machinery (Buhr and Takahashi, 2013; Ko and Takahashi, 2006; Partch et al., 2014) and its entrainment mechanisms (Golombek and Rosenstein, 2010), the application of chronobiological principles to clinical medicine and, more specifically, therapeutics, has not followed at the same pace. As an integrative discipline in physiology and medical research, chronobiology renders possible the discovery of new therapeutic tools addressing central mechanisms in various diseases. Indeed, recent research has paved the path for specific chronobiological applications for the clinical practice in diverse fields, including neurology (Bruni et al., 2015), psychiatry (Baron and Reid, 2014), cardiac and respiratory disease (Smolensky et al., 2014a) and clinical oncology (Innominato et al., 2014). Moreover, there is an increasing understanding of the role of the biological timing system in metabolic processes, with the implications that disrupted sleep and/or circadian rhythms can lead to severe metabolic disturbances (Depner et al., 2014; Summa and Turek, 2014).

In the case of human sleep, its duration and organization critically depend on its circadian phase (Czeisler et al., 1980) and is regulated by the interplay of homeostatic and circadian processes which run independently, but in complementary fashion. The homeostatic component ("process S") drives to sleep about a third of every 24-hour cycle, and the circadian component ("process C") links the desire to sleep to daily fluctuations in hormones timed to the body clock (Achermann and Borbely, 2003). Melatonin, a pineal hormone

secreted in daily surges, is a synchronizer of the SCN clockwork and promotes sleepiness (Cardinali et al., 2012a).

The general health detrimental effect of disrupted sleep has long been established empirically. Epidemiological studies have shown that disturbed sleep-comprising short, low-quality, and mistimed sleep-increases the risk of metabolic diseases, especially obesity and type 2 diabetes mellitus (Cedernaes et al., 2015) as well as in neurodegenerative disorders (Landry and Liu-Ambrose, 2014). In cancer sleep disorders are very common (Howell et al., 2014) but they generally remained underdiagnosed and poorly treated (Dahiya et al., 2013).

Insomnia is a condition of unsatisfactory sleep, either in terms of sleep onset, sleep maintenance, early morning awakening or feeling unrefreshed. It is also a disorder that affects daytime and subjective well-being, skills and performance. Akin to pain disorder, insomnia is a subjective disorder amenable of diagnosis through clinical observations rather than through objective measurements. Epidemiological surveys indicate that up to 40% of individuals over 65 years of age are dissatisfied with their sleep or report trouble in initiating and maintaining sleep, and that 12 - 25% complain of persistent insomnia (Neikrug and Ancoli-Israel, 2010; Wolkove et al., 2007a,b). Hence up to 30 to 40 % of seniors use sedative hypnotic benzodiazepines (BZD) and related medication (type Z drugs). This is a cause for concern due to undesirable side effects, e.g. dependency. It is also known that the older population responds to drugs differently and less predictably than their younger counterparts (Boyle et al., 2010; Faught, 2007). Since there is consensus in that therapies for treating disruptions to sleep must be focused on normalizing the underlying cause of these disruptions (Smolensky et al., 2014b), a breakthrough in chronopharmaceutical formulation against insomnia would be one that addresses the oscillatory nature of the human sleeping

process. The main purpose of this review article is to offer an update of chronopharmacological concepts, implications and applications, with a specific emphasis on the use of the pineal hormone melatonin for the treatment of sleep disorders.

2. Some basic concepts on chronopharmacology

Chronopharmacology was recognized in the early days of biological rhythm research as one obvious application of chronobiology, which takes into account the variations of drug effects depending on the timing of administration (Halberg, 1969). Chronopharmacology involves both the investigation of drug effects as a function of biological timing mechanisms and the investigation of drug effects upon body rhythms. In terms of drug effects, temporal variations might affect their pharmacokinetics (i.e., chronokinetics) because of underlying changes in absorption, distribution, metabolism and general bioavailability (Bruguerolle et al., 2008), or its pharmacodynamics, reflected by changes in the expression of drug receptors or signal transduction mechanisms. In terms of psychotropic drugs, chronodynamics is attributed to a rhythmic neurotransmission system, such as temporal changes in neurotransmitters, receptors, and second messengers. In the case of BZD, they have been shown to phase shift the circadian clock in a nonphotic pattern, probably by acting on γ-aminobutyric acid (GABA) receptors in the SCN (Mrosovsky and Biello, 1994; Turek and Losee-Olson, 1987; Van and Turek, 1989). In addition, time-related variations in toxicity and undesired side effects must also be taken into account (chronotoxicity) (Beauchamp and Labrecque, 2007; Erkekoglu and Baydar, 2012). Indeed, the general idea of "chronotherapeutics" has been defined as the optimization of drug effects and/or minimization of toxicity by timing medications with regard to biological rhythms (Lemmer

