

A Systematic Review of the Effectiveness of Oral Melatonin for Adults (18 to 65 Years) with Delayed Sleep Phase Syndrome and Adults (18 to 65 Years) with Primary Insomnia

Kenneth M A MacMahon, Niall M Broomfield, Colin A Espie*

Section of Psychological Medicine, Division of Community Based Sciences, University of Glasgow, Gartnavel Royal Hospital, 1055 Great Western Road, Glasgow, G12 0XH, UK

Abstract: Oral melatonin supplementation has been heralded as a treatment for the sleep disorders of delayed sleep phase syndrome (DSPS) and primary insomnia (PI) in adults (18 to 65 years). However, there is inconsistency in the literature and many of the claims for melatonin appear to be based upon its effect in older adults (> 65 years). This article reviews, systematically, studies of oral melatonin in adults (18 to 65 years) with either delayed sleep phase syndrome (DSPS) or primary insomnia (PI).

Following electronic database searching, and hand-searching of relevant journal titles, fourteen articles that examined the use of melatonin in adults with PI or DSPS were identified for inclusion in this review (eight for DSPS and four for PI). Generally, the quality of articles is limited, particularly with regard to reporting of sleep parameters. However, results indicate that melatonin may phase-advance the sleep of individuals diagnosed with DSPS, although the majority of this evidence comes from uncontrolled trials. There is little evidence to suggest that melatonin is an effective treatment for PI. Further research, addressing deficiencies in the current literature, and considering long-term efficacy and safety are necessary before definitive conclusions as to the value of oral melatonin can be drawn.

Keywords: Insomnia, delayed sleep phase syndrome, disorders of initiating and maintaining sleep, melatonin, treatment efficacy.

INTRODUCTION

Melatonin is a pineal hormone that plays a central part in regulating bodily rhythms. Circulating levels of this hormone tend to be relatively low during the day, and rise to a high concentration in the bloodstream during the normal sleeping period at night. This correlation led to studies that suggested exogenously ingested melatonin, in an oral tablet form, facilitated more rapid sleep onset by phase advancing circadian rhythms in 'normal' sleepers [1].

From this standpoint, some authors have stated that melatonin is an efficacious treatment for sleep onset and maintenance disorders [2], although others contend that current evidence is not strong enough to conclude that melatonin is truly of benefit [3, 4]. Whilst there is fairly convincing evidence that melatonin can reduce the psychological and physiological effects of jet-lag (in essence an artificially-induced disorder of sleep timing) [5], its effectiveness in chronic sleep-onset and maintenance disorders, such as delayed sleep phase syndrome (DSPS) and primary insomnia (PI), is unclear.

Melatonin has an inherent attraction as an alternative to current benzodiazepine related drug treatments for sleep onset disorders, as it involves a process of 'supplementation' of endogenous production. Furthermore, it is not a licensed drug, and is available in the United States and elsewhere

without prescription. The combination of ease of availability, and marketing as a 'natural' product, may influence over-the-counter consumers, even if the evidence base from clinical trials is not conclusive.

This review sets out to clarify the existing literature by systematically examining available evidence for the effectiveness of oral melatonin for the treatment of DSPS and PI.

Characterisation of Sleep Disorders

The sleep disorders of PI and DSPS were, until the early 1980s, relatively synonymous, being subsumed under the term, 'insomnia.' Both disorders share the common difficulty of initiating sleep at the desired clock time, with consequent effects upon mood, social and occupational functioning. However, it was not until Weitzman *et al.* [6] identified a sub-group of 'insomnia' patients whose only sleep complaint was the lateness of their sleep period, that DSPS became identified as a sleep disorder distinct from primary insomnia.

Delayed Sleep Phase Syndrome (DSPS)

The cardinal feature of DSPS is difficulty falling asleep at the 'socially expected' time. Instead, sleep does not arrive until the early hours of the morning, with rising times subsequently delayed, often until midday or later. The sleep period of the person with DSPS is relatively unbroken and refreshing, with the cause of problems lying with desynchrony between the sleep-wake cycle of the individual

*Address correspondence to this author at the Section of Psychological Medicine, Division of Community Based Sciences, University of Glasgow, Gartnavel Royal Hospital, 1055 Great Western Road, Glasgow, G12 0XH, UK; Tel: 00 44 141 211 3903; Fax: 00 44 141 357 4899; E-mail: c.espie@clinmed.gla.ac.uk

and that of the outside world. Endogenous melatonin, entrained by environmental time cues, or *zeitgebers*, of ambient light and social activities, provides a 'signal' that 'night' is approaching. Unfortunately, in DSPS, this process appears to be delayed by several hours, leading to the delay in sleep onset [7].

Although there has been little work on the possible influence of psychological factors in DSPS, at present there remains no clear evidence for psychological factors as necessary pre-cursors or maintaining factors in this disorder [8-11]. Instead, genetic factors have been promoted as a possible aetiological factor for DSPS [12]. DSPS is thus characterised, at present, as a disorder of circadian timing, with little or no reference to 'psychological' factors [13, 14]. If this is indeed the case, and it can be considered a 'pure' circadian disorder, one would predict that melatonin will be an effective treatment for this condition. If it is not effective, other maintaining factors may need to be considered in a model of DSPS.

Primary Insomnia (PI)

PI is defined as difficulty initiating or maintaining sleep or non-restorative sleep, associated with significant distress and daytime impairment and not due to other medical, psychiatric or sleep disorders [13]. In other nosologies, it is referred to as 'psychophysiological insomnia' [14], which emphasises the interaction of physiological arousal and cognitive processes that are argued to underpin the disorder [15, 17]. There are some indications in the literature of lowered nocturnal melatonin production and circadian abnormalities in this population [18, 19], so oral melatonin may ameliorate PI. Furthermore, combined psychological and pharmacological interventions have been the focus of recent attention [20], thus melatonin may form an appropriate adjunctive treatment.

