Adverse events associated with melatonin for the treatment of primary or secondary sleep disorders: a review

Running heading: Adverse events with melatonin for the treatment of sleep disorders

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Abstract

Objectives: To assess the evidence for adverse events (AEs) associated with short-term and longer-term melatonin treatment for sleep disorders.

Background: Melatonin is widely available either on prescription for the treatment of sleep disorders or as an over-the-counter dietary supplement. Melatonin has also recently been licensed in the UK for the short-term treatment of jet-lag. Little is known about the potential for AEs, in particular AEs resulting from long-term use. Particular concern has been raised over the possible risks of exposure in certain populations including pre-adolescent children and patients with epilepsy or asthma.

Methods: A literature search of the PubMed/Medline database and Google Scholar was conducted to identify randomised, placebo-controlled trials (RCTs) of exogenous melatonin administered for primary or secondary sleep disorders. Studies were included if they reported on both the types and frequencies of AEs. Studies of pre-term infants, studies of less than one week in duration or involving single doses of melatonin and studies in languages other than English were excluded. Findings from open-label studies that raised particular concerns relating to AE reports in patients were also examined. Studies were assessed for quality of reporting against the Consolidated Standards of Reporting Trials (CONSORT) checklist and for risk of bias against the Cochrane Collaboration risk of bias criteria.

Results: Thirty-seven RCTs met criteria for inclusion. Daily melatonin doses were from 0.15 to 12 mg/day. Subjects were monitored for up to 29 weeks, but most studies were of much shorter duration (four weeks or less). The most frequently reported AEs were daytime sleepiness (1.66%), headache (0.74%), other sleep-related AEs (0.74%), dizziness (0.74%) and hypothermia (0.62%).. Very few AEs that were considered to be serious or of clinical significance were reported. These included agitation, fatigue, mood swings, nightmares, skin irritation and palpitations. The large majority of AEs either resolved spontaneously within a few days with no adjustment in melatonin, or immediately upon withdrawal of treatment. Melatonin was generally regarded as safe and well-tolerated. Many studies predated publication of the CONSORT checklist and consequently did not conform closely to the guidelines. Similarly, only eight studies were judged 'good' overall with respect to the Cochrane risk of bias criteria. Of the remaining papers 16 were considered 'fair' and 13 'poor' but publication of almost half of the papers preceded that of the earliest version of the guidelines.

Conclusion: Few, generally mild to moderate, AEs were associated with exogenous melatonin. No AEs that were life threatening or of major clinical significance were identified. The scarcity of evidence from long-term RCTs, however, limits the conclusions regarding the safety of continuous melatonin therapy over extended periods. There are insufficient robust data to allow a meaningful appraisal of concerns that melatonin may result in more clinically-significant adverse effects in potentially at-risk populations, for example disruption of circadian patterns and

development in pre-term babies and neonates exposed through their mothers. Future studies should be designed to comply with appropriate quality standards for RCTs, which most past studies have not.

Compliance with ethical standards

Conflicts of interest: Frank MC Besag, Michael J Vasey, Kim SJ Lao and Ian CK Wong declare that they have no conflict of interest.

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Key points

- Adverse events reported in clinical trials of melatonin for primary or secondary sleep disorders were generally infrequent, mild or moderate in severity, and were either self-limiting or resolved quickly on withdrawal of treatment.
- The possibility that more clinically-significant adverse effects might emerge with long-term treatment cannot be discounted, but there is no current evidence to suggest this.
- Many RCTs do not comply with best practice for reporting methodology and findings.

1. Introduction

Melatonin is an indolamine hormone, secreted primarily by the pineal gland [1]. In humans, melatonin mediates diverse physiological processes including the regulation of circadian rhythms [2, 3] and immune response [4-6] and disease-prevention [7-9] as well as associated ancillary functions including anti-inflammatory [10, 11] and oncostatic effects [12], largely as a result of its potent anti-oxidant potential [13-18]. These effects have been extensively documented elsewhere. There is evidence that melatonin also plays a role in mammalian sexual maturation and reproductive cycles [19, 20], although its reproductive effect in humans has yet to be fully elucidated [14, 21]. Melatonin is produced under low-light conditions in response to cues imparted by the suprachiasmatic nucleus [1] and is principally recognised as the regulator of sleep-wake cycles [22, 23]. It possesses both hypnotic (sleep-inducing) [24-26] and chronobiotic effects [22, 27, 28], thereby regulating sleep onset and circadian and seasonal biological cycles [29]. Disruption of melatonin patterns, either as a result of lifestyle factors, pineal damage or due to increasing age, is implicated in the onset of both transitory and chronic disorders of sleep.

Exogenous melatonin has been used for over two decades in the treatment of sleep disorders, including jet-lag and shift-work syndrome, primary insomnia, delayed sleep phase syndrome (DSPS) and non-24-hour sleep-wake disorder [30, 31]. Until recently, the treatment of age-related insomnia was the only licensed indication in any major market. In the United States, melatonin is classified as a dietary supplement, not a drug, and as such is regulated by the Food and Drug Administration (FDA) in accordance with the Dietary Supplement Health and Education Act of 1994 [32]. In the European Union (EU), regulation of melatonin varies between member states. In the UK [33] and Denmark [34], among other current EU countries, melatonin is a prescription-only drug and is not available as an over-the-counter (OTC) product. This regulatory approach has also been adopted in Australia, Japan, Canada [35] and New Zealand [36]. In France OTC supplements are available containing up to 2 mg of melatonin [37]. In Italy and Spain, the maximum melatonin content is 1 mg [38]. Germany and Belgium limit melatonin content in OTC products to 0.3 mg [38]. With regard to prescription products, a sustained-release preparation, Circadin (2 mg), was licensed across the EU by the European Medicines Agency (EMA) in June 2007 solely for short-term (up to 13 weeks) treatment of primary insomnia in patients ≥ 55 years [39]. In addition, an immediate-release preparation, Bio-Melatonin (3mg), is licensed in some EU countries, but not in the UK [33]. More recently (September 2018) the EMA licensed a novel melatonin product, Slentyo, for insomnia in children and adolescents (2 - 18 years) with autism spectrum disorder (ASD) or Smith-Magenis syndrome [40]. This product has not been licensed in the UK and is the only case of which we are aware of a licensed melatonin product for this age group. Melatonin is, however, increasingly commonly used off-label in the treatment of children and adolescents with sleep disorders secondary to a broader range of neurological or behavioural conditions, for example patients with attention deficit hyperactivity disorder (ADHD) [41]. In addition, in April 2019, a 3 mg immediate-release formulation was approved in the UK for the short-term (up to five days) treatment of jet-lag in adults [42, 43], the first licensed indication for a condition other than chronic sleep disorders.

