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

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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-hour sleep wake syndrome in people who are blind, and REM-Behaviour Disorder. Meta-analyses were performed to determine the effect of magnitude in studies of melatonin in improving sleep.

A total of 5030 studies were identified; of these citations, 13 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.

Keywords: melatonin, sleep disorders, insomnia, delayed sleep phase syndrome, blind, REM-behaviour disorder, randomised controlled trials

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

Hrs: Hours

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

Mins: Minutes

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

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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 [5,6,7] 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 [9] 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, [10] 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' [11], and no adverse effect on alertness or mood the following day [12], as well as minimal side-effects (e.g., headache, dizziness, nausea, drowsiness) [13,14] if administered at a low dose. [15] Melatonin has a short half-life of only 30-50 minutes and can 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. [16]

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BIOLOGY OF MELATONIN

In humans, the primary physiological function of melatonin is to reinforce darkness-related behaviour, such as sleep propensity. [16] 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. [17]

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. [16] Melatonin production declines as we age [18] due to several factors. The lower peak levels of endogenous serum melatonin [19] may be due to decreased pineal melatonin synthesis at night [20], or gradual pineal gland calcification [21]. Endogenous melatonin synthesis may be further reduced by drugs (e.g. benzodiazepines, 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. [22]

In terms of the soporific effect of acutely administered melatonin, studies have indicated healthy volunteers receiving a single dose (0.3mg and 1.0mg orally) of

melatonin had significantly improved sleep efficiency [23] and there are no observable toxicological or side-effects in the short-term daily use of melatonin (10mg for 28 days). [24] 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-hour light-dark cycle [25,26] 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. [27] 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.

Primary Sleep Disorder	Current Recommended Treatment	Role of Melatonin
Rapid Eye Movement-Behavioural Disorder (RBD)	1. Modify sleep environment 2. Clonazepam; use with caution in dementia and concomitant obstructive sleep apnoea. [28]	Melatonin has been recommended since 2005 - associated with fewer side effects and may be effective in patients resistant to clonazepam. [28]
Delayed Sleep Phase Syndrome (DSPS)	Schedule sleep earlier and decrease late night activity. Phototherapy and strict sleep schedule.[29]	Evening administration of melatonin (0.3-5mg) between 7pm and 8pm shifts circadian rhythms to an earlier time.[29,30]
Advanced Sleep Phase Syndrome (ASPS)	Combined phototherapy and bright light exposure in the evening.[31]	Insufficient data to recommend use of melatonin for treatment of ASPS in adults.[31]
Non-REM Parasomnia	Clonazepam, tricyclic antidepressants and benzodiazepines.[19]	No trials conducted for the use of melatonin in parasomnias in adults. [19]
Blind/non-24 h Sleep Wake Syndrome	Regulation of bed-times.[32]	Evening administration of melatonin achieved phase advance in sighted individuals.[32] Timed melatonin also successfully entrained rhythms in blind individuals.[33,34]
Primary Insomnia	1. Cognitive behavioural therapy, relaxation techniques and sleep hygiene measures. 2. Non-benzodiazepine agonists and MT1/MT2 receptor agonists are safer for long term use than traditional benzodiazepines.[35]	Melatonin agonist ramelteon approved in 2005.[35]

METHODS

Method: Meta-analysis of published, peer-reviewed randomised controlled trials (RCT) on the use of exogenous melatonin to treat primary sleep disorders.

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. [36] 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 were undertaken and all relevant articles for this review were identified for a systematic review. [37-39] 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 years)".

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 pre-defined criteria from the Jadad scale. [40] 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 met the inclusion criteria they met to compare results and discuss which articles would be included in the final analysis.

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Study Type: The inclusion criteria were the trials had to be RCT, single or double-blind, cross-over or parallel. All studies that did not meet the criteria or were not peer-reviewed, published trails were not included in the meta-analysis. There was no time limit on trial duration. The effect of melatonin was compared with placebo treatment in primary sleep disorders: primary insomnia, RBD, DSPS, or non-24 h sleep wake disorder. Qualitative, unpublished, duplicate studies, and those, which were not easily translated, were excluded.

Study Group: Adults over the age of 18 years with an established primary sleep disorder.

Date of Publication: Studies published between 1990 - 2015 were eligible.

Sample Size: There were no restrictions on sample size.

Data Extraction and Analysis: The author, year of publication, number of participants, type of study, details of melatonin regimen, and methods used were recorded for each of the chosen RCTs (Table 1). Data were assessed by two independent reviewers and relevant extracted data were tabulated (Table 1). Data were analysed using the latest reviewing software available from the Cochrane Collaboration: Review Manager Version 5.2. [41] Where necessary, calculations using standard mathematical techniques were undertaken to transform data for analysis.