The Influence of Aging

Endogenous production of melatonin waxes and wanes during the human lifecycle, with the highest peaks recorded at six months of age. From that point onwards, there is a fall until late teens, at which point levels stabilise, albeit with a very gradual reduction until age 70 when there is a dramatic fall-off [21]. Thus, oral melatonin may redress a growing deficiency in older adults with sleep difficulties. In contrast, within the general adult population, levels remain relatively stable. Whilst this does not preclude melatonin as a treatment for older adults with DSPS or PI (on the contrary, it would indicate it), it does suggest that generalising from studies with older adults is problematic. For example, in a systematic review, Olde- Rikkert & Rigaud [22] cautiously suggested that melatonin may be an effective 'anti-insomnia drug', but they add the clear *caveat* that the studies they reviewed only addressed the older adult population. Unfortunately, in some cases, statements on the efficacy of melatonin have been made for a general adult population, by drawing on studies conducted with older adult samples [23]. The present review will overcome this confounding factor by including only studies that draw upon the adult (\Rightarrow 18 years and \leq 65 years) population.

Timing and Magnitude of Dose

Endogenous levels of melatonin alter during the circadian cycle, which has led some authors to suggest that the timing of dose may be crucial. Specifically, ingested melatonin might make more consistent therapeutic gains if doses are timed in relation to the evening rise or nocturnal peak in a patient's endogenous melatonin levels, or otherwise timed to some other circadian rhythm markers such as the daily body temperature rhythm [24]. Indeed, in healthy volunteers, the response of the endogenous rhythm in the production of melatonin to the exogenous administration of melatonin has been shown to follow a phase response curve that mirrors the phase-response curve for light, suggesting that timing of dose may influence whether it has an additive effect upon sleep likelihood [25].

However, in order to characterise the patient's circadian rhythms of sleep and temperature, various laboratory procedures, including measurements of core temperature and endogenous melatonin production in an environment strictly controlled for light and other *zeitgebers*, would be required. Given that this may be an influencing factor, the timing of dose will be considered in this review. However, it will be borne in mind that a requirement for such specialist assessment would severely limit the practical widespread use of this substance.

Whilst doses of 0.3 to 0.5mg are reported to reach physiologic levels, the half-life of melatonin is relatively short, and even doses as large as 50mg may be cleared by morning [26]. Thus, large doses may be feasible, and may in fact be necessary for clinical efficacy. This review will therefore take account of any correlation between dose and efficacy.

Possible Adverse Health Effects

As melatonin sits outside the sphere of licensed medication, it has no record of safety tests, or notified adverse reactions. However, concerns about its safety have been mooted: for example; alterations to sleep architecture [27], next-day 'hangover' effects impacting upon cognitive function [28], and exacerbation of symptoms in individuals with sleep apnoea [29]. Furthermore, no long-term studies have, as yet, been conducted with melatonin in a human population [3]. Thus, this review will consider adverse side-effects.

Clear Differentiation of Sleep Disorders

Notwithstanding the possibility that there may be a circadian element to PI, it is essential that studies in this area clearly delineate participants with DSPS from PI and vice-versa. This is never a particularly easy differentiation to make, as, in some individuals, elements of both disorders may be present. However, studies should seek to identify and include participants for whom a clear diagnosis can be made. Thus, the clarity and depth of assessment of participants will be noted in narrative form, and be reflected in the objective measures of study quality used in this review.

Objectives

This review will assess the available evidence for the effectiveness of oral melatonin for the alleviation of PI and DSPS in adults (>=18 years, <= 65 years). Specifically, it will examine reductions in sleep onset latency (SOL) and wake time after sleep onset (WASO) in PI; and advances in time of sleep onset and time of sleep offset in DSPS. Increases in sleep efficiency (SE) and total sleep time (TST) will be taken as an indication of efficacy in both PI and DSPS.

METHODS

Search Strategy

The following databases were searched electronically using the terms *insomnia, sleep-onset insomnia, delayed sleep phase syndrome, circadian disorder* and *melatonin* from the start of indexing until April 2004: PsychINFO, MEDLINE, The Cochrane Library of Systematic Reviews and the Cochrane Controlled Trials Register. *Sleep* (Nov 1997 to April 2004), *Sleep Medicine Reviews* (Nov 1997 to April 2004), *Chronobiology International* (Jan 1999 to April 2004), *The Journal of Physiology* (Jan 1990 to April 2004) and *The American Journal of Physiology* (Jan 1990 to April 2004) were hand-searched to identify trials that are not electronically indexed. Citation lists of relevant studies were examined for other relevant trials.

Types of studies

Randomised controlled trials, controlled trials, controlled single-case designs, uncontrolled case-series and uncontrolled single-case designs where the main purpose of the study was the evaluation of oral melatonin as therapeutic agent to treat PI or DSPS were all considered.

Types of participants

Inclusion criteria: 18 years to 65 years (inclusive); diagnosis of PI or diagnosis of DSPS.

Exclusion criteria: < 18 years old or > 65 years old; organic cause of sleep difficulties; blind or visually impaired [30]; learning disability [31]; deteriorating neurological condition or other co-morbid physical condition, such as cardiac or pulmonary disease, which could influence sleep [32].