While safety and tolerability are considered to be good, with a favourable adverse event (AE) profile compared with alternative hypnotic agents [31, 44], the scarcity of long-term RCTs, and specifically those with safety as a primary outcome measure, has led to recommendations that melatonin therapy be approached cautiously [45]. In particular, the as-yet undetermined effects of prolonged exposure to supraphysiological levels on sexual maturation, fetal development and neonatal development, has prompted some researchers to advocate a conservative policy when treating pre-pubescent children and pregnant or breast-feeding women [44-47]. The significance of melatonin in neonatal development has yet to be clarified, although the greater number, and wider distribution, of melatonin receptors in infants indicates a potentially pivotal role during the early stages of life [48]. The known actions of the hormone may, in fact, offer potential beneficial treatments in this population [49]. Theoretical risks associated with

growth, nocturnal asthma and seizures as a result of the broad range of observed interactions involving melatonin have also been discussed [50].

Melatonin receptors, although concentrated in the suprachiasmatic nucleus and pars tuberalis, have a wide anatomical distribution [30] and melatonin itself is detected at various levels throughout the human body [50, 51]: melatonin can be absorbed by all body tissues and the majority of its documented effects are not mediated by receptor agonism [52]. Accordingly, a range of potential therapeutic and/or adverse side effects might be expected when exogenous melatonin is administered [53].

In addition to its licensed and off-label prescription for sleep disorders and jet-lag, melatonin has been proposed and/or utilised in the ancillary treatment of a number of chronic conditions including cancer [12, 54-56], neurodegenerative diseases [57-62], oxidative stress [63] and autoimmune disorders [5, 64-66], although there is some inconsistencies in the findings from these studies. It is also widely used as a supplement for general health. Some of the earliest studies of therapeutic melatonin were conducted in subjects with jet-lag [67] for which it is widely taken, despite regulatory approval only recently having been granted in the UK for this indication (see above). A notable recent review by Foley and Steel [68] summarised AE findings from controlled studies of melatonin for all indications. However, a few of the more prominent recent studies of melatonin for sleep disorders in paediatric samples, including the MENDS study in children with neurodevelopmental disorders by Appleton et al. [50] and that by Gringras et al. in children with ASD [69], were omitted from this analysis. A number of other recent reviews have focused exclusively on studies of the efficacy and safety of melatonin in children and adolescents, a population considered potentially to be at elevated risk of adverse reactions [47, 70-74]. The conclusions from these reviews will be summarised briefly in the discussion.

In this review, the quality of available data regarding treatment-emergent AEs associated with melatonin treatment for primary and secondary sleep disorders from placebo-controlled studies is investigated. Open-label studies are also reviewed for signs of possible longer-term treatment-emergent AEs. In addition, findings from studies which have raised concern for the short-term and/or long-term safety of melatonin administration in specific populations are summarised.

2. Methods

2.1 Search

The PubMed and Google Scholar databases were searched for studies of exogenous melatonin published as of the beginning of April 2019. The search terms were: “melatonin AND (exogenous OR oral) AND (‘adverse effects’ OR ‘adverse events’ OR ‘side effects’ OR safety OR tolerability) AND (sleep OR insomnia OR ‘delayed sleep phase disorder’ OR DSPD OR ‘delayed sleep phase syndrome’ OR DSPS OR ‘delayed sleep wake phase disorder’ OR DSWPD)”. Duplicate studies were removed and the remaining studies screened to determine relevance. The reference lists of retrieved studies were also searched to identify additional papers.