and Labrecque, 1987). All these concepts converge into the definition of chronopharmaceutics, which deals with the design and evaluation of drug-delivery systems that release a bioactive agent with a rhythm that ideally matches the biological requirement of a given disease therapy (Lemmer, 1996, 2005; Youan, 2004). Chronotherapy advocates for the use of temporal characteristics of the patient and of the disease process to optimize the therapeutic response and minimize the undesirable side effects of a drug, e.g. treatment of sleep and psychiatric disorders with either light therapy or hormonal intervention (Kaur et al., 2013; Ohdo et al., 2011a).

While an increasing number of drugs have been demonstrated to vary their effects according to the time of administration (Baraldo, 2008; Ritschel and Forusz, 1994), the application of such concepts remains elusive. The main examples of chronopharmacological treatment refer to drugs affecting blood pressure (Hermida et al., 2013; Portaluppi et al., 2012; Schillaci et al., 2015; Stranges et al., 2015), kidney disease, respiratory disease (Byers and Noll, 1995; Martin, 1993; Smolensky et al., 1999; Smolensky et al., 2007) and cancer (Levi et al., 2010; Ohdo et al., 2011b; Ortiz-Tudela et al., 2013; Sewlall et al., 2010). Since the time-related effect of drugs depends on the activity of circadian clocks, we will give a brief overview of such pacemakers' activity before focusing on chronopharmacological implications on sleep management.

3. Biological rhythms: an overview

Circadian rhythms are driven by endogenous pacemakers that have periods that, in the absence of external time cues, are approximately 24 hours in length. In the presence of time cues, generally with a period equal to that of the solar day, the clock and the rhythms it

drives are adjusted to an exact 24-h period (Golombek and Rosenstein, 2010). The external rhythms that achieve this entrainment of the endogenous oscillator are termed zeitgebers. In humans, the most important is the light/dark cycle, perceived by the visual pathways, but rhythmic release of the hormone melatonin from the pineal gland is important also. These circadian clocks are remarkably widespread, having been documented from cyanobacteria to angiosperms and from protozoa to mammals, including Homo sapiens. The hypothalamic SCN plays a key role in the co-ordination of circadian rhythms (Moore, 2013; Weaver, 1998) and its output coordinates the activity of widespread peripheral oscillators throughout the body (Brown and Azzi, 2013; Dardente and Cermakian, 2007; Dibner et al., 2010; Menaker et al., 2013; Mohawk et al., 2012).

Circadian rhythms can be altered in terms of their three main components (i.e., period, amplitude and phase) by a variety of stimuli that includes light, non-photic stimuli and a plethora of chemical perturbations that can influence the biological clock. Drugs directly affecting circadian phase and, therefore, the output of the biological clock, are termed chronobiotics and, indeed, represent a promising line of research for the treatment of circadian disorders, particularly if they lack undesirable side effects. The term was introduced in the early 70s (Simpson et al., 1973) and was later defined broadly as a drug that affects the physiological regulation of biological time structure and, specifically, is capable of therapeutically re-entraining short-term dissociated or long-term desynchronized circadian rhythms, or prophylactically preventing their disruption following environmental insult (Dawson and Armstrong, 1996). The magnitude and the direction of the phase shifts depend on the circadian phase at which these compounds are administered, that in turn

produces pronounced phase shifts in behavioral rhythms. The requirements for an ideal chronobiotic are outlined in Fig. 1.