Results of Literature Search

Electronic database searching under the search terms above (with a restriction of human only studies) initially retrieved a total of 313 studies. Limiting the search to adults (=> 18 years and <= 65 years) reduced this to 264 studies. Further limiting to studies that were indexed as reports of clinical trials or case reports reduced the total to 82 studies. Removal of duplicate studies, or those unrelated to the effect of oral melatonin on sleep, reduced this by 38 studies to 44 studies. A further 34 articles were excluded for the following reasons: participants were ‘normal’ sleepers (six studies);

participants had visual impairments (five studies); learning disabilities (one study); physical illnesses (five studies); psychiatric illnesses (five studies); participants aged under 18 years (four studies) or over 65 years (six studies). Two further studies used melatonin as part of a benzodiazepine reduction programme and were thus excluded. This left a total of ten studies (six DSPS; four PI). A further four studies on DSPS were identified through the process of hand-searching and consultation of reference lists [33-36].

Article Selection and Data Abstraction

The data abstracted from each article related to the complexities of the topic area and included subject demographics; duration of sleep difficulties; dose of melatonin; timing of dose; duration of treatment; method of sleep assessment (self-report, actigraphy, polysomnography); sleep parameters including: pre- and post-sleep onset latency (SOL), wake time after sleep onset (WASO), total sleep time (TST), sleep efficiency (SE), time of sleep onset, time of sleep offset; adverse health-effects; and data relating to study eligibility, quality and outcomes.

Table 1. Sleep Study Quality Measure (Derived from Mendelson [4])

1.	Self-report measure used to assess sleep quality (1 point).
	Sleep parameters reported for PI studies only (0.5 points for each): WASO, SOL, TST.
	Sleep parameters reported for DSPS studies only (0.5 points for each): SleepOnset and SleepOffset, TST.
2.	Objective measure PSG (2 points) and/or actigraphy (1 point) used (Maximum 3 Points).
	Sleep parameters reported for PI studies only (0.5 points for each): WASO, SOL, TST.
	Sleep parameters reported for DSPS studies only (0.5 points for each): SleepOnset and SleepOffset, TST.
3.	Appropriate diagnostic measures used to assign diagnosis, and clear assessment and exclusion of other sleep disorders; e.g., apnoea. (2 points for Yes; 1 for Partial).
4.	Measures of clinical significance reported (1 Point) or sufficient data quoted to be able to calculate (0.5 points).
Weighing Scheme:	Points in 1, 2 and 3 multiplied by two. Points in 4 multiplied by one.
Total Possible Points	19
Quality Rating:	Actual Score/ 19

Quality Ratings for Studies Considered

To assess the methodologic quality of each study, two complementary measures were used. Firstly, Cho & Bero’s [37] instrument for the assessment of quality of drug studies. This instrument rates each study on several factors including study design, inclusion and exclusion criteria, blinding of participants and raters, and statistical merit. The instrument yields an overall score of between zero and one

for each study; one representing the highest possible quality. Cho & Bero [37] reported a mean quality score of .60 (SD =.13; range =.36 -.74) on studies assessed for the development of their instrument.

Secondly, as the studies under review relate to sleep, a specific measure to determine quality for sleep-related studies was developed from the suggestions of Mendelson ([4]; personal communication, 24th May 2004). This instrument takes account of subjective and objective measures of sleep and detail of reporting of sleep parameters. Again, the instrument yields a score between zero and one for each study; one representing the highest quality (see Table 1).

Each study was evaluated by two independent raters, and intra-class correlation co-efficients were calculated between their ratings (+.99 for Cho and Bero's measure [37] and +.96 for the sleep quality measure). Disagreements were discussed between the raters, and a consensus on quality score reached for each measure.

Synthesis of results

It was intended that, if adequate data were available, effect-sizes would be combined into a meta-analysis, with the relative contribution of each study dependent upon its quality rating and number of participants. It was also planned that correlations between melatonin dose, age of participants and the above sleep variables would be calculated if sufficient data were available.

Any adverse health effects were intended to be noted in narrative form.

Melatonin and Delayed Sleep Phase Syndrome (DSPS)

Details of the eight DSPS papers that met criteria for inclusion are shown in Table 2, with a summary of sleep parameters reported in each study given in Table 3. Of these papers, three reported double-blind, placebo-controlled trials, with total participant numbers of 60 [38-40]. Each of these studies received a high rating on the Cho and Bero scale [37] (.78, .80 and .85, respectively). Sleep quality ratings were slightly lower at .71, .68 and .74, respectively. Notably, however, none of these studies made use of a control group who received treatment as usual. Instead, crossover, within-subject designs were utilised. Four further papers report uncontrolled case-series studies (with participant numbers of 54, in total) [33-36], and a final paper reports a retrospective uncontrolled case-series study with 61 participants [41]. As would be expected from their design, none of these case series papers rated particularly highly on the Cho and Bero measure [37] (mean of .36), and their sleep quality measures were generally low (mean of .36). Thus, none of the retrieved studies met the 'gold-standard' criteria of a fully controlled, randomised clinical trial. Furthermore, the majority of studies failed to describe all sleep parameters, even when articles state that they have been recorded (see Table 3).