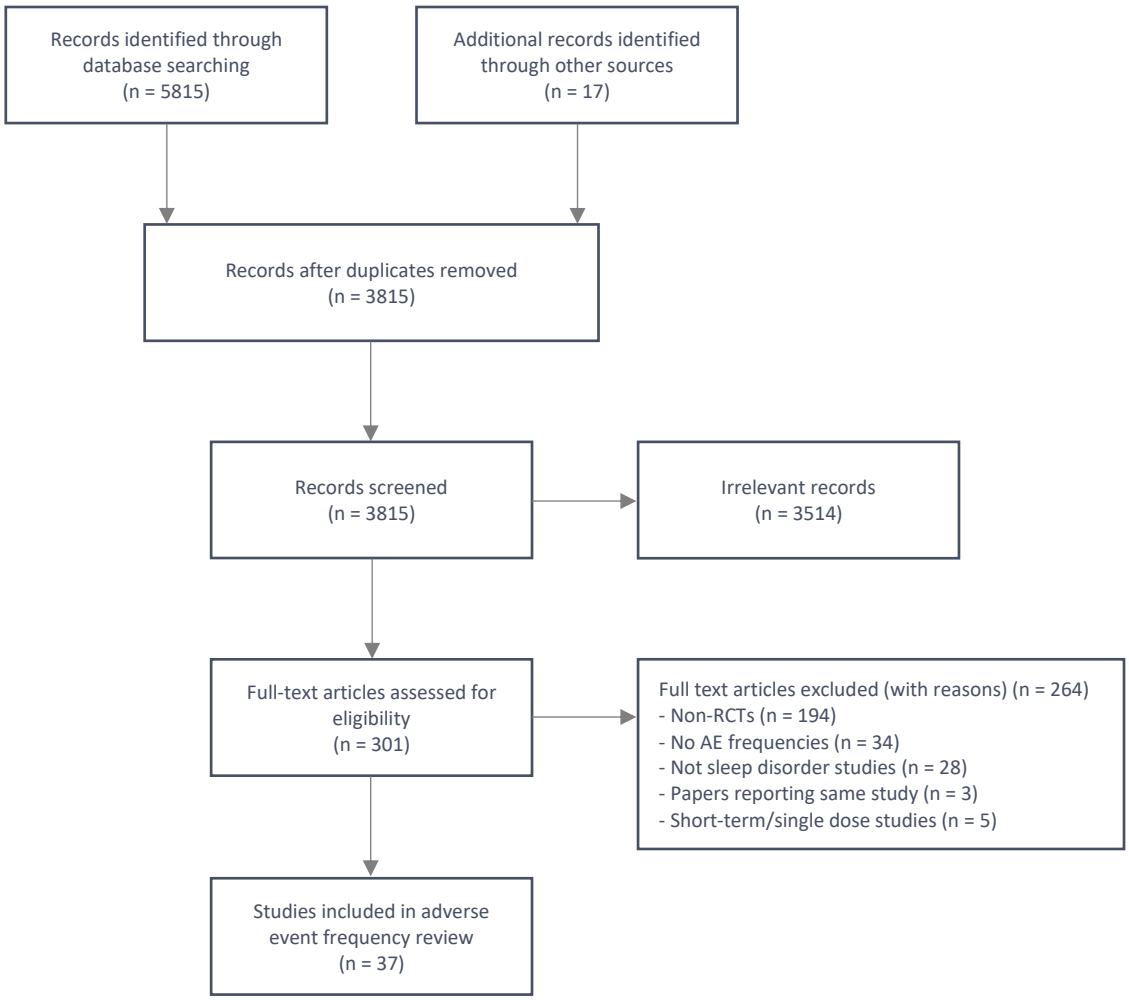

Figure 1 - Search flow diagram

2.2 Inclusion criteria

1. Randomised, placebo-controlled studies of melatonin given for the treatment of primary or secondary sleep disorders, or with sleep efficacy as a primary or secondary outcome measure.
2. Studies reporting the frequencies of treatment-emergent AEs where symptoms were specified, or studies reporting unambiguously that no AEs were identified

2.3 Exclusion criteria

1. Open-label or single case studies (these are considered separately in the discussion)
2. Studies not reporting AE frequencies
3. Studies in pre-term infants
4. Single dose, or very short-term (< 1 week) studies
5. Studies in languages other than English
6. Animal studies

3. Results

3.1 Search results

The search flow diagram for the review is shown in Figure 1. Thirty-seven randomised, placebo-controlled studies met the inclusion criteria. The studies varied greatly with regard to number of subjects, dosage regimes, study duration, subject age and primary medical conditions. The total number of subjects across all studies who received at least one dose of melatonin was 1625 (mean per study: 44; range across studies: 5 - 534). Melatonin doses ranged from 0.15 mg/day to 12 mg/day. Study duration ranged from one to 29 weeks, with the majority lasting four weeks or less. Only three studies were longer than 12 weeks. Subject ages were between one and 93 years. Reported primary or co-morbid medical conditions, other than primary sleep disorders, included: epilepsy (8 studies), ASD (6), ADHD (4), cerebral palsy (3), diabetes (3), hypertension (3), major depressive disorder (2), asthma (2), Parkinson disease (2), Alzheimer disease (1), Rett syndrome (1), chronic obstructive pulmonary disease (1), ischaemic heart disease (1), tuberous sclerosis (1), cancer (1), spondyloarthrosis (1), atopic dermatitis (1), blindness (1) and fragile X syndrome (1). Several studies included patient samples in which more than one condition was present. Ten studies were in subjects with primary sleep disorders. The characteristics of the included studies are summarised in Supplementary Tables 1 - 3.

3.2 Quality of reporting and risk of bias

Studies were assessed for quality of reporting and risk of bias according to criteria specified by the Consolidated Standards for Reporting Trials (CONSORT) statement guidelines and the Cochrane Collaboration risk of bias tool respectively. The CONSORT checklist was introduced in 2010 and many of the studies were published before the guidelines were available. Consequently these studies often did not fulfil the CONSORT criteria well. In particular, reporting of all aspects of randomisation (method, type, implementation and person responsible) was poor, as were indications of the generalisability of results, trial registration, availability of full trial protocol and source of funding. Many of the studies also failed to include details of sample size calculations or a full discussion of trial limitations. Full details are in Supplementary Table 4

Risk of bias was considered with reference to the seven-item Cochrane Collaboration risk of bias criteria. Few studies achieved an overall rating of ‘good’ (n = 8), with the majority considered to be either fair (n = 16) or poor (n = 13). The studies which were judged "poor" frequently failed to report complete outcome data. One study also failed to report adequately on blinding with respect to both participants and outcome assessments. Almost half the studies (18/37) were published prior to the release of the earliest version of the criteria in 2008. Only one of these studies was judged ‘good’ overall [75]. Full details are in Supplementary Table 5.