The molecular oscillator underlying circadian rhythms is composed by a series of positive and negative feedback loops that affect transcription and translation of the so-called clock genes and their post-translational modifications (Buhr and Takahashi, 2013; Ko and Takahashi, 2006). In summary, a number of positive transcription factors, in mammals as represented by the CLOCK-BMAL heterodimer, increases the transcription of clock genes such as *Per* and *Cry*, which are expressed and accumulate in the cytoplasm and, in turn, repress the activity of CLOCK-BMAL. The positive step of the cycle also affects the expression of other clock-controlled genes that respond to CLOCK-BMAL and are therefore transcribed in a circadian fashion. This feedback loop is intertwined with secondary loops that add robustness and fine-tuning to the whole system (Schibler and Sassone-Corsi, 2002), as well as controlled by post-translational modifications (notably phosphorylation) and epigenetic mechanisms that control the speed and accuracy of the molecular clock (Masri et al., 2015; Mehra et al., 2009; Sahar and Sassone-Corsi, 2013). Indeed, chronobiotic activity must rely on the interaction of drug treatment with the molecular circadian clock, which offers a diversity of targets for modulation (Huang et al., 2011; Ohdo, 2007; Ohdo et al., 2011a; Okamura et al., 2010; Paschos et al., 2010). Recent studies have thus found a molecular basis for chronopharmacology, which paves the way for current and future industrial-based drug discovery in order to find new drugs aimed at the hands of the circadian clock (Chen et al., 2012; Chen et al., 2013; Hirota et al., 2010).

4. Rationale for a chronopharmacological approach

Temporal organization of living organisms makes it possible to predict the rhythmic aspects of cellular metabolism and proliferation. Synchronized individuals display cellular metabolism and physiology with predictable rhythmic peaks and troughs. As already mentioned, these rhythms may influence the pharmacology and the efficacy of psychotropic drugs. Conversely, a lack of synchronization, or an alteration of circadian clock function makes these rhythmic peaks and troughs unpredictable, and may require specific therapeutic measures (i.e., chronobiotics) to restore normal circadian function (Ebisawa, 2007; Skene and Arendt, 2006), also depending on the genetic constitution of the subjects (Jones et al., 2013).

In the treatment of disease the timing of drug administration is as important as its dosing regimen. Predictable rhythmic variations in the body functions in health and disease, can affect the drug effects. Circadian rhythms alter pharmacokinetics and pharmacodynamics across the day, as the body is not constant in terms of time. As already mentioned, drugs can be administered at an appropriate biological time to maximize desired effects and minimize undesired effects and, as we shall see, psychotropic drugs commonly used in the treatment of sleep disorders also fall into this general consideration. In addition, sleep therapy is increasingly adopting the use of chronobiotics as special medications designed to induce rapid change (resynchronization) of the circadian time structure (Kunz, 2004; Touitou and Bogdan, 2007) – although a note of caution regarding the statistical analysis of chronobiotic treatment and effects has been elegantly proposed elsewhere (Atkinson et al., 2001).

5. The sleep-wake cycle, a window of the circadian timing system

The sleep/wake cycle reliably reflects circadian clock function in several animal species, including humans. Its endogenicity was demonstrated by its persistence in constant environmental conditions, in several species, including humans. This rhythm is controlled by the molecular clock genes in mammals. In humans, the sleep/wake cycle is considered and used as a marker of the circadian timing system in isolation studies and in psychiatry (Czeisler and Gooley, 2007). The relative ease of monitoring of the sleep-wake cycle by using actigraphy has further supported its use as a reference rhythm for the circadian timing of medications and for the evaluation of circadian clock function. Actigraphs are portable devices usually worn on the wrist that records movement over an extended period of time. Sleep-wake patterns are estimated from the pattern of movement. Software is available to estimate total sleep time and wake time from the data. The sleep/wake pattern of actigraph data is extremely valuable in documenting circadian rhythm sleep disorders (Morgenthaler et al., 2007).

Sleep-inducing drugs, including hypnotics such as BZD and Z-drugs, have clear chronopharmacological effects that might rely on temporal changes in their pharmacokinetics profiles (Lemmer, 2007; Reinberg, 1986; Roehrs et al., 2002). In addition, since a side effect of diverse drug families include sleep-inducing properties (for example, in asthma and other respiratory disease medications), prescriptions should take into special account the time of administration in order to take full advantage of such “secondary effects” (Novak and Shapiro, 1997).