Double-Blind, Placebo-Controlled Studies

Dahlitz *et al.* [38] (see Tables 2 and 3) found that melatonin produced a subjective advance in sleep onset and

sleep offset time of 82 and 117 min respectively. They also found a reduction in TST of 34 min. Whilst participants reported that their sleep parameters had altered, they did not report any changes in ratings of daytime alertness. From their results, Dahlitz *et al.* [38] concluded that melatonin was effective in advancing the sleep-wake phase, but did not increase alertness in this population. No definitive adverse effects of melatonin were noted, although one participant reported headache during use of melatonin, but not placebo, and one participant (not stated if same) was reported as having high alkaline phosphatase concentration during initial melatonin treatment, which fell back to normal levels after twenty weeks of continued melatonin treatment. The authors did not provide an explanation for this, nor did they suggest that it is connected with treatment. The limitations of this study (see Table 2) include the use of a small, exclusively male, sample and the lack of an objective sleep measure to corroborate self-report diaries. Nagtegaal *et al.* [39]. (see Tables 2 and 3) attempted to measure *individual* dim light melatonin onset (DLMO) through 24 hr recording of rectal temperature and endogenous melatonin production with blood assays. Theoretically, affording ingestion of melatonin five hours prior to individual DLMO, a point at which it should be maximally effective [24]. However, their study includes a total of 25 participants, but only thirteen are reported to have completed the procedure; the authors do not state how DLMO was estimated for other participants.

Mean advance of DLMO of 98 minutes during melatonin treatment was reported by Nagtegaal *et al.* [39], but reduction of SOL (as measured by PSG in 22 participants) was limited to ten minutes, and no other sleep parameters recorded on PSG were altered (see Table 3). Actigraphy was also employed in a sub-set of participants ($n = 13$), and shows an advance in time of sleep onset from 00:41 hrs to 00:03 hrs, a statistically significant difference ($p < .05$). No change in time of sleep offset is noted. Self-report sleeplogs, kept by 22 of the participants, show a similar advance in time of sleep onset from 00:37 hrs to 00:05 hrs, but again no change in time of sleep offset is noted.

The authors concluded that oral melatonin advanced DLMO by around one-and-a-half hours, but did not alter sleep-offset time. They suggest that measurement of individual DLMO may be useful, but they do admit that in their present study it did not have notable benefits. A particular note about this study is the early baseline sleep on- and off-set times (around 00:30 and 08:00 hrs respectively) of participants. Dagnan and Eisenstein [9] suggest that the criterion times of these variables, for DSPS, should be 02:00 hrs or later, and 10:00 hrs or later, respectively. This begs the question of whether this group of participants might more accurately have been classified with PI, rather than DSPS. Furthermore, whilst 25 participants are reported to have completed the study, diary data are only available from 22, actigraphic data from thirteen, and PSG from 22. There is no explanation for these differing numbers of participants, or any attempt to sub-group any who may have received all three assessments from those who received only one or two.

The final double-blind, placebo controlled study retrieved is that of Kayumov *et al.* [40]. In this case, baseline

Table 2. Summary of Studies Examining the Effectiveness of Melatonin in the Treatment of DSPS

Study	Type of Study	Cho & Bero [37] Quality	Sleep Study Quality	# participants	Age of Participants (years)	Diagnostic Criteria	Pre-Trial Assessment Instruments	Dose (mg) and Timing	Limitations	Results	Authors' Conclusions
Dahlitz <i>et al.</i> , 1991	Double-blind, placebo-controlled	0.78	0.71	8 (8 male)	14-61 years (X not stated)	Not stated	PSG and self-report	5mg at 22:00	Small N. Noobjective measure of sleep parameters.	SleepOn advanced 82 min; SleepOff advanced 117 min; TST < 34 min.	Melatonin may act as a phasemaker for sleepwake cycles in DSPS
Nagtegaal <i>et al.</i> , 1998	Double-blind, Placebo-controlled	0.80	0.68	30 (14 male)	X=37.3 (SD=15.3). Range not stated	ICSD	PSG, self-report and actigraphy	5mg at 5 hours prior to individual DLMO	No clear evidence that participants have DSPS. Sleep variables not reported. Not all participants completed PSG, actigraphy and self-report.	32 min advance in SleepOn	Melatonin can advance sleep onset, but not offset
Kayumov <i>et al.</i> , 2001	Double-blind, placebo-controlled	0.85	0.74	22 (15 male)	Male X=35.6; Female X=30.8	ICSD	PSG and self-report	5mg at 19:00, 21:00 or 23:00	Enforced restriction of sleep period	Mean reduction of 38 min for SOL	Can reduce SOL, particularly for younger age.
Kamei <i>et al.</i> , 2000	Uncontrolled, case-series.	0.35	0.21	30 (22 male)	X=24.0 (SD=7.6). Range not stated	ICSD	Actigraphy and self-report	0.3mg + 1mg. 5, 3 or 1 hr before bedtime	No placebo. No criteria for 'effectiveness'	12 (40%) of DSPS showed response	Significant effect especially for those with short
Okawa <i>et al.</i> , 1998	Uncontrolled case-series	0.21	0.21	9 DSPS and 2 Non-24 (8 male)	16-46 years. X not stated	Not stated	Actigraphy and self-report	1.0mg to 3.0mg	No placebo. Small N.	'Effective' for 5/9 participants	Evidence of phase advance of biological clock.
Dagan <i>et al.</i> , 1998	Uncontrolled, retrospective case-series	0.47	0.32	61 (37 male)	Not stated	Not stated	Actigraphy and self-report	5mg at 22:00 hours	No criteria for effectiveness. Relies on retrospective participant report.	96.7% of participants said melatonin 'effective'.	Melatonin will help most people with DSPS.
Olandi <i>et al.</i> , 1994	Uncontrolled case-series	0.39	0.63	7 (0 male)	Not stated	Not stated	Ambulatory PSG.	5mg between 17:00 and 19:00 hours	No placebo. Small N.	Mean SleepOn advance of 115 min; mean SleepOff advance of 106 min.	Effective treatment for DSPS
Tzischinsky <i>et al.</i> , 1993	Uncontrolled case-series	0.38	0.53	8 (7 male)	17-38 years (X=28.4)	Not stated	Actigraphy	5mg at 19:00 hours	No placebo. Small N	Mean SleepOn advance of 119 min; mean SleepOff advance of 122 min	Effective in advancing sleep onset.