3.3 RCTs

The frequency of AEs across studies was low, with the majority considered to be mild in severity and not significantly more frequent than for placebo. The majority of these were said to have resolved within a few days without an adjustment in dose, or immediately on withdrawal if melatonin was discontinued. Sixteen studies (42%) reported no AEs in any patients. The most common AEs by proportion of affected patients (adjusted for the frequency in placebo groups) were daytime sleepiness (1.66%), headache (0.74%), other sleep-related AEs (0.74%), dizziness (0.74%) and hypothermia (0.62%). AE rates were not obviously correlated with either dose or formulation (immediate/fast-release or controlled/prolonged-release). None of the included studies reported any statistically significant difference in the frequencies of AEs between melatonin and placebo groups. It should be pointed out, however, that in the majority no statistical analysis of AEs was performed and only the numerical frequencies of symptoms were given.

Serious AEs were very rarely reported and were, in most cases, either an exacerbation of a pre-existing condition, for example worsening migraine [76], characteristic of the study population, for example agitation and mood swings in patients with ADHD, ASD or other developmental or behavioural disorders [69], or more severe episodes of otherwise commonly reported AEs, for example fatigue, nightmares and skin irritation.

The AEs with the highest frequencies are listed in Table 1. Figures are corrected for the frequencies in patients in the corresponding placebo groups.

Table 1

Adverse event	No. studies	Melatonin subjects with AE (AE_{MLT})	Placebo subjects with AE (AE_{PLB})	Subjects with AE corrected for placebo (AE_{MLT} - AE_{PLB})	AE frequency (%) corrected for placebo
Daytime sleepiness[+]	9	50	23	27	1.66
Headache	15	44	32	12	0.74
Other sleep-related AEs[†]	6	21	9	12	0.74
Dizziness	4	14	2	12	0.74
Hypothermia[‡]	2	14	4	10	0.62
Decreased appetite	3	7	1	6	0.37
Restlessness	2	6	0	6	0.37
Rash*	4	15	9	6	0.37
Burping	1	5	0	5	0.31
Tearfulness	1	5	0	5	0.31
Fatigue	3	25	21	4	0.25
Seizures (not increased rate)	2	12	8	4	0.25
Insomnia[^]	4	7	4	3	0.18
Gastrointestinal illness/diarrhea	3	10	7	3	0.18
Muzziness/fuzzy feeling/hung-over	3	3	0	3	0.18
Hyperactivity	2	4	1	3	0.18
Enuresis	1	3	0	3	0.18

Number of studies reporting each AE with numerical and percentage frequencies for melatonin and placebo groups.

[+]Some of the studies specified "daytime sleepiness" and others simply stated "sleepiness" (or similar) but since it is unlikely that night-time sleepiness after the melatonin dose would have been listed as an AE, these have been categorised together as "daytime sleepiness".

[†] Including "red eyes", "vivid dreams" and nightmares; [‡] including "cold feelings"; * including skin irritation and pruritus; [^] including "poor sleep"

3.4 Open studies

Twenty-six open-label studies involving a total of 1,044 subjects monitored for up to six years were reviewed. Overall, the more common AEs were broadly similar in type to those observed in the RCTs summarised above, with headache (5.1%), fatigue (2.2%), gastrointestinal illness (1.7%), daytime sleepiness (1.3%), dizziness (1.2%) and enuresis (0.67%) among the most frequently recorded. In addition, ear, nose and throat conditions (5.9%), physical aches (4.6%) and respiratory tract infections (3.8%) were reported in relatively high percentages of patients.

Among other AEs not reported in the RCTs, change in skin pigmentation was noted in three studies [77-79], one of which involved a patient with hyperpigmented skin [77].

Serious AEs were rarely reported. An apparent worsening of seizures was recorded in a small number of patients in two studies [80, 81]. One of these also noted new onset of seizures in a single patient [81]. Only one long-term study reported abnormal pubertal timing in a single patient with severe brain damage [82]. Menorraghia was reported in two adolescent and one adult patient in a single study [78].

4. Discussion

4.1 General comment

The more commonly reported AEs in RCTs involving patients with sleep disorders reflect closely those reported in other clinical studies of melatonin. A recent review [68] summarised AEs recorded in controlled studies of melatonin for any indication and studies in healthy participants. Most AEs were considered minor, of limited duration and easily managed or self-limiting, and were most commonly related to fatigue, mood, or psychomotor or neurocognitive functions. A few studies, however, reported possible endocrine effects associated, for example, with reproductive parameters such as levels of prolactin [83, 84] or luteinising hormone [85], or acutely impaired insulin sensitivity and glucose metabolism [86-89]. Cardiovascular effects, including changes in blood pressure and heart rate, were also indicated in patients with pre-existing cardiovascular conditions who were taking antihypertensive medication (nifedipine), suggesting a possible drug-to-drug interaction [90, 91]. In several other studies in patients without cardiovascular conditions no evidence of of cardiovascular abnormalities with melatonin was found [88, 92-97]. In the two studies where cardiovascular effects were observed, it was not possible to determine conclusively whether they resulted from a direct effect of melatonin, or from interaction with cardiovascular medication [90, 91]. These categories of event were often correlated with dosage and timing of administration as well as co-medication with antihypertensive drugs in the case of cardiovascular effects. In general, the safety profile of melatonin was considered favourable. The findings of some of these studies, as well as reports of similar AEs in studies of patients with and without sleep disorders, are discussed in more detail in later sections.

In light of the recent authorisation in the UK of an immediate-release preparation of melatonin for the treatment of jet-leg, it is interesting to note that AEs reported in early field studies of short-term melatonin use for this indication were similar to those reported in the longer duration RCTs in patients with sleep disorders reviewed here [98]. More broadly, a recent review and meta-analysis of melatonin and the melatonin agonists ramelteon, agomelatine and tasimelteon for a range of primary health conditions, including sleep disorders, also found a similar range of symptoms reported [18].