On the other hand, chronobiotic treatment is able to effectively restore the normal onset and/or offset of sleep and wake phases. Particular emphasis is placed on the methoxyindole melatonin as an effective chronobiotic widely used in a variety of sleep disruptions, including

phase changes, jet-lag or shiftwork conditions. Melatonin is a ubiquitous molecule widely distributed in nature, with functional activity occurring in unicellular organisms, plants, fungi and animals. It, as well as several analogs that have been synthesized specifically for the treatment of sleep phase disruptions, acts as an "internal sleep facilitator" and promote sleep (Cardinali and Golombek, 2009). In mammals, melatonin is synthesized in the pineal gland in a rhythmic manner, with high levels during nighttime and low levels during daytime. Melatonin phase-shifts circadian rhythms in the SCN by acting on MT_1 and MT_2 melatonin receptors expressed by SCN neurons, thus creating a reciprocal interaction between the SCN and the pineal gland (Hardeland et al., 2011).

The circadian rhythm in the secretion of melatonin has been shown to be responsible for the sleep/wake rhythm in both normal and blind subjects (i.e., in the absence of the synchronizing effect of light). Melatonin's sleep-facilitating properties have been found to be useful for treating insomnia symptoms in elderly and depressive patients. A recently introduced melatonin analog, agomelatine, is also effective for the treatment of major depressive disorder and bipolar affective disorder (Cardinali et al., 2012b).

The melatonin rhythm is disrupted in many chronic conditions, e.g. in shift work, and the possibility that working non-day hours is associated with an increased risk of cancer, most notably breast and prostate cancer, has been entertained (Haim and Zubidat, 2015; Stevens et al., 2014). The major idea behind this is that the reduced melatonin secretion in shift workers plays a crucial role in the occurrence of cancer.

6. Utility of melatonin as a chronobiotic

Melatonin's chronobiotic properties have been shown to have value in treating various circadian rhythm sleep disorders, such as jet lag or shift-work sleep disorder (Arendt et al., 2008). A temporal relationship between the nocturnal rise in melatonin secretion and the increase in sleep propensity at the beginning of the night, coupled with the sleep-promoting effects of exogenous melatonin, indicate that melatonin is involved in the regulation of sleep. Additionally, besides its clear modulation of sleep, the pineal hormone has been demonstrated to exert a number of time-dependent effects (Golombek et al., 1992) and chronopharmacological variations have been reported for melatonin activity as an anticonvulsant (Ramgopal et al., 2013), neuroprotective (Cecon and Markus, 2011) and antitumoral agent (Akagi et al., 2004) or for the treatment of mood disorders (Fuchs et al., 2006; Quera Salva et al., 2011; Quera Salva and Hartley, 2012).

The sleep promoting actions of melatonin, which are demonstrable in healthy humans, have been found useful in subjects suffering from circadian rhythm sleep disorders and in elderly patients, who tend to have low nocturnal melatonin production and secretion (Pandi-Perumal et al., 2008). The effectiveness of melatonin in treating sleep disturbances of these patients is relevant because the sleep-promoting compounds that are usually prescribed, such as BZD and related drugs, have many adverse effects, such as next-day hangover, dependence and impairment of memory. Melatonin has been promoted as a drug to improve sleep in patients with insomnia mainly because it does not cause hangover or show any addictive potential (Wilson et al., 2010). In many aspects melatonin fulfills the requirements of an ideal chronobiotic drug (Fig. 1).

BZD exert sedative actions at the $GABA_A$ complex via BZ1 and BZ2 receptor subtypes and hypnosedative, anxiolytic and anticonvulsant activities via the BZ1 receptor subtype

(Mandrioli et al., 2010). The α1-subunit of the $GABA_A$ receptor mediates the sedative and anxiolytic effects of BZD. The efficacy of BZD in treating insomnia is supported by several meta-analyses, e.g. (Winkler et al., 2014) but significant adverse effects like cognitive and psychomotor impairment, anterograde amnesia, next-day hangover and rebound insomnia have also been documented.

Non-BZD (Z type) drugs like zolpidem, zaleplon and zopiclone all have high affinity and selectivity for the α1-subunit of the $GABA_A$ receptor complex (Morin and Willett, 2009). Zolpidem improves sleep maintenance shortly after administration, but the effect disappears at a later stage (Monti and Pandi-Perumal, 2014; Wilson et al., 2010). It may cause adverse effects like daytime drowsiness, dizziness, headache and nausea. Zaleplon is effective to decrease sleep onset latency (SOL) and to improve sleep quality (Ancoli-Israel et al., 2005) and because of its efficacy and safety, it is advocated for treating subjects with sleep initiation difficulties. Zopiclone and its active stereoisomer eszopiclone have both been shown effective and safe in patients with primary insomnia (Hair et al., 2008; Monti and Pandi-Perumal, 2007; Verster et al., 2011). In general Z-type sedative hypnotics, although effective in reducing SOL, are only moderately effective in increasing sleep efficiency (SE) and total sleep time (TST).