TST: Total Sleep Time; SleepOn: Time of Sleep Onset; Drug Trial Quality: Cho & Bero (1994) Criteria; SOL: Sleep Onset Latency; SleepOff: Time of Sleep Offset; Sleep Study Quality: Mendelson (1997); WASO: Wake-Time After Sleep Onset; PSG: Polysomnography; DLMO: Dim Light Melatonin Onset

Table 3. Summary of Sleep Parameters Reported in DSPS Studies

Study	Measure	Pre-SOL (SD)	Post SOL (SD)	SOL ES	Pre-WASO (SD)	Post-WASO (SD)	WASO ES	Pre-TST (SD)	Post-TST (SD)	TST ES	Pre-Sleep On (SD)	Post-Sleep On (SD)	SleepOn ES	Pre-Sleep Off (SD)	Post-Sleep Off (SD)	Sleep Off ES
Dahlitz et al., 1991	Self-Report	NS	NS	NS	NS	NS		549 (NS)			149 (NS)	67 (NS)	NS	NS	NS	NS
	PSG (fixed 23:00 bedtime)	NS	NS		NS	NS		549.6 (49.8)	526.8 (36)	+46	229 (37.2)	132 (65.4)	+2.61	616.2 (70.2)	559.2 (60)	+81
Nagtegaal et al., 1998	Self-Report	NS	NS	NS	NS	NS		NS	NS		37 (18.1)	5 (16.6)	+1.77	NS	NS	
	Actigraphy	NS	NS		NS	NS		NS	NS		41 (31.5)	3 (29.6)	+1.21	NS	NS	
	PSG	25.3 (26.8)	15.3 (16.2)	+37	NS	NS		NS	NS		NS	NS		NS	NS	
Kayumov et al., 2001	PSG	58.9 (30.3)	20.2 (17.7)	+94	42 (38.8)	42 (50.6)	0	382.0 (55.5)	404.3 (60.4)	-40	Not possible to estimate due to enforced restriction of sleep period					
Kamei et al., 2000	Self-Report	NS	NS		NS	NS		NS	NS		NS	NS		NS	NS	
	Actigraphy	NS	NS		NS	NS		NS	NS		NS	NS		NS	NS	
Okawa et al., 1998	Self-Report	NS	NS		NS	NS		NS	NS		NS	NS		NS	NS	
	Actigraphy	NS	NS		NS	NS		NS	NS		NS	NS		NS	NS	
Dagan et al., 1998	Self-Report	NS	NS		NS	NS		501 (47)	NS		189 (86.2)	NS		691.0 (98.6)	NS	
	Actigraphy	NS	NS		NS	NS		NS	NS		NS	NS		NS	NS	
Olandi et al., 1994	PSG	12.9 (9.2)	11.1 (6.8)	+20	26.0 (36.6)	39.6 (33.6)	-37	470 (41)	467 (78)	+07	216 (61)	101 (65)	+1.89	720 (62)	614 (66)	+1.61
Tzischinsky et al., 1993	Actigraphy	NS	NS		NS	NS		447.8 (60)	443.1 (55)	+08	169 (40)	51 (40)	+2.95	598 (82)	474 (42)	+1.51

NS: Parameter not stated SOL: Sleep Onset Latency Sleep Off: Time of Sleep Onset (minutes after 00:00 hrs)
 ES: Effect Size WASO: Wake Time After Sleep Onset SleepOn
 TST: Total Sleep Time Sleep on: Time of Sleep Onset (minutes after 00:00 hrs)

recordings of sleep parameters were taken whilst participants were free to select their desired bed- and rising-times. However, during the study period, sleep was restricted to the ('socially desirable') interval between 00:00 hrs to 08:00 hrs. Thus, the variable of particular interest is SOL, which should be reduced if melatonin phase advanced sleep.

Self-report sleep-logs indicated a reduction in SOL by a statistically significant margin, from 58.9 min on placebo to 20.2 min with melatonin (see Table 3). Notably, baseline SOL was 35.8 min, suggesting that the placebo *increased* SOL. The authors do not compare, statistically, baseline to melatonin, but it appears unlikely that a difference would have been found if they had. Subjective total sleep time increased with melatonin treatment from 382.0 min with placebo to 404.3 min, a statistically significant difference. Again, baseline values for this parameter are higher (at 446.1min), with no statistical comparison being made by the authors. No statistical differences in objective (PSG) measures of sleep architecture are evident on any parameter. No differences in subjective ratings of daytime alertness are found.

Kayumov *et al.* [40] conclude that melatonin is effective in reducing SOL when sleep is restricted to a 'socially desirable' interval in patients with DSPS, but note that there are no other effects on sleep parameters. Unfortunately, given the design of the study, and its limited sleep period, it is not possible to ascertain whether participants would have phase advanced without the need for artificial restrictions. Also, the authors fail to report sleep onset and offset times, which would have allowed comparison between baseline and placebo phases, possibility allowing assessment of the effect of the artificial sleep period.