4.1.1 Placebo-controlled studies

Descriptions of AEs reported in patients with sleep disorders were in broad agreement with those presented in previous surveys of melatonin safety [30, 44, 45, 99, 100]. The types and frequencies of AEs did not differ substantially between melatonin and placebo groups and there was little indication of more severe AEs in patients treated with the hormone. Neither the type, frequency or severity of symptoms were obviously correlated with either dose, formulation or duration of treatment. Two studies compared melatonin at different doses [75, 101]. Van Der Heijden et al. [75] found that AEs did not differ significantly between 3 mg and 6 mg daily doses (Fisher's exact test p = 1.00), while Van Geijlswijk et al. [101] found higher weight-adjusted doses (0.15 mg/kg and 0.1 mg/kg) were associated with a greater frequency of Aes than a lower dose (0.05 mg/kg). The difference in AE frequency between groups was expressed as a between-dose ratio (5:4:3 for high, medium and low doses, respectively) without any measure of significance reported. AE frequencies were considered to be low for all three doses. Daytime sleepiness

and other sleep-related AEs, including fatigue, were reported for both studies in which subjects were administered immediate/fast-release and those in which controlled/prolonged-release formulations were administered. In most studies patients were instructed to take the study medication at set times or at set intervals before habitual bedtimes (usually between 30 minutes and 2 hours) in order to ensure sleep onset at an appropriate time and to reduce the potential for residual morning effects. One study reporting daytime drowsiness in three patients administered controlled-release melatonin observed that the symptoms resolved when medication was taken at the recommended time (9 pm) [102]. The implication was that if the melatonin was given too late, this could result in daytime sleepiness because of a carry-over effect. The effects of daytime sleepiness may extend to impaired psychomotor function and increased reaction times, highlighting the importance of appropriate timing of doses [103-105]. However, next-day residual effects on vigilance and cognitive function following evening melatonin have not been reported frequently [44]. On the contrary, some studies have shown improvements in performance in morning cognitive tests and alertness compared with placebo [106, 107], likely reflecting improved sleep. Interactions between exogenous melatonin and other hypnotics may, however, be associated with a greater detrimental effect on psychomotor performance and memory [108]. Of the other common AEs, it is notable that the majority were only reported in single studies or a small number of studies. In some cases, AEs were characteristic of the underlying medical conditions of the subjects but were remarkable due to an apparent exacerbation in severity. In a notable early study, exogenous melatonin was said to be associated with worsening dysphoric symptoms and sleep disturbance in a small sample of patients with major depression or Huntington disease in a double-blind cross-over study by Carman et al. [109] but, the melatonin doses in this paper were extraordinarily high - 150 mg/day to 1600 mg/day. Although this study was identified as a double-blind crossover trial, and placebo was administered to all patients at some point in the study, we did not include it in our AE summary due to ambiguity regarding the trial methodology including the randomisation of subjects which made it difficult to ascertain whether it was a true placebo-controlled RCT. In addition, the doses were an order of magnitude higher than those generally used in clinical practice and in some cases were administered intravenously. This was the only study we were able to identify in which melatonin was associated with an increase in pre-existing dysphoric mood and depression. The study also reported auditory hallucinations, mutism and feelings of unreality, effects we were unable to find evidence for in other studies. Severe depression was reported *de novo* in one patient in a randomised, double-blind study of melatonin in healthy volunteers with no previous or current diagnosis of any psychiatric disorder, which also did not meet inclusion criteria for the main part of this review [110]. An RCT in elderly dementia patients found some evidence of low mood and withdrawn behaviour in individuals treated for circadian rhythm disturbances [111]. Patients treated with additional whole-day bright light exposure did not exhibit the same symptoms however. Other studies have found improvements [112, 113], or no change [102, 114] in mood and depressive symptoms in patients receiving melatonin. While worsening dysphoria and depression were identified uniquely in the Carman study, low mood, anxiety and tearfulness have been reported elsewhere [50, 69, 115, 116]. However, the frequency of these AEs was not very different from placebo, and samples included individuals with developmental, neurological and behavioural disabilities. In keeping with our findings, headache, dizziness, reduced appetite, tearfulness, rash and low mood are among the adverse reactions listed in the product characteristics for Circadin [39] and/or side effects listed in the guidance for melatonin provided by the BNF [42]. Of these, only headache is considered to be ‘common’ or ‘very common’. All were noted in at least one RCT involving patients with sleep disorders. Vomiting, diarrhea or constipation or other gastrointestinal complaints, anxiety, irritability, reduced alertness (concentration impaired), confusion (disorientation), abdominal pain, seizures and mild tremor (movement disorders) are also listed as potential adverse reactions. All are considered to be ‘uncommon’, ‘rare’ or ‘very rare’ [39, 42]. In the current survey, of these additional AEs, only confusion, diarrhea and abdominal pain were more frequent for melatonin than for placebo, with a very low number of individual reports for each AE. Vomiting was commonly reported but was more frequent overall in the placebo groups in the studies reviewed. Moreover, twenty-three out of twenty-five recorded occurrences in

subjects receiving melatonin were in studies involving patients between the ages of three and 17 years; vomiting is common in children with no other pathology. Other frequently reported AEs that were more common in patients administered placebo included increased excitability/activity, mood swings/labile mood and nausea.

