Sleep Medicine Reviews 34 (2017) 10–22

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

Evidence for the efficacy of melatonin in the treatment of primary adult sleep disorders

Fiona Auld [a], Emily L. Maschauer [a], Ian Morrison [a, b], Debra J. Skene [c], Renata L. Riha [a, *]

[a] Department of Sleep Medicine, Royal Infirmary Edinburgh, 51 Little France Crescent, Little France EH16 4SA, Scotland, United Kingdom
[b] Department of Neurology, Ninewells Hospital, Dundee DD1 9SY, Scotland, United Kingdom
[c] Chronobiology, Faculty of Health and Medical Sciences, University of Surrey, Guildford, Surrey GU2 7XH, England, United Kingdom

ARTICLE INFO

Article history:
Received 17 December 2014
Received in revised form
14 June 2016
Accepted 14 June 2016
Available online 20 July 2016

Keywords:
Melatonin
Sleep disorders
Insomnia
Delayed sleep phase syndrome
Blind
REM-behaviour disorder
Randomised controlled trials

SUMMARY

Melatonin is a physiological hormone involved in sleep timing and is currently used exogenously in the treatment of primary and secondary sleep disorders with empirical evidence of efficacy, but very little evidence from randomised, controlled studies. The aim of this meta-analysis was to assess the evidence base for the therapeutic effects of exogenous melatonin in treating primary sleep disorders.

An electronic literature review search of MEDLINE (1950-present) Embase (1980- present), PsycINFO (1987- present), and Scopus (1990- present), along with a hand-searching of key journals was performed in July 2013 and then again in May 2015. This identified all studies that compared the effect of exogenous melatonin and placebo in patients with primary insomnia, delayed sleep phase syndrome, non 24-h sleep wake syndrome in people who are blind, and rapid eye movement-behaviour disorder. Meta-analyses were performed to determine the magnitude of effect in studies of melatonin in improving sleep.

A total of 5030 studies were identified; of these citations, 12 were included for review based on the inclusion criteria of being: double or single-blind, randomised and controlled. Results from the meta-analyses showed the most convincing evidence for exogenous melatonin use was in reducing sleep onset latency in primary insomnia ($p = 0.002$), delayed sleep phase syndrome ($p < 0.0001$), and regulating the sleep-wake patterns in blind patients compared with placebo.

These findings highlight the potential importance of melatonin in treating certain first degree sleep disorders. The development of large-scale, randomised, controlled trials is recommended to provide further evidence for therapeutic use of melatonin in a variety of sleep difficulties.

Melatonin use in sleep disorders

Clinically significant sleep disorders affect at least 10% of Western populations, and one third or more of the population suffers daily from a sleep disturbance or excessive daytime sleepiness [1]. Management of many of these sleep disorders often requires complex therapeutic regimens, involving both pharmacological and non-pharmacological interventions.

When considering pharmacological management of sleep disorders, drugs which have a short half-life are preferable to minimise 'hangover' effects the following morning. It is strongly recommended long term drug therapy should also be avoided, as dependence and tolerance can develop [2,3]. Previous studies have highlighted the potential use of melatonin in treating primary and secondary [4] sleep disorders in adults [5–7] and others have indicated melatonin can decrease sleep onset latency and increase the total time asleep, thus improving sleep quality overall [8]. Ferracioli-Oda et al. [8] verified using melatonin in adults with primary sleep disorders improves sleep parameters (i.e., a higher dose has a greater effect on sleep latency and total sleep time).

Melatonin was first described in 1958 by dermatologist, Aaron Lerner [9], as a hormone produced by the pineal gland from the essential amino acid tryptophan (N-acetyl-5-methoxytryptamine). Exogenous melatonin has no reported tolerance, dependence, or 'hangover effect' [10], and no adverse effect on alertness or mood the following day [11], as well as minimal side-effects (e.g., headache, dizziness, nausea, drowsiness) [12,13] if administered at a low dose [14]. Melatonin has a short half-life of only 30–50 min and can

* Corresponding author.
E-mail address: rlriha@hotmail.com (R.L. Riha).

http://dx.doi.org/10.1016/j.smrv.2016.06.005
1087-0792/

List of abbreviations

ASPS	advanced sleep phase syndrome
CI	confidence intervals (fixed, 95%)
CGI	clinical global impression
DSM-IV	diagnostic and statistical manual of mental disorders- fourth edition
DSM-V	diagnostic and statistical manual of mental disorders- fourth edition
DSPS	delayed sleep phase syndrome
ICSD-2	international classification of sleep disorders- second edition
ICSD-3	international classification of sleep disorders- third edition
ISRCTN	international standard randomised controlled trials number
MT1/MT2	melatonin type 1/2 receptor
NSAIDs	non-steroidal anti-inflammatories
PSG	polysomnography
RBD	rapid eye movement-behaviour disorder/REM-behaviour disorder
RCT	randomised control trial
REM	rapid eye movement sleep
SD	standard deviation
Vs	versus

induce phase shifts in the circadian timing system (both central and peripheral clocks) and when administered acutely, reduces core body temperature and lowers alertness, encouraging sleep propensity [15].