Meta-analysis was performed using a continuous outcome measure across all the included evidence. The measure of effect size was the total mean difference, comparing the change from baseline for both melatonin and placebo in improving sleep onset latency. Alternative treatments, such as cognitive-behavioural therapy [42] were not included to keep the meta-analysis strictly between melatonin and placebo and remove any other non-medication variables, such as therapy. A fixed

95% confidence interval (CI) for the mean difference was used to determine a beneficial treatment effect of melatonin compared with placebo, with a significance level of p<0.05. The Z-test determined an overall significance of treatment effect versus placebo with values of p<0.05. Heterogeneity of data was assessed using Chi-squared test of heterogeneity and I^2 test in accordance with Cochrane collaboration's guidance for assessing heterogeneity in meta-analyses. Data were considered heterogeneous if Chi-squared test yielded P-values <0.10 and I^2 >50%. [43] Potential publication bias among studies was assessed by the use of funnel plots for each sleep disorder.

RESULTS

A total of 5030 articles were identified in the initial database and hand search (3696 EMBASE, 790 MEDLINE, 496 PsycINFO, 48 SCOPUS) of journals. From this, 361 abstracts were assessed and 28 met inclusion criteria. Fifteen articles were then excluded for reasons described below, resulting in a final 13 which were included (Fig.1). The studies included in analysis comprised a total of 1,510 patients, all aged between 18-80 years with either primary insomnia, DSPS, blindness, or RBD. Each study compared the effects of oral melatonin and placebo administration on different sleep parameters. The dose of melatonin ranged from 0.1mg to 10mg with treatment duration time ranging from two to five weeks. The outcomes and data findings for each included study are shown in Table 1 (Supplementary Data: Table One).

Primary Insomnia: Primary insomnia comprises of difficulty initiating and/or maintaining sleep lasting for a minimum of one month, resulting in significant impairment of normal daytime functioning. This definition is from the International Classification of Sleep Disorders- Second Edition (ICSD-2) [56] and Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition (DSM-IV), [57] which is now

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updated as "insomnia disorder" in the International Classification of Sleep Disorders-Third Edition (ICSD-3) [58], and carries a slightly different definition. The ICSD-2 and DSM-IV definition were used in this review due to the fact that the studies assessed were conducted before the current versions of the ICSD-3 [58] and Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) [59] were published, and therefore, the participants were selected based on those diagnostic criteria. If these studies were replicated now using the new diagnostic codes, findings might differ due to slightly different populations being tested. The ICSD-3 differs from the ICSD-2 in that the ICSD-2 "…described primary insomnia subtypes such as psychophysiological insomnia, idiopathic insomnia, inadequate sleep hygiene, and paradoxical insomnia, as discrete diagnostic entities." [58] Patients who meet the diagnostic criteria for only one subtype are very rare and the diagnostic criteria have been established for the subtypes of insomnia "…represent generic characteristics (e.g., engaging in sleep-disruptive habits; underestimation of sleep time, evidence of conditioned arousal) of insomnia…and do not facilitate discrimination among these subtypes or between these subtypes and those presumed to have "secondary" forms of insomnia." [58] The ICSD-3 also states, "…the current manual abandons the previously employed complex and highly specific insomnia classification scheme described by the original ICSD and the ICSD-2 in favour of a more global and defensible nosology." The ICSD-3 now includes three categories to diagnose insomnia: chronic insomnia disorder, short-term insomnia disorder, and other insomnia disorder. [58]

Primary insomnia is not due to a medical or psychiatric condition or medicine/substance abuse. It is particularly common in the elderly population and is often a long term problem; 69% of older people monitored for one year still suffer

from the condition due to their vulnerability to persistent symptoms and the decreased production of endogenous nocturnal melatonin. [60-62] Haimov et al. recommend melatonin replacement therapy may prove beneficial due to peak excretion of melatonin being almost half that of younger patients. [63] Vural et al's [64] review reports melatonin is effective in older adults, but advises in order to avoid prolonged, supra-physiological blood levels, older adults should use the lowest dose possible of immediate-release melatonin as long-term effects have not been studied. Abhinav et al [65] reported melatonin is beneficial in older adults for metabolic syndrome components when used in 10-week periods and Haimov et al [66] reported melatonin can be safe and effective for up to two months of treatment.

Quantitative analysis of the five eligible RCTs [44,46-49] showed an overall significant reduction in the time to fall asleep between the effect on sleep onset latency for melatonin in patients with primary insomnia compared with placebo (Total mean difference = -5.05 minutes, 95% CI: -8.51, -1.59). The overall estimated score of melatonin treatment was significant (Z=2.86, P=0.004) (Fig.2). No significant heterogeneity was present across the five studies (χ^2 =3.19, P=0.53, I^2=0%). There was no asymmetry in funnel plots suggesting there was no reporting bias between the studies.

In all five studies for primary insomnia [44-49] there were large sample sizes, which increased reliability of results (n=40-791). The studies used a thorough pre-screening assessment which was deployed to reduce confounding factors and use of medications such as benzodiazepines were stopped beforehand.