Systematic reporting of AEs was highly variable. Studies were excluded if there was no mention of treatment-emergent AEs or if no frequencies for individual AEs were stated. There was considerable heterogeneity in the strategies used to collect AE data and the extent to which AEs were reported in the included studies. Some studies identified only the most frequent AEs or only AEs that resulted in a patient discontinuing melatonin. Only 13 RCTs included safety and/or tolerability as a stated primary or secondary outcome measure [50, 69, 75, 88, 101, 107, 113, 115-120] and very few reported AEs systematically or performed post-hoc analysis on AE data [75, 88, 118]. Fifteen studies specified the methodology used for collection of AE reports [50, 69, 75, 76, 88, 112, 113, 116-123]. These included weekly reviews during patient interviews with a focus on specific predefined AE types [50], patient-completed questionnaires with checklists of predefined AEs [117, 123, 124] and weekly telephone interviews [121, 122, 125] or unstructured in-person interviews with patients during clinical visits [88, 116, 120]. In two studies in paediatric patients, AEs were reported by the parents of subjects, either as part of regularly completed sleep diaries [119] or at interviews conducted three weeks after treatment was commenced [75]. In the remaining studies, no information regarding AE reporting strategies was stated and reliance on spontaneous patient self-reporting was assumed. Due to the mild nature of most of the AEs that emerged, the last approach may not have been adequate to reveal all occurrences of potential adverse effects. A number of confounding factors should also be considered. In the majority of studies, melatonin was administered for sleep disorders secondary to other medical, psychiatric or behavioural conditions, which may have been severe. In most of these studies melatonin was taken alongside existing medication for primary health complaints. Co-medications included antidepressants (including fluoxetine), lithium, anti-parkinsonian medication (levodopa, amantadine), antiepileptic drugs (including phenobarbital, carbamazepine, ethosuximide, sodium valproate, gabapentin, and felbamate), beta-blockers, and medications for Alzheimer disease, asthma (beclomethasone, salbutamol, methyldopa), and diabetes (including metformin and insulin). In many of these studies, however, no AEs were reported in any patients. One RCT in patients with major depression attributed many of the AEs to fluoxetine which was taken by all subjects [102]. This was the only study that specifically differentiated AEs that were likely to be attributable to co-medication. It should be noted that fluoxetine is a powerful enzyme inhibitor that raises the blood level of a number of other drugs. The effect of fluoxetine on endogenous melatonin levels is not clear. A study by Carvalho et al. [126] found evidence of elevated melatonin secretion in patients treated with fluoxetine, duloxetine or hypericum perforatum for eight weeks compared to those taking placebo. However, an earlier study by Childs et al. [127] reported significantly decreased melatonin levels in patients with seasonal affective disorder treated with fluoxetine over six weeks. Härtter et al. [128] reported on the effects of fluoxetine, fluvoxamine, paroxetine and citalopram on melatonin metabolism in vitro. While fluvoxamine exhibited a strong inhibitory effect (see below), of the other medications only paroxetine had a demonstrable suppressive influence on melatonin metabolism and only at supratherapeutic concentrations (20 microM). Notably, CYP1A2, the cytochrome primarily responsible for the hepatic metabolism of melatonin has been shown not to be affected by fluoxetine [129]. The risk of other drug interactions involving melatonin has yet to be quantified [130], although there is some evidence that CYP1A2 inhibitors, including fluvoxamine [131], caffeine [132] and oral contraceptives [133] may result in elevated serum levels of melatonin. In practice, few interactions have been reported [106, 134-136], and no evidence of interaction was reported in any of the RCTs we reviewed. The possibility that melatonin might increase the effects of other hypnotics has been suggested [108], and a possible pharmacokinetic interaction with the antidepressant citalopram in one patient resulting in severe sedation was reported [137]. Herxheimer and Petrie [67] raised concern over a possible interaction with vitamin K antagonists such as warfarin. As stated earlier, fluvoxamine [131, 138] and caffeine [132] have been

found to elevate endogenous melatonin levels. Conversely, the use of GABAergic antiepileptic drugs, including sodium valproate, may be associated with suppressed endogenous melatonin levels [139]. Benzodiazepines have also been shown to exert an inhibitory effect on nocturnal melatonin secretion [140]. The British National Formulary warns of a severe risk of interaction with fluvoxamine and a theoretical risk interactions with the antibiotics ciprofloxacin and rifampin, combined hormonal contraceptives, leflunomide, mexiletine, phenytoin, ritonavir and teriflunomide. The possibility of augmented effects when melatonin is taken with other central nervous system depressants is also indicated [141].

AEs observed in a number of studies were probably related to underlying medical conditions. Hyperactivity, increased excitability, mood swings and irritability/agitation were variously reported in samples including patients with attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD) or other behavioural or developmental disorders [50, 69, 75]. In most of these cases, however, there were no clear differences between rates in melatonin and placebo groups and the AEs were often more frequent in placebo-treated patients. In other cases, underlying medical conditions may have obscured any adverse effects of melatonin. A study involving patients with cancer [142] found no evidence of adverse effects, but the authors noted that the more frequent potential adverse effects such as headache, dizziness, nausea, and vomiting would have been difficult to attribute to melatonin due to their common occurrence in the study population.

Very few AEs considered severe or serious were reported in any study or population. In many cases, serious AEs either represented an increase in severity of pre-existing conditions or were symptoms associated with primary medical conditions. One study reported heart palpitations in a single patient with a pacemaker which led to withdrawal of the drug but was considered unrelated to melatonin [112]. The only exception was the study by Carman et al. [109], discussed earlier, in which very high melatonin doses were administered. In the literature more broadly, isolated studies have raised concerns about a number of more serious AEs, including increased seizure frequency or severity or new onset seizures [81], delayed puberty [143, 144], reproductive dysfunction [145, 146], insulin resistance [87, 89] and other endocrine effects [77, 84, 145, 147-157] and asthma symptoms [5, 158, 159]. The evidence for these effects is, in the majority of cases, based on findings from a single study or a very small number of studies and remains controversial. However, in the absence of substantial data from long-term RCTs, caution is routinely advised when melatonin is administered for extended periods and in certain populations. In section 4.2 we discuss these effects and the evidence for each of these potential AEs.