In aging individuals a combination of altered sleep and sleep pathologies increases the risk of drug-induced insomnia or excessive diurnal somnolence (Neikrug and Ancoli-Israel, 2010; Wolkove et al., 2007a,b) and many old adult patients are treated for longer periods or with higher dosages of hypnotic drugs than are recommended, generally with a lack of individual dosage titration. An ideal hypnotic drug should not only decrease SOL but should also increase TST and SE (Wilson et al., 2010). In addition, the ideal hypnotic should not

produce undesired side effects such as impairment of memory, cognition, next psychomotor retardation and day hangover effects, or potentiality of abuse. Melatonin as a chronobiotic fulfills many of these requirements (Wilson et al., 2010) and a recent meta-analysis supports the efficacy of melatonin in primary sleep disorders (Ferracioli-Oda et al., 2013).

The chronic and extensive use of BZD/Z drugs has become a public health issue and has led to multiple campaigns to reduce both their prescription and consumption. Since melatonin and BZD shared some neurochemical (i.e. interaction with GABA-mediated mechanisms in brain (Cardinali et al., 2008) and behavioral properties (e.g., a similar day-dependent anxiolytic activity (Golombek et al., 1996), melatonin therapy was postulated as an effective tool to decrease the dose of BZD needed in patients. Two early observations pointed out to the possible beneficial effect of melatonin in this respect. One of us reported in an open label study that 8 out of 13 insomnia patients either discontinued or reduce BZD use by 50-75% after giving a 3 mg dose of fast release melatonin (Fainstein et al., 1997). Dagan et al. (1997) published a case report on the efficacy of 1 mg of controlled release melatonin to completely cease any BZD use in a 43 year old woman who had suffered from insomnia for the past 11 years.

A double-blind, placebo controlled, study followed by a single blind period enlisted 34 primary insomnia outpatients aged 40-90 years who took BZD and had low urinary 6-sulphatoxy melatonin levels, 14 out of 18 subjects who had received prolonged-release melatonin (2 mg), but only 4 out of 16 in the placebo group, discontinued BZD therapy (Garfinkel et al., 1999). An open label study further supported the efficacy of fast release melatonin to decrease BZD use, i.e. 13 out of 20 insomnia patients taking BZD together

melatonin (3 mg) could stop BZD use while another four patients decreased BZD dose to 25–66% of initial doses (Siegrist et al., 2001).

Mild cognitive impairment (MCI) is an etiologically heterogeneous syndrome defined by cognitive impairment in advance of dementia. One of us reported on a retrospective analysis of 96 MCI outpatients, 61 of who had received daily 3 - 24 mg of a fast-release melatonin preparation p. o. at bedtime for 15 to 60 months. There was a significant improvement of cognitive and emotional performance and daily sleep/wake cycles (Cardinali et al., 2012c). The comparison of the medication profile in both groups of MCI patients indicated that 9.8 % in the melatonin group received BZD vs. 62.8 % in the non-melatonin group thus supporting administration of fast release melatonin to decrease BZD use.

A retrospective analysis of a German prescription database identified 512 patients who had initiated treatment with prolonged release melatonin (2 mg) over a 10-month period (Kunz et al., 2012). From 112 patients in this group who had previously used BZD, 31% discontinued treatment with BZD 3-months after beginning melatonin treatment. The discontinuation rate was higher in patients receiving two or three melatonin prescription (Kunz et al., 2012). Therefore melatonin can help to facilitate BZD discontinuation in older insomniacs.

In a study aimed to analyze and evaluate the impact of anti-BZD/Z-drugs campaigns and the availability of alternative pharmacotherapy (melatonin) on the consumption of BZD and Z-drugs in several European countries it was found that campaigns failed when they were not associated with the availability of melatonin in the market (Clay et al., 2013). In this pharmacoepidemiological study the reimbursement of melatonin supports better penetration rates and a higher reduction in sales for BZD/Z-drugs.