Uncontrolled Case-Series Studies

Kamei *et al.* [33] examined the effects of oral melatonin on 46 individuals with circadian disorders, 30 of whom were diagnosed with DSPS, according to ICSD (1990) criteria. Kamei *et al.* [33] differentiate the DSPS participants in their results, thus merited inclusion in this review. As shown in Table 3, no sleep parameters were reported by the authors who chose, instead, to report participants as 'responders' or 'non-responders'. The former group were described as 'those who achieved proper sleep phase advance and woke up before 09:00 hrs within three months.' Twelve of the 30 DSPS patients were regarded as responders. The authors concluded that melatonin had 'favourable' effects on circadian rhythm sleep disorders, but those of a younger age and with initially shorter total sleep times were more likely to respond to treatment.

A further uncontrolled case-series was reported by Okawa *et al.* [34] Again, patients with other circadian rhythm disorders (non-24-hour sleep-wake schedules) were included, but were differentiated by the authors in the results section. Although self-report sleep diaries and wrist actigraphy were used to assess sleep-wake cycles, diagnostic criteria were not reported and no sleep parameters, either objective or subjective were reported (see Table 3). Okawa *et al.* [34] state that treatment was 'effective' in five patients with DSPS, and that participants 'definitely showed phase advance of the biological clock.' Unfortunately, there are no

reported data to support this assertion. Side effects of 'tiredness' in two patients, and 'bad feeling at rising' for one patient were noted, but not elaborated upon, by the authors.

Olandi *et al.* [35] reported an uncontrolled case-series of six patients diagnosed with DSPS, according to ICSD criteria [42]. Whilst this study is small in terms of participants (see Table 2), the authors do report all sleep parameters from baseline and follow-up PSG assessments. As shown in Table 3, they report mean sleep onset and offset advances of 115 and 106 min, respectively. No significant changes in sleep architecture were found between baseline and follow-up. Unfortunately, no subjective measures of sleep parameters or sleep quality were taken from participants. The authors concluded that melatonin was an effective means of advancing the sleep phase, without altering sleep architecture.

The final uncontrolled case-series study retrieved was that of Tzischinsky *et al.* [36]. They assessed the effects of oral melatonin on eight patients with DSPS (see Table 2). Participants took melatonin two hours prior to their desired bedtime, and, once this desired bedtime had been achieved, they were instructed to discontinue treatment, but keep to their new sleeping pattern for at least a two-month period. Actigraphy was used to assess sleep parameters at baseline and following a month of treatment. Participants were also followed-up six months later for a subjective report on their sleep patterns. Tzischinsky *et al.* [36] found that melatonin advanced sleep onset and sleep offset by 1.98 hrs and 2.04 hrs respectively (see Table 3): a statistically significant margin ($p < .05$). There were no other changes in sleep parameters, not any reported adverse side-effects. Perhaps the most interesting aspect of this study was the finding that, six months hence, only two of the participants relapsed to their previous sleep pattern; the remaining six retaining a 'persistent improvement in sleep and daytime behavior.' Although speculative, this sustained improvement may have been the result of the requirement that participants maintain a strict sleep schedule at the conclusion of melatonin treatment.

Retrospective Uncontrolled Case-Series

Dagan *et al.* [41] conducted a retrospective follow-up study of participants who had been treated with melatonin at their sleep clinic (see Table 2). Self-report sleep diaries were kept by participants prior to commencement on treatment (see Table 3), but not during or after treatment with melatonin. A followup postal questionnaire was sent to participants twelve to eighteen months after the end of treatment. Of the respondents, 96.7% percent reported that melatonin treatment was 'helpful', with 'almost no side effects'. However, of these, 91.5% reported a relapse to their pre-treatment sleeping patterns within one year of the end of treatment. 28.8% reported that relapse occurred within one week; the authors suggested that this 'relapse' group had pre-treatment sleep onset and waking times significantly later than the group who did not relapse so immediately.

The authors suggest that melatonin will help most individuals with DSPS to develop more 'adaptive' sleeping patterns, with few side effects, but the improvement is not preserved over time. It is unfortunate that this study did not

include measures, either subjective or objective, of sleep parameters either during the treatment period or on follow-up, as 'improvement' is undoubtedly a subjective matter, and it is possible that demand characteristics may have altered the responses of individuals.

Summary of Literature on Melatonin and Delayed Sleep Phase Syndrome (DSPS)

Perhaps the most striking aspect of the literature reviewed so far, is the lack of quoted sleep parameters. Only Olandi *et al.* [35] reported all sleep parameters measured (see Table 3). In terms of quality of studies, whilst some of the literature reaches a high level of quality (as measured by Cho & Bero's instrument [37]) they universally fail to meet all of the criteria laid down by Mendelson [4]. Given the paucity of information available, any form of statistical meta-analysis would be unreliable. This highlights the need for increased reporting of *all* data, and less reliance on overarching statements that a treatment has been 'effective', without clear definition of what criteria define 'effective'.

In terms of treatment efficacy, of the double-blind placebo-controlled studies reported, only that of Dahlitz *et al.* [38] shows a demonstrably large effect of treatment on sleep onset (effect size of +2.61). Nagtegaal *et al.* [39] showed favourable effects of melatonin on sleep-onset (effect sizes of +1.77 and +1.21 for self-report and actigraphy, respectively), but the relatively early sleep onset and offset times of their participants calls into question whether they truly met criteria for DSPS. Kayumov *et al.* [40] showed a reduction in sleep onset latency as measured by PSG (effect size of +.94), but their study was conducted with an artificially imposed sleep schedule, and no analysis of the possible impact of this schedule on sleep parameters was made.