4.1.2 Open-label studies

Results from twenty-six open-label studies were broadly in agreement with those found in the RCTs. Among AEs not recorded in controlled studies, two studies found an increase in seizure activity in subjects treated with melatonin [80, 81], most notably a study by Sheldon [81] which also found *de novo* seizures in one patient. Other studies have reported no change in seizure frequency or severity [160-163], or improvements in some or all patients with pre-existing epilepsy [80, 164-166]. We return to this topic in the next section. Two studies noted a change in skin pigmentation in five patients, three adults with circadian rhythm disorders treated with 5 mg daily doses of melatonin [78] and two children with ADHD and chronic sleep onset insomnia treated with 3 - 6 mg [79]. One further study found a large daily dose (1 g) of melatonin lightened hyper-pigmented skin in one patient but had no lightening effect in four other patients with similar skin tone [77]. Reproductive and developmental AEs were rarely observed. Menorrhagia was reported in three patients aged 14, 17 and 42 years in a study in which patients were treated for between two and 12 months with 5 mg melatonin [78]. The authors suggested this reaction might have been the result of a decrease in plasma levels of luteinizing hormone and follicle stimulating hormone, an effect reported elsewhere in patients administered melatonin [77, 85, 153, 167, 168], although there no investigations were undertaken to confirm theses

suspicions. A study of long-term melatonin therapy in eight blind subjects reported a single case of delayed puberty in one fourteen-year-old boy with severe brain damage who had been receiving melatonin (0.5 mg - 1 mg/day) for six years [82]. The patient was described as having developed a 'eunuchoid body habitus, without any sign of continuing pubertal development' and normal prepubertal levels of gonadotrophic hormone. It is possible that delayed puberty in this patients might have been the result of brain damage rather than associated with the administration of melatonin. Reports of the effect of elevated melatonin on timing of puberty and hypothalamic-pituitary hormone levels found elsewhere in the literature are inconsistent [84, 143, 153, 169, 170] and are discussed further in a later section.

4.2 Potential serious adverse effects

4.2.1 Effect on seizures.

This topic has been reviewed by one of the authors elsewhere [171]. Low endogenous melatonin levels have been reported in some patients with epilepsy, and melatonin supplements have shown efficacy in improving sleep in these patients [26, 171], perhaps as a result of GABA receptor agonism [172]. Despite some concerns [81], there is no clear evidence of a proconvulsive effect. A double-blind crossover study of controlled-release melatonin in 16 paediatric patients, with an open-label clinical follow-up in a further 28 patients, all with chronic sleep-wake cycle disorders and severe neurological disabilities, and over half with epilepsy, reported that anticonvulsant medication had to be adjusted after initiation of melatonin therapy, though no significant exacerbation in seizure activity requiring discontinuation of melatonin occurred [163]. On the contrary, there is some evidence that melatonin exhibits a neuroprotective effect [173-175] that may lessen susceptibility to seizures [165, 176-179]. A recent Cochrane review, however, found that studies of the safety and anticonvulsant effect of melatonin in patients with epilepsy were of insufficient methodological quality to perform a meta-analysis, and no firm conclusions could be drawn regarding any association between supplemental melatonin and a reduction in seizure activity [180], a conclusion echoed by other authors [181, 182]. A review of the effect of melatonin on epileptic seizures by Jain and Besag [171] found no difference in seizure rate in two RCTs and a statistically significant reduction in one RCT. Peled et al. [165] observed a significant clinical improvement in seizure rate in 5/6 children with severe neurological deficit disorders, and a decrease in nocturnal epileptic activity in 2/3 children who underwent monitoring during treatment. Other studies have found that melatonin may reduce the severity of seizures in patients with treatment-resistant epilepsy, possibly as a secondary effect of improved sleep quality [164, 182]. We found no evidence of an increased risk of seizures in any of the subjects who participated in the RCTs included in this review.

4.2.2 Delayed puberty

Evidence indicating that endogenous melatonin levels in humans show a sharp decline just before the onset of puberty [169, 183-188] has raised some concern of a potential risk of delayed sexual maturity in pre-pubertal children taking melatonin over extended periods [50]. It is not yet firmly established whether the marked decrease in plasma melatonin at this juncture has a causal relationship with subsequent pubertal development, although the decline appears to precede pubertal onset. In addition, studies of precocious puberty have found lower melatonin secretion in affected individuals than in age-matched controls [143], although findings are inconsistent [189]. The hypothesis that melatonin may suppress puberty was first presented in an editorial by Kolata in 1984 [144] but remains controversial [189]. However, several studies have suggested a role of melatonin in human reproductive function [1, 190, 191] and an association between hypothalamic-pituitary-gonadal axis disorders and altered melatonin profiles [189]. Evidence from animal studies strongly supports a regulatory influence on reproductive cycles [192-194]. A possible explanatory mechanism for melatonin-mediated pubertal delay involving the suppressive influence of melatonin on the neuropeptide kisspeptin (which was discovered to have an activating effect on gonadotropin-releasing hormone

(GnRH) neurons) has been proposed [195], but the effects of short-term and long-term exposure differed considerably and no firm conclusions have emerged.