Delayed Sleep Phase Syndrome: DSPS is the most common circadian rhythm disorder, causing delayed habitual bedtime and delayed rising time, roughly three to

six hours after conventional sleep-wake times. It is particularly common in adolescents and can be also associated with depression. [67,68]

Meta-analysis of the two eligible trials [52,53] investigating the role of melatonin in treating DSPS demonstrated an overall significant improvement in sleep onset latency compared with placebo (total mean difference = -22.05 minutes, 95% CI: -32.02, -12.09). The overall estimated score of melatonin treatment was significant (Z=4.34, P<0.0001) (Fig.3). There was significant heterogeneity between these two studies (χ^2 =7.76, P=0.005, I^2=87%). There was slight asymmetry in the funnel plot, indicating there was potential publicaiton bias present.

The two studies diverged in the way sleep was measured (e.g., PSG versus wrist actigraphy), and by method of melatonin administration (e.g., 5mg daily for four weeks versus 5mg for two weeks double-blind and two weeks open setting, successively or interrupted with two weeks of placebo). Nevertheless, both studies highlighted a decrease in sleep onset latency after melatonin administration.

The third study included for DSPS in this review [51] showed melatonin significantly reduced REM latency and wake time. However, there was no effect on total sleep time or alertness ratings. This indicates a potential role for melatonin in inducing phase-shift in sleep times for patients with DSPS.

One study used adolescents and young adults (aged 16-25) [69,70] examining the measures of subjective and objective sleepiness and cognitive function focusing on the short- and long-term effects of bright light and melatonin coupled with advanced rise times. Gradual advanced rise times coupled with bright light and melatonin were found to be effective with patients with DSPS immediately as well as showing lasting effectiveness over time. We recognize the combination of bright light and melatonin created a positive effect on sleep, which might make it difficult to tease out an

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independent effect of melatonin; it would be beneficial to replicate this study in older adults to compare it to other studies reviewed.

Non 24-hour Sleep Wake Syndrome in Blind Patients: Non 24-hour sleep wake syndrome is almost exclusively seen in people who are completely blind or have visual impairment with an absence of light perception. It rarely affects the general population and it is largely associated with behavioural issues and psychiatric illness. This syndrome involves progressive delay of sleep onset time due to a lack of light perception by the photoreceptor cells located in the retina resulting in a cyclic non-24 h sleep wake disorder characterised by periods of short night sleep and severe daytime sleepiness.

Three studies [54,55,58] highlighted the use of melatonin in phase advancement and entrainment of circadian rhythm in patients who are blind. Two of these trials [54,55] were eligible for meta-analysis. There was no overall significant difference between the effects of melatonin and placebo on sleep onset latency in blind patients (total mean difference = -3.17 minutes, 95% CI: -11.88-5.54). It is speculated that the use of melatonin has no effect when used on nights when the circadian rhythm is congruent with pre-established/routine sleep habits, reinforcing the concept that melatonin does not provoke sleep but facilitates the desire to sleep when awake. [55] The overall estimated score of treatment effect for these patients was not significant (Z=0.71, P=0.48). No significant heterogeneity was found between these compared studies (χ^2 =0.00, P=0.99, I^2=0%). No publication bias was present indicated by the symmetrical funnel plot (Fig.4).

Only subjective measures were used by Hack et al [54] to assess sleep parameters with a small sample size (n=10). The use of daily diary reporting measures increased the likelihood of bias due to inaccurate reporting and therefore PSG or wrist

actigraphy methods would have been more reliable, more representative of sleep behaviour, and a less erroneous strategy. In comparison, Sack et al [55] used PSG which increased reliability of the findings despite the similarly small sample size (n=7). A reduction in total sleep time after melatonin administration was also shown, due to melatonin inducing additional consolidated sleep in blind patients and shortening their overall sleep time by reducing frequency of daytime napping. Thus, melatonin is an effective treatment to promote the free-running circadian rhythm in these patients, allowing for a more structured 24-hour sleep-wake cycle.

REM-Behaviour Disorder: RBD involves loss of normal voluntary muscle, atonia, during REM sleep resulting in complex motor behaviour (the body is active instead of being paralysed) when dreaming. RBD is predominantly seen in males and is more common in the elderly. [71]

Only one study has addressed the role of melatonin in the treatment of this disorder. [50] Participants were administered 3mg of melatonin daily over 4 weeks. A small sample size was used (n=8, all male), but results highlighted a significant improvement in clinical global impression (CGI) (6.1 vs 4.6; P=0.024) and improvement in REM sleep muscle atonia (39% vs 27%; P=0.012), despite the heterogeneity of the RBD included. This provided evidence in favour of melatonin as a useful adjunct to clonazepam which is often prescribed in the treatment of RBD. There were sufficient pre-screening measures taken before participation in the trial, such as alcohol avoidance and prohibiting exercise, since studies have shown exercise can improve symptoms of RBD. [72] The authors concluded any improvement in sleep parameters was due to melatonin administration alone in this trial.