Of the remaining uncontrolled studies, all reported melatonin as being an efficacious agent for the treatment of DSPS. However, by their nature they are uncontrolled and therefore open to the 'placebo' effect, particularly if participants have been 'prescribed' melatonin in a sleep clinic setting. Furthermore, of these six studies, only Olandi *et al.* [35] and Tzischinsky *et al.* [36] make full reports of sleep parameters. The remaining studies simply state that treatment has been 'effective'. Without a clear definition of 'effective', it is difficult to unquestioningly accept their findings.

There is insufficient variability in doses within the literature to statistically examine any dose-response relationship, as six out of eight studies chose 5mg (see Table 2). This is particularly so for the doubleblind placebo-controlled studies, where all three use 5mg doses. Further work on possible doseresponse effects in this particular population would be of great value.

Reported adverse events within these eight studies were limited to occasional headache, [38] or daytime tiredness during the first few days of use [34]; the latter most probably being the consequence of an advance in sleep phase. However, a note of caution should be sounded as further, longer term, robust trials of melatonin are necessary before it could be declared a 'safe' treatment for DSPS [26].

Perhaps one of the most interesting studies is that of Tzischinsky *et al.* [36] who found that when participants were required to continue on a strict sleep 'window', once their sleep-wake cycle had been entrained to its desired state, relapse appeared to be the exception, rather than the rule. Although their study contained very few participants, it does raise the possibility that melatonin could be used with DSPS sufferers to entrain circadian rhythms, on a short-term basis, before a strict behavioural programme of sleep scheduling is introduced. This would circumvent the possible health implications of long-term use, and provide an alternative to initial entrainment through sleep scheduling or light therapy, both of which might encounter compliance difficulties if used as a first-line treatment.

Melatonin and Primary Insomnia (PI)

A literature search yielded four papers that examined the effects of oral melatonin on sleep variables in PI (see Table 4) [43-46]. All four studies are double-blind placebo-controlled, although none employ a control group who receive only treatment as usual. The total number of participants combined across all studies is only 48, suggesting that any conclusions reached will be difficult to generalise from. Quality of all four studies in terms of general drug trials is high, according to the quality criteria measure of Cho and Bero [37] at a mean of .74. Sleep quality criteria is, equally high in two of the studies [43, 44] with sleep quality measures of both these studies scoring .71. The quality of the remaining two studies [45, 46] is markedly lower at .39 and .37, respectively.

James *et al.* [43] (see Table 4) assessed the effects of melatonin on ten participants with a diagnosis of Disorder in Initiating or Maintaining Sleep (DIMS) persistent type without objective findings [47]. Melatonin preparations (of either 1 or 5 mg) or placebo were given to participants fifteen minutes prior to bedtime. Neither a significant decrease in sleep latency, nor an increase in sleep duration, was found with either the 1 or 5mg doses (see Table 5). Neither was there a change in the number of awakenings during sleep. A non-significant trend toward earlier onset of sleep was present, although, in mean terms this amounted to only eight minutes per night. In terms of subjective report, subjects felt they slept less during melatonin treatment, but, paradoxically, they reported that the quality of sleep had improved. No 'serious' adverse reactions were reported.

Almeida-Montes *et al.* [44] reported a study of melatonin treatment for PI using 0.3 and 1.0mg preparations of melatonin (see Table 4). Although the age range of participants in this study extends to 72 years, the mean age is 50. Thus it was judged acceptable to include in this review, with the clear *caveat* that any positive findings might be attributable to the older participants in this study. However, even with this sample, the authors report no significant alterations in sleep parameters, recorded by PSG, with melatonin use (see Table 5). As with other authors, they failed to report specific data on this. They reported no differential impact on subjective amount or quality of sleep. No side effects of either melatonin or placebo were reported. The authors concluded that melatonin did not ameliorate sleep difficulties in their sample of individuals with PI.

Table 4. Summary of Studies Examining the Effectiveness of Melatonin in the Treatment of PI

Study	Type of Study	Cho & Bero [37] Quality	Sleep Study Quality	# participants	Age of Participants (years)	Diagnostic Criteria	Pre-Trial Assessment Instruments	Dose and Timing	Limitations	Results	Authors' Conclusions
James <i>et al.</i> , 1990	Double-blind, placebo-controlled	0.80	0.71	10 (6 male)	20 – 57 (X=33.4)	DIMS (ASDA, 1979)	PSG and Self Report	1mg + 5mg	Small N	No significant changes on PSG Subjective improvement in sleep quality	Melatonin may alter perception of sleep.
Almeida-Montres <i>et al.</i> , 2003	Double-blind, placebo-controlled	0.80	0.71	10 (6 male)	30 – 72 (X=50.0)	DSM-IV	PSG and Self-Report	0.3mg + 1.0mg	Small N	No significant changes on PSG or self report.	Melatonin has no beneficial effect in PI.
Ellis <i>et al.</i> , 1996	Double-blind, placebo-controlled	0.65	0.39	15 (9 male)	X = 46 (SD = 11). Range not stated.	ICSD	Self-Report	5mg at 20:00 hours	Subjects selected from sleep clinic	No significant changes in sleep parameters.	Melatonin probably has 'no clinical value' for PI.
MacFarlane <i>et al.</i> , 1991	Double-blind, placebo-controlled	0.69	0.37	13 (8 male)	25 – 65 years (X not stated)	Not specified	PSG and Selfreport	75mg at 22:00 hours	Small N. Diagnostic criteria not explicitly stated	Statistically significant increase in TST	Additional research required to confirm findings.