A post marketing surveillance study of prolonged release melatonin (2 mg) was performed in Germany. It examined the effect of 3 weeks of treatment on sleep in 597 patients. Most of the patients (77%) who used traditional hypnotics before melatonin treatment had stopped using them and only 5.6% of naïve patients started such drugs after melatonin discontinuation (Hajak et al., 2015). A major advantage of melatonin use as a chronobiotic is that it has a very safe profile, it is usually remarkably well tolerated and, in some studies, it has been administered to patients at very large doses and for long periods of time without any potentiality of abuse.

Melatonin has a very short half-life. Therefore, an immediate-release melatonin is rapidly metabolized and totally diminished after 90 minutes from time of intake. It has been claimed that immediate-release melatonin products are helpful only in shortening the sleep latency (time it takes to fall asleep), but useless in improving the night time awakenings or quality of sleep, as the melatonin is not present in the last part of the night when needed. On this basis, a prolonged-release preparation of melatonin 2 mg (Circadin™, Neurim) has been approved for the treatment of primary insomnia in patients aged >55 years in the European Union. It must be noted that regular fast release melatonin dose (3 -5 mg) assures melatonin levels higher than the physiological range throughout the night.

Because of melatonin´s nature as a natural product, efforts of the pharmaceutical industry has been concentrated in developing more potent melatonin analogs with prolonged effects (Cardinali et al., 2012a). Two MT_1 and MT_2 melatonergic receptor analogs, ramelteon and tasimelteon, have been approved by the USA Food and Drug Administration and are now in the market. Ramelteon (Rozerem™, Takeda Pharmaceuticals) was effective in increasing total sleep time and sleep efficiency, as well as

in reducing sleep latency, in insomnia patients. Tasimelteon (Hetlioz™, Vanda Pharmaceuticals) was introduced for sleep resynchronization in blind individuals without light perception and having a non-24-hr sleep-wake disorder. In Europe, agomelatine (Valdoxan™, Servier), a melatonergic analog displaying potent MT_1 and MT_2 melatonergic agonism and relatively weak serotonin $5HT_{2C}$ receptor antagonism, was approved by the European Medicines Agency as an antidepressant. Long-term safety studies are lacking for these melatonin agonists, particularly considering the pharmacological activity of some of their metabolites (Cardinali et al., 2012a).

In view of the higher binding affinities, longest half-life and relative higher potencies of the different melatonin agonists, studies using 2 or 3 mg/day of melatonin are probably unsuitable to give appropriate comparison of the effects of the natural compound. Hence, clinical trials employing melatonin doses in the range of 50–100 mg/day are warranted before the relative merits of the melatonin analogs versus melatonin can be settled.

It must be noted that food supplements including melatonin are sold over-the-counter at pharmacies and supermarkets in several countries. These supplements are not medicinal products and therefore are sold in a totally uncontrolled manner as they are not subjected to review or regulation approval of any health authority. Their content and efficacy were never tested in clinical trials and their quality is questioned, since their production is not regulated and the purity of the melatonin is unknown.

7. Concluding remarks

A large proportion of insomniac patients under BZD treatment fail to achieve a complete and sustained recovery and are left with residual symptoms that make relapse or recurrence

more likely with a poor quality of life. Given the impact that impaired daily functioning by insomnia may have on a patient's life, it is evident that more attention should be paid to daily functioning when assessing treatment´s response (Solomon et al., 2004). In this respect most safety concerns with use of hypnotics do not apply to melatonin, a fact recognized by the British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders that recommended melatonin as a first line therapy in insomnia patients aged 55 years and older (Wilson et al., 2010).

The possible integrated therapeutic actions including both melatonin and behavioral interventions deserve to be examined. This effect of a chronobiotic in assisting with insomnia treatment so that BZD use is decreased is an example of the utility of chronopharmacotherapy that should in turn be applicable to a variety of other circadian rhythm sleep disorders.

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Conflicts of Interest

S.R. Pandi-Perumal is a stockholder and the President and Chief Executive Officer of Somnogen Canada Inc., a Canadian Corporation. He declares that he has no competing interests that might be perceived to influence the content of this article. All remaining authors report no conflicts of interest in this work.

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Figure legend

An ideal chronobiotic drug must display efficacy for restoring and stabilizing the body rhythms, must not induce over- or sub-correction of rhythms and must have the capacity to keep internal synchronization as well as synchrony with the environment.