Discussion

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This review has shown evidence that melatonin has a role in the treatment of some primary sleep disorders, namely primary insomnia, DSPS, non-24 hour sleep-wake disorder in people who are blind, and RBD. Melatonin facilitates achieving better sleep for these patients by reducing the sleep-onset latency [73] or by regulating sleep-wake times to coincide with the natural circulatory cycle, as well as reducing sleep episodes without muscle atonia. [50] The mechanism by which the occurrence of reducing sleep episodes without muscle atonia in RBD is still unknown and requires further study.

The search strategy used in this review was thorough and the inclusion criteria were broad so all relevant publications from a wide variety of sources from 1950 to 2014 were included. There is unpublished research and commercially sponsored work in the area of sleep disorders, but the data were not included in this review due to the fact that unpublished research has not been subject to peer review. Futhermore, commercially sponsored/sensitive work can potentially be biased and/or contain inaccurate data. Kuriyama et al [74] reviewed published and unpublished data from randomised placebo-controlled trials performing an analysis on the efficacy of ramelteon, a selective melatonin receptor agonist used in the treatment of insomnia. Ramelteon was effective in improving some sleep parameters with insomnia, was not included in the meta-analysis as we focused on exogenous melatonin only. After we had concluded our analysis, Lockley et al [75] published the effectiveness of once-daily tasimelteon, which is a new dual-melatonin receptor agonist in non-24 h sleep/wake disorder in blind people. Tasimelteon was found to be effective in entraining totally blind people, but continued treatment was necessary to maintain the improvements. Again, our focus was on melatonin per se. Brzezinski et al [98] conducted a similar meta-analysis of randomised, placebo-controlled trials of

melatonin in healthy normal volunteers, individuals with insomnia, Alzheimer's disease patients, and individuals with schizophrenia. Although our analysis focused on individuals with established primary sleep disorders, Brzezinski's findings that melatonin decreased sleep onset latency, reinforce our conclusions. Brzezinski also reported similar findings to the publications we reviewed noting melatonin increased sleep efficiency and total sleep duration. [76]

The most relevant databases for this topic were chosen; MEDLINE, EMBASE, and SCOPUS cover a wide range of medical topics from across Europe and internationally and provide studies performed recently. PsycINFO is a comparatively smaller database, but indexes more than journal articles alone; it is also useful for social aspects of medicine. [35] Papers which were included for analysis were reviewed by two authors independently using defined inclusion criteria and then discussed to ensure they were relevant and appropriate. All studies used a variety of sleep measures to assess the effect of melatonin on sleep which provides a broad set of variables, thus impacting on the reliability of results. The symmetrical funnel plots for primary insomnia and blindness demonstrated the negligible publication bias present in this meta-analysis. This use of funnel plots was important as it quantified and evaluated publication bias rather than it being discussed in a superficial and abbreviated manner. Publication bias cannot be excluded through the use of a funnel plot alone, since "…asymmetry should be used when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry." [77] However, we used this tool to alert us to any problems which needed to be considered in the meta-analysis.

There were some potential limitations to the review; only published study data were included which may increase susceptibility to publication bias. It was particularly evident in the funnel plot for studies investigating DSPS (Fig.3), whereby all trials were distributed around the line of no effect; it is unlikely that studies with negative or findings of no effect would be ultimately published. Unfortunately, this is a common theme in scientific and medical publications. Funnel plots give an idea of whether the study results are scattered symmetrically around a central effect of melatonin on primary sleep disorders, however asymmetry may also be due to heterogeneity between the studies. [78] We focused on primary sleep disorders as previous meta-analyses have been conducted on secondary sleep disorders and shift-work diagnosis specifically. [79]

Some RCTs included in our meta-analysis had only a small number of participants (Table 1), which may not be representative of the large population afflicted by these sleep disorders. [80] Furthermore, not all studies included in the search were eligible for meta-analysis, as they differed with respect to sleep outcomes measured (i.e., some studies assessed the role of melatonin on sleep parameters other than sleep onset latency). Nevertheless, the findings from the trials included were still convincing and highlight the potential for further large-scale studies in the future.

This review has focused on the effects of melatonin on adult patients with much of the insomnia work carried out in those aged 55-80 years, as sleep disorders have increased prevalence in this age group. Studies have shown melatonin can lack effectiveness depending on the circumstances relating to when it is taken, dose, if it a quick or slow release formula, and on some clinical disorders. [81] Further investigation needs to be done to assess its effectiveness at varying times, varying dose, and comparing variable ways of dose intake. However, further research may

be hindered by the intellectual property issues around the use of melatonin and lack of financial incentives that may decrease the motivation to undertake such trials. Funding agencies are more likely to support research on novel medications, which leads to new treatments and increased revenue for pharmaceutical companies, than to supply funding for a supplement (melatonin) that has been easily purchased over the counter since the 1990's in some countries. Since studies are continuously being developed and deployed a search of the International Standard Randomised Controlled Trials Number (ISRCTN) [82] registry yielded few current studies focusing on the benefits of melatonin on participants who have sepsis or cancer and on asphyctic newborns, but none focusing on primary sleep disorders assessed in this review.