Biology of melatonin

In humans, the primary physiological function of melatonin is to reinforce darkness-related behaviour, such as sleep propensity [15]. Inadequate sleep can not only lead to a reduction in daytime performance and excessive sleepiness, but chronic inadequate sleep may lead to immunosuppression and increased cancer-stimulatory cytokine production [16].

Endogenous melatonin synthesis is finely regulated by visual light cues received by the hypothalamic suprachiasmatic nucleus in the brain, the site of the major circadian oscillator. During daylight hours, perceived light signals inhibit melatonin production. Conversely, at night when no light signals are received, melatonin synthesis and release occur with levels peaking in the early hours of the morning.

Melatonin is metabolised by the liver, which processes >90% of the circulating hormone and together with its metabolites, is excreted in the urine. There is vast inter-individual variability in the quantity of melatonin produced depending on pineal gland size. Despite this, each person will have a similar bell-shaped production curve, which is reproducible from day to day [15]. Melatonin production declines as we age [17] due to several factors. The lower peak levels of endogenous serum melatonin [18] may be due to decreased pineal melatonin synthesis at night [19], or gradual pineal gland calcification [20]. Endogenous melatonin synthesis may be further reduced by drugs (e.g., benzodiazepines, non-steroidal anti-inflammatories (NSAIDs), and calcium channel blockers) which many elderly patients are likely to be prescribed. Beta-blockers, such as albuterol, have also been shown to oppose the sympathetic stimulation of melatonin synthesis [21].

In terms of the soporific effect of acutely administered melatonin, studies have indicated healthy volunteers receiving a single dose (0.3 mg and 1.0 mg orally) of melatonin had significantly improved sleep efficiency [22] and there are no observable toxicological or side-effects in the short-term daily use of melatonin (10 mg for 28 d) [23]. Other situations where therapeutic administration of melatonin has been shown to be useful include volunteers who are fully blind with free-running circadian rhythms where the circadian timing system is desynchronised from the 24-h light–dark cycle [24,25] due to a lack of perceived external time cues. Thus, melatonin has a potential role in treating both disorders of sleep initiation and maintenance as well as circadian phase disturbance.

In summary, exogenous melatonin administration can be used to mimic the physiological functions of endogenous low level melatonin when administered in a specifically timed manner (i.e., to correct abnormalities in circadian timing), or be used as a soporific/other agent when given in high doses for other types of sleep disorders since melatonin does not appear to suppress rapid eye movement (REM) sleep nor does it delay the onset of REM [26]. Recent reviews in the medical literature have demonstrated exogenous melatonin is safe with short term use, but evidence of its effects on secondary sleep disorders is of low quality [4].

The aim of this systematic review was to summarise the current evidence-base for the role of exogenously administered melatonin in the treatment of primary sleep disorders.

Methods

Method

A meta-analysis was performed including the published, peer-reviewed randomised controlled trials (RTC) on the use of exogenous melatonin to treat primary sleep disorders that we included in this review.

Search strategy

The databases used to search the literature for this review were MEDLINE (1950- present), Embase (1980- present), PsycINFO (1987- present), and Scopus (1990- present). These databases allowed for a wide range of clinical medical material to be covered over a broad base of global journals [35]. Each database was searched between 12/07/2013 and 17/08/2013 and a hand search of relevant journals was conducted on 09/05/2015. Recommendations from the Cochrane collaboration for a comprehensive, sensitive, and wide variety search were followed to ensure all the highest standard in evidence-based research was undertaken and all relevant articles for this review were identified for a systematic review [36–38]. No conflicts of interest were identified. The following search terms were used; ([Melatonin] OR [Melatonin*ti,ab.]) AND [(sleep disorders) OR (insomnia* or DSPS or ASPS or parasomnia).ti,ab] OR [(sleep adj3 disorder*).ti,ab.]. The additional limit was “to all adult (plus 18 y)”.

Study selection

All titles and abstracts were assessed and full texts of the relevant studies were obtained if they fulfilled the required inclusion criteria (see below). Selected publications were assessed by two reviewers (FA & RR) separately to reduce selection bias using predefined criteria from the Jadad scale [39]. Although the Jadad scale for scoring does have its critics, it is a widely-used standard instrument for the assessment of papers to be included in a meta-analysis. Once a list of articles was created that each reviewer felt