Table 5. Summary of Sleep Parameters Reported in PI Studies

Study	Measure	Pre-SOL (SD)	Post SOL (SD)	SOL ES	Pre-WASO (SD)	Post-WASO (SD)	WASO ES	Pre-TST (SD)	Post-TST (SD)	TST ES	Pre-Sleep On (SD)	Post-Sleep On (SD)	SleepOn ES	Pre-Sleep Off (SD)	Post-Sleep Off (SD)	Sleep Off ES
James <i>et al.</i> , 1990	Self Report	NS	NS		NS	NS		NS	NS		NS	NS		NS	NS	
	PSG	30.3 (6.3)	22.0 (5.5)	+1.50	15 (5.1)	25 (4.1)	-1.96	395 (12.7)	391.7 (17)	+26	NS	NS		NS	NS	
Almeida-Montres <i>et al.</i> , 2003	Self-Report	69.2 (29.1)	57.4 (47.2)	+41	NS	NS		270 (84)	306 (138)	-43	NS	NS		NS	NS	
	PSG	NS	NS		NS	NS		NS	NS		NS	NS		NS	NS	
Ellis <i>et al.</i> , 1996	Self Report	NS	NS		NS	NS		366.8 (81)	295.2 (97.8)	+88	33 (65)	55 (101)	-35	364.8 (78)	337.8 (115.2)	+35
MacFarlane <i>et al.</i> , 1991	Self-Report	NS	NS		NS	NS		NS	NS		NS	NS		NS	NS	

A further study of melatonin and PI was conducted by Ellis *et al.* [45] (see Table 4). The authors reported that, in comparison to placebo, melatonin did not improve, or adversely affect, any sleep parameter, although seven of the participants reported that melatonin treatment had subjectively improved their sleep to a minor extent in the week of active treatment. Melatonin appears, ironically, to have delayed sleep onset in comparison to baseline, and reduced TST (see Table 5). Side effects reported were headache and an 'odd taste in the mouth'. The authors concluded that melatonin is probably of 'no clinical value' in the management of PI.

The only retrieved study on PI that found a positive effect of melatonin is that of MacFarlane *et al.* [46]. In their case, participants were administered a 75mg dose of melatonin, or placebo (see Table 4 for details). Whilst the authors report that initial diagnosis was based upon subjective sleep logs, PSG evaluation and exclusion of other sleep disorders or psychiatric conditions, the criteria for diagnosis of PI are not explicitly stated, and no sleep parameters are quoted in the text (see Table 5). The authors reported a statistically significant ($p < .05$) increase in subjective assessment of TST and daytime alertness with melatonin but not with placebo. However, no sleep parameters are given in the text, aside from a graph of TST and subjective alertness. Furthermore, the baseline TST appears to be around three-and-a-half hours per night, which would seem to be a dramatic underestimate, given that this level of sleep deprivation would be unsustainable over time [48].

Summary of Literature on Melatonin and Primary Insomnia (PI)

As with studies on DSPS, all four of those on PI failed to report all subjective or objective sleep parameters, which is unfortunate as these are precisely the symptoms that any treatment would seek to address. Any form of meaningful meta-analysis is again impossible due to the lack of reported data (see Table 5).

Aside from these limitations, it is clear that only MacFarlane *et al.* [46] provides some suggestion of an improvement in sleep quality following melatonin treatment. None of the other studies considered in this review found any efficacy for melatonin. One point of note is the relatively high dose used in this study (75 mg as opposed to the 5 mg of all other studies). This raises the possibility that larger doses of melatonin may be necessary for this population. However, it should be borne in mind that this study was also rated as the lowest quality of all four studies in terms of sleep quality criteria (.37) and second lowest on Cho and Bero's [37] criteria (.69). As with the studies on DSPS, there is a suggestion that melatonin may cause headache, [45] although no major adverse events are reported. In summary, at present there is no clear evidence to suggest that melatonin is an effective treatment for PI in adults.

Limitations of the Available Literature

Whilst the studies reviewed give limited indications that melatonin is effective for DSPS but not for PI, there are

serious limitations to the depth and breadth of currently available literature. Of the fourteen studies reviewed, the total number of participants is only 223, 61 of whom comprise a single, retrospective, study. Without exception, no study reports a power calculation, making it difficult to conclude whether null findings are the result of a lack of statistical power, or the absence of an effect.

Most importantly, authors failed to report full sleep parameters, even when these had been measured, rendering full interpretation or meta-analysis impossible (see Tables 3 and 5). Studies also lack sleep history details, including age of onset and severity. For studies that address PI, clearer differentiation of possible co-morbidity with circadian disorders is essential.

CONCLUSIONS

The available evidence supports, to a limited degree, the use of melatonin in adults with DSPS; however, the majority of positive reports use uncontrolled case-series designs with low participant numbers (see Table 2). Of the blinded, placebo-controlled studies on melatonin and DSPS, only that of Dahlitz *et al.* [38] finds a clear effect of melatonin in the absence of possible confounding factors such as imposed sleep-wake schedules. The literature is undoubtedly sparse, with small sample sizes, shortduration studies, limited reporting of sleep parameters and lack of parallel waiting-list controls. Further research is needed to address these shortcomings.

At present, there is no clear evidence that melatonin has any efficacy in the treatment of adults with PI. Of the four studies in this area that were retrieved, only MacFarlane *et al.* [46] reported a positive effect of melatonin. Two others report no clinical value [44, 45], and the remaining study suggests, only tentatively, that it may alter subjective perception of sleep [43]. Again, further work, addressing previous shortcomings is required. One particular area of future consideration might be the therapeutic dose necessary for those with PI. The only positive report in this literature used a dose fifteen times higher than in other studies; thus, future research should carefully consider this factor. Nonetheless, at present, there is scant evidence to back-up the numerous claims in the literature that melatonin is an effective treatment for PI in adults.

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