Numerous studies have also highlighted the use of melatonin in paediatric sleep-wake cycle disorders and AD's, [83] however there have been no RCTs or long term studies showing evidence for its therapeutic use in this age group.

Little evidence is available regarding the potential adverse effects of long-term melatonin use as it may take years for the toxicities to develop. [84] Wade et al [48] preformed a trial over six months of daily melatonin use and demonstrated no adverse effects or rebound withdrawal symptoms. Two studies [62, 85] investigated the treatment of primary insomnia of older people (aged ≥55) with melatonin (2mg 1-2 hours before bedtime orally) and concluded long-term use of melatonin (for 13-24 weeks) is well-tolerated, safe, and effective. Zhang et al. also reported that exogenous melatonin improves sleep quality in elderly individuals with underlying neurodegenerative disorders. [86] However, there have been concerns regarding chronic use of melatonin; in large doses it can interact with other medications and also suppress reproductive hormones over long periods of time. [87] Side-effects

potentially include headaches, dizziness, vomiting, and nausea. [78] Since melatonin physiology varies between individuals, it is important to consider the optimum dose required when prescribing the hormone exogenously. Buscemi et al. reported that melatonin is not effective in treating secondary sleep disorders or sleep disorders that arise from sleep restriction (e.g., jet lag, shift-work), [4] but the results of their review may be partly attributable to trial limitations similar to those discussed in the current paper.

In conclusion, this review has found evidence from a small number of trials for melatonin in treating primary insomnia, DSPS, and Non 24-hour sleep wake syndrome in people who are blind. Meta-analyses of the data emphasised in particular the improvement of sleep onset latency with melatonin in these patients. This result has been reproduced in the meta-analysis by Ferracioli-Oda, et al. [9] Based on the current inclusion of melatonin in the management of RBD, it is hoped in future there will be an increase in robust evidence for its widespread use. For such a commonly used medication, there are very few trials which have been performed sufficiently rigorously to examine the long-term efficacy of exogenous melatonin or any long-term side-effects. Clinicians should be alert to these limitations but also aware of the important role exogenously administered melatonin has in the sleep medicine armamentarium.

Practice Points

1. Exogenously administered melatonin has been shown to improve sleep onset latency in primary insomnia, DSPS, and to normalise free-running rhythms in people who are blind.

2. Melatonin may play a role in the treatment of RBD.

3. There is currently no evidence of efficacy of melatonin for treating arousal disorders in adults.

4. There is currently no trial evidence for the use of melatonin in secondary insomnia; since this is no longer a diagnosable DSM-V disorder there will probably not be any future studies on secondary insomnia [88].

Research Agenda

1. There is an absolute lack of well-structured clinical trials focusing on the utility and efficacy of melatonin in the treatment of RBD, arousal disorders and adult secondary insomnia.

2. The efficacy of different formulations of melatonin and timing of administration in the treatment of various sleep disorders needs to be ascertained in RCTs.

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Fig.1 Consort diagram of Study inclusion

EMBASE
(n=3696)

MEDLINE
(n=790)

PsycINFO
(n=496)

SCOPUS
(n=48)

Titles and Abstracts Identified and Screened

n=5030

Records excluded (Irrelevant on initial scanning)
(n=4671)

Abstracts retrieved and assessed for eligibility
(n=311)

Excluded (n=285)

Design not Relevant (n=102)

Duplicates (n=183)

Publications handpicked (screening reference list)   (n= 2)

15 Articles excluded for the following reasons:

Participants unsuitable   (n= 5)[26-30]

Insufficient data for analysis (n= 2)[31,32]

Inappropriate method and data collection (n= 4)[33-36]

No clear comparison group (n= 4)[37-40]

Full publications chosen for assessment (n=28)

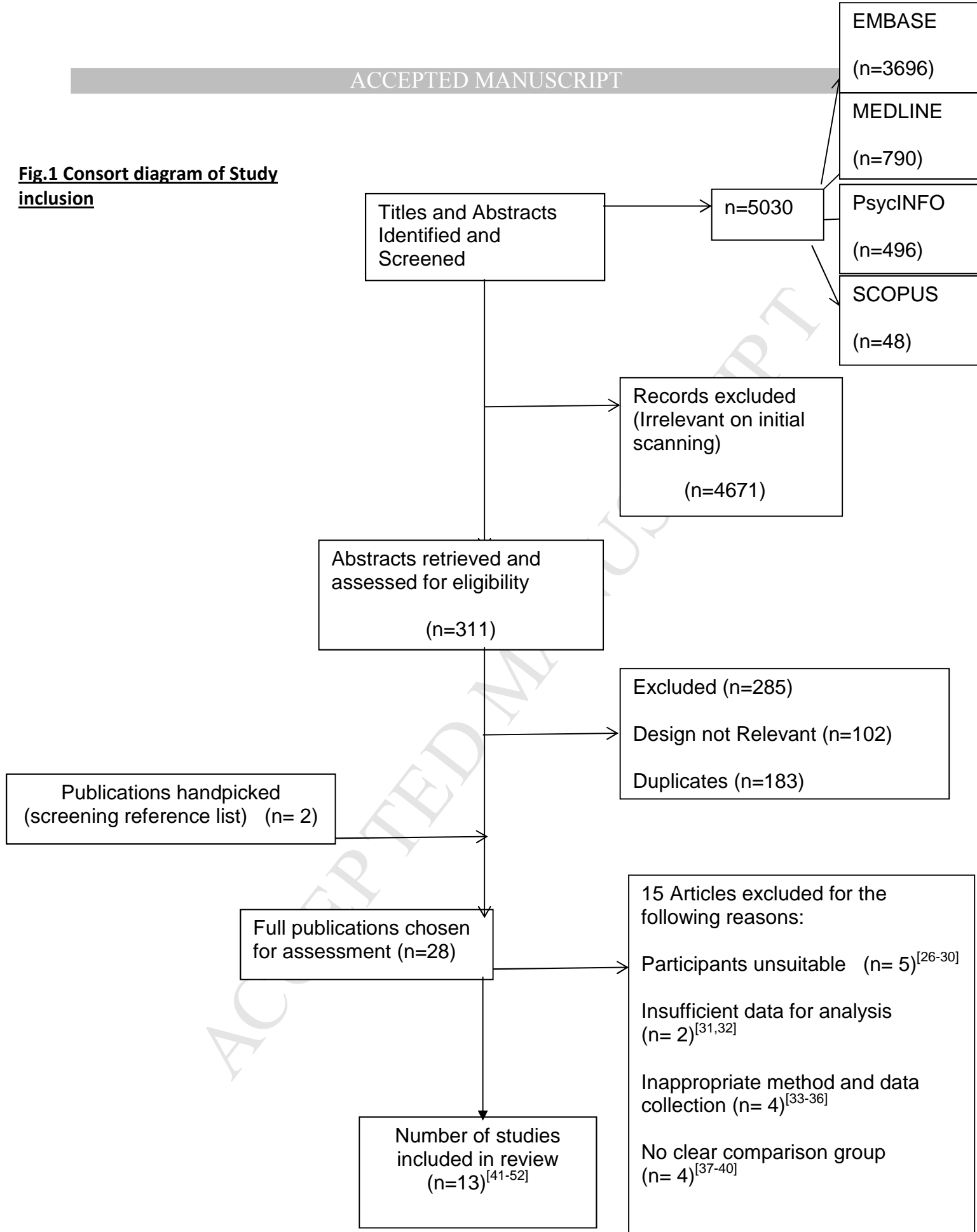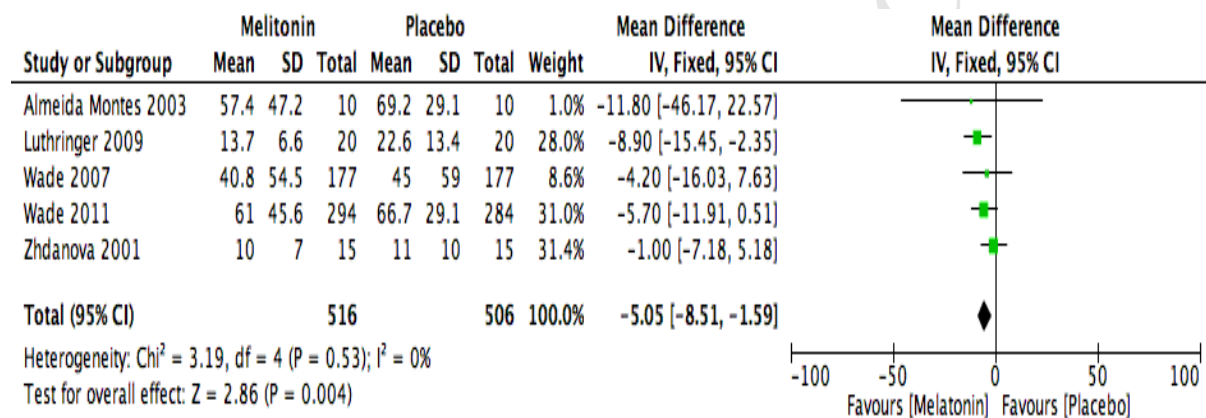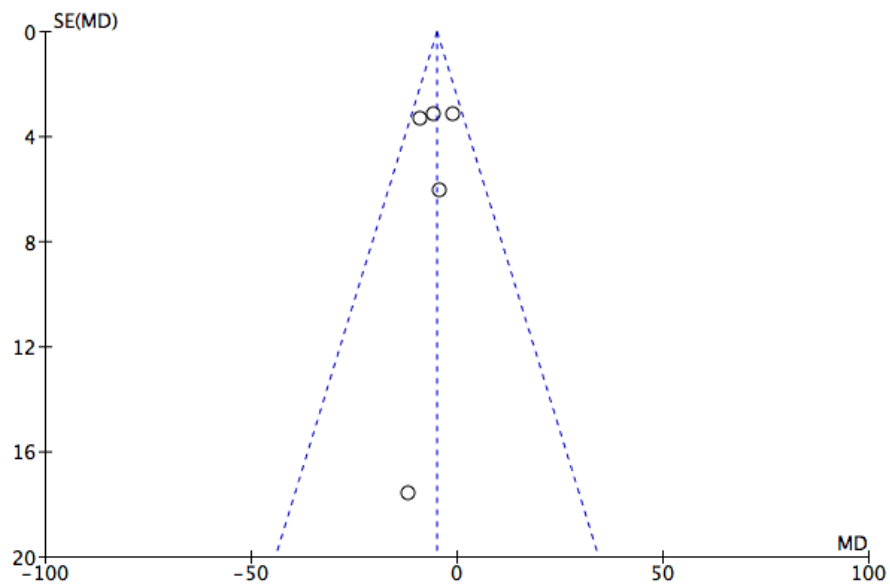Number of studies included in review (n=13)[41-52]

Fig.2: Effect of Melatonin on Sleep Latency in Primary Insomnia:

(A) Conventional meta -analysis with fixed 95% confidence intervals using Cochrane RevMan Software. Squares indicate mean difference between melatonin and placebo on sleep onset latency in patients with primary insomnia. Horizontal lines indicate 95% confidence intervals for the mean difference in effect. Diamond represents pooled mean effect with 95% confidence intervals in favour of melatonin improving sleep onset latency. All mean and standard deviation (SD) values in minutes. (B) Symmetrical funnel plot indicated minimal publication bias. SE(MD): Standard error of the mean difference

(A)

Study or Subgroup	Melitonin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Almeida Montes 2003	57.4	47.2	10	69.2	29.1	10	1.0%	-11.80 [-46.17, 22.57]
Luthringer 2009	13.7	6.6	20	22.6	13.4	20	28.0%	-8.90 [-15.45, -2.35]
Wade 2007	40.8	54.5	177	45	59	177	8.6%	-4.20 [-16.03, 7.63]
Wade 2011	61	45.6	294	66.7	29.1	284	31.0%	-5.70 [-11.91, 0.51]
Zhdanova 2001	10	7	15	11	10	15	31.4%	-1.00 [-7.18, 5.18]
Total (95% CI)			516			506	100.0%	-5.05 [-8.51, -1.59]

Heterogeneity: Chi² = 3.19, df = 4 (P = 0.53); I² = 0%
Test for overall effect: Z = 2.86 (P = 0.004)

Mean Difference IV, Fixed, 95% CI

-100   -50   0   50   100
Favours [Melatonin]   Favours [Placebo]

(B)

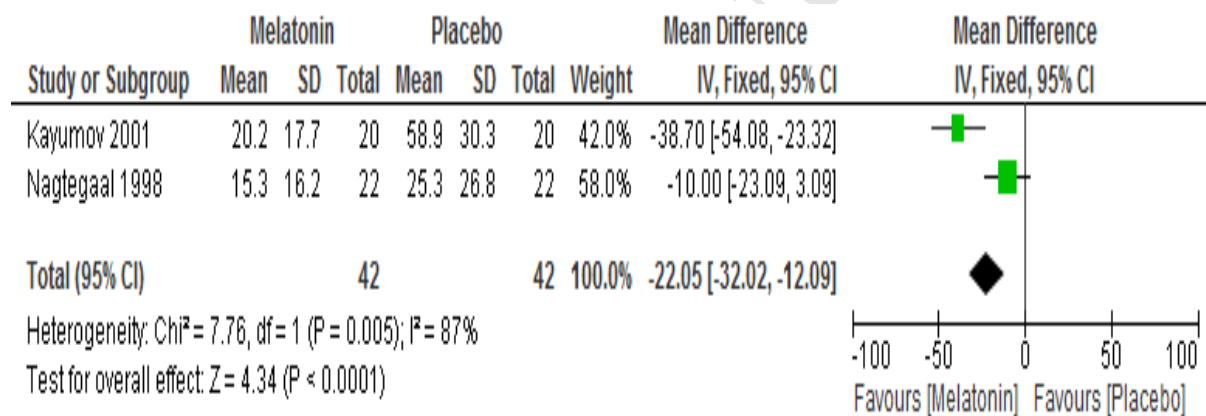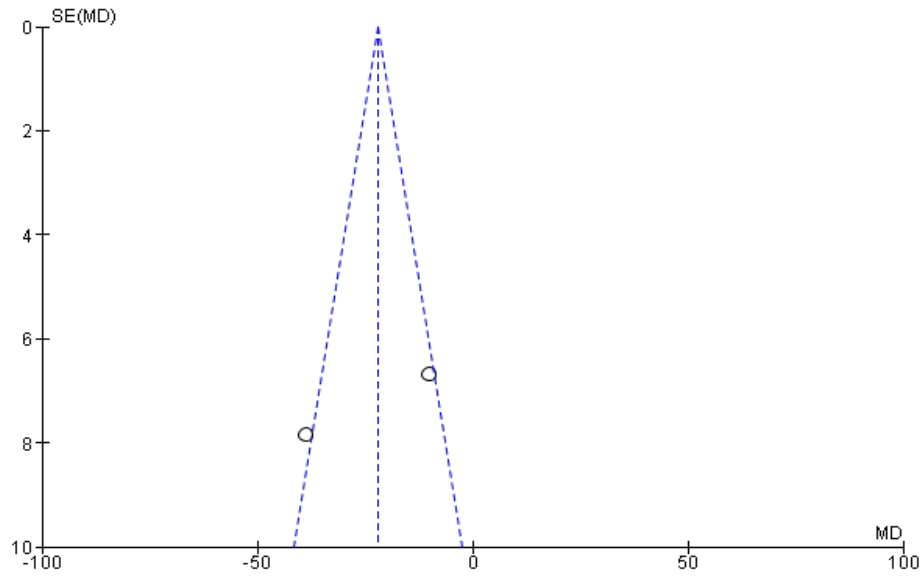## Fig.3: Effect of Melatonin on Sleep Latency in DSPS

(A) Conventional meta -analysis with fixed 95% confidence intervals using Cochrane RevMan Software. Squares indicate mean difference between melatonin and placebo on sleep onset latency in patients with DSPS. Horizontal lines indicate 95% confidence intervals for the mean difference in effect. Diamond represents pooled mean effect with 95% confidence intervals in favour of melatonin improving sleep onset latency. All mean and SD values in minutes. (B) Slight asymmetry of funnel plot indicated potential for publication bias. SE(MD): Standard error of the mean difference

(A)

Study or Subgroup	Melatonin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Kayumov 2001	20.2	17.7	20	58.9	30.3	20	42.0%	-38.70 [-54.08, -23.32]
Nagtegaal 1998	15.3	16.2	22	25.3	26.8	22	58.0%	-10.00 [-23.09, 3.09]
Total (95% CI)			42			42	100.0%	-22.05 [-32.02, -12.09]

Heterogeneity: Chi² = 7.76, df = 1 (P = 0.005); I² = 87%
Test for overall effect: Z = 4.34 (P < 0.0001)

(B)

Fig.4: Effect of Melatonin on Sleep Latency in Blind Patients

(A) Conventional meta -analysis with fixed 95% confidence intervals using Cochrane RevMan Software. Squares indicate mean difference between melatonin and placebo on sleep onset latency in patients with sleep wake disorder in association with blindness. Horizontal lines indicate 95% confidence intervals for the mean difference in effect. Diamond represents pooled mean effect with 95% confidence intervals in favour of melatonin improving sleep onset latency. All mean and SD values in minutes. (B) Symmetrical funnel plot indicated minimal publication bias. SE(MD): Standard error of the mean difference
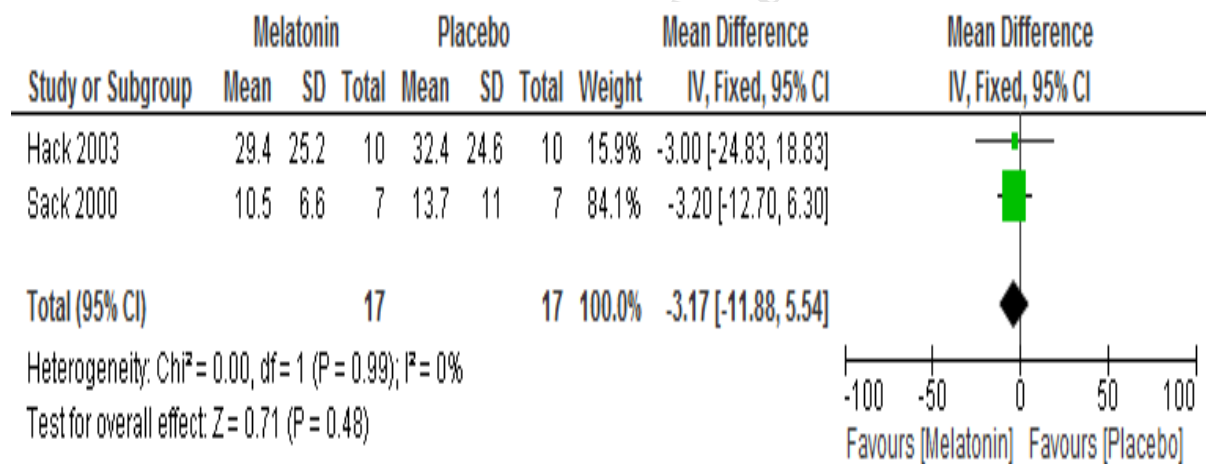
(A)

Study or Subgroup	Melatonin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Hack 2003	29.4	25.2	10	32.4	24.6	10	15.9%	-3.00 [-24.83, 18.83]
Sack 2000	10.5	6.6	7	13.7	11	7	84.1%	-3.20 [-12.70, 6.30]
Total (95% CI)			17			17	100.0%	-3.17 [-11.88, 5.54]

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.71 (P = 0.48)

(B)