No clear evidence that exogenous melatonin interferes with normal pubertal development in humans was found in the studies in the current review, but the scarcity of long-term RCTs in children and adolescents implies that there is very limited data available. A long-term open-label study [196] of melatonin therapy in 51 children observed over a 3 year follow-up period after an initial short-term dose-finding study (Meldos) [101] found no significant differences in sexual development, weight, or height compared to age-matched and gender-matched controls. A further follow-up at between 9 and 12 years after the original study reported that 31.3% of 33 patients who responded self-identified as having experienced delayed puberty [197]. However, the uncertain reliability of patient self-report means these findings should be interpreted with caution. A small number of other long-term open studies in paediatric populations have monitored subjects for signs of precocious puberty but have found no evidence of an association with melatonin treatment [161, 198]. Carr and colleagues found onset of puberty to be age appropriate in all but five of 41 children with neurodevelopmental disabilities taking melatonin for sleep disorders for periods of up to 9.6 years. The five remaining children all displayed signs of precocious puberty prior to the start of melatonin therapy [161]. Sixteen of the RCTs we reviewed included subjects of pre-pubertal age. However, none was of a sufficient duration to detect anything but the most acute effects. A one-week dose-finding RCT by van Geijlswijk et al. [101] led into a long-term observational phase in which Tanner stages were assessed in comparison with healthy controls. As stated above, no significant differences were detected during the initial trial or follow-up period.

Several recent reviews of melatonin use in paediatric samples have been published [47, 70-74]. Notably, a review of the effects of melatonin on pubertal timing by Boafo et al. [47] reported the findings from the two follow-up studies from the Meldos trial and the Carr et al. study discussed above [161]. The authors concluded that to investigate the putative correlation between long-term exogenous melatonin in pre-adolescence fully, extended RCTs would be needed, but such studies would be ethically problematic.

The current absence of substantial confirmatory data on long-term safety in pre-pubertal children has led to a consensus that melatonin should not be recommended as a first-line treatment for chronic sleep disorders in this population. However, this recommendation appears to be based on lack of data rather than firm evidence for an effect of melatonin on puberty. A number of studies have investigated more specifically various endocrine interactions involving melatonin, including the effects of exogenous melatonin on reproductive hormones which may be of particular relevance to this question. Findings from these studies are summarised in the next section.

4.2.3 Other endocrine effects and reproductive dysfunction (including effects on luteinizing hormone, growth hormone, follicle stimulating hormone and prolactin)

It has been suggested that endogenous melatonin mediates a number of neuroendocrine actions [199-201], although the precise nature and extent of such effects are yet to be established and the evidence is inconsistent [28]. Indications that melatonin may have a role in the regulation of growth hormone (GH) led to a placebo-controlled study of the effects of oral melatonin on the GH profiles of thirty-two healthy male subjects [147]. Basal GH levels increased in response to melatonin administration as did GH responsiveness to GH-releasing hormone (GHRH) measured at 15 minute intervals after melatonin was taken. The observed stimulatory effect was weak, however. A GH response to melatonin was also shown in an RCT comparing single doses of 0.05 mg, 0.5 mg and 5 mg administered to eight healthy male volunteers [148]. Serum GH levels were found to be elevated in measurements taken up to 150 minutes after 0.5 mg and 5 mg doses compared to placebo. In contrast, an earlier open-label study [77] found evidence of an inhibitory effect of a 1 g daily dose of melatonin on GH secretion in some patients. The scarcity of data on the interaction between melatonin and GH, and the effect of exogenous melatonin on normal GH profiles, mean that any

possible consequences of long-term exposure to supranormal melatonin levels remain uncertain. However, the potential adverse consequences of elevated GH levels in children, including possible effects on longitudinal bone growth, have contributed to recommendations of a conservative approach to melatonin therapy in children and adolescents [48].

Evidence of a mediating role of melatonin in the regulation of plasma levels of other hormones has also been reported. A small number of studies have indicated an inhibitory effect on luteinizing hormone release in both males [77, 145, 149] and females [85, 150, 151]. A case study reported by Kocher et al. found levels of follicle stimulating hormone (FSH) showed a tendency to decrease after 10 months of treatment with controlled-release melatonin, although they remained within the normal range [145]. In addition, a number of studies have reported elevated prolactin levels in patients administered melatonin [84, 152-157]. In general these effects were reported to be modest, however, and other studies on the response of reproductive hormones to melatonin levels have reported contrary findings [84, 110, 120, 145, 202-205]. The long-term consequences of possible melatonin-induced dysregulation of hormonal balance has not been established. However, studies have found an apparent association between elevated melatonin plasma concentrations and decreased semen quality in healthy men [145, 146], and amenorrhea in women [190, 191]. As discussed earlier, the peak in endogenous melatonin levels seen just prior to the onset of puberty might suggest a correlation with gonadal development [30], and the effect of extended melatonin therapy on normal pubertal and endocrine development in children and adolescents remains unclear. It should also be noted that research on the contraceptive potential of melatonin in the 1990s found significant decreases in luteinizing hormone, progesterone and estradiol in women treated with oral melatonin when taken alone or in combination with progestin. While the doses of melatonin in this study were high (300 mg/day taken over four months), the disruption of ovarian cycles that were observed led the authors to propose that melatonin/progestin combinations may offer novel options for oral contraception [85].

4.2.4 Diabetes, glucose tolerance and insulin resistance

Evidence of an association between abnormal melatonin profiles and deficiencies in insulin sensitivity, glucose tolerance, lipid metabolism, and antioxidant capacity has emerged over the past decade [206-208]. Melatonin acts principally as a chronobiotic, regulating biological rhythms, including metabolic processes, in line with photic stimuli relayed by the suprachiasmatic nucleus. Irregular melatonin secretion is associated with desynchronisation of circadian regulated processes, and disruption of the endocrine signalling responsible for mediating them. Dysregulated melatonin may therefore influence regulation of metabolic function, with associated decreased sensitivity to metabolic hormones, and increased risk of developing metabolic diseases, including type 2 diabetes [209]. Interestingly, genetic surveys have found a correlation between a common variant of the melatonin receptor (MTNR1B) gene, responsible for encoding melatonin receptor 2, and impaired glucose regulation, reduced insulin levels, and risk of type 2 diabetes [209].

A study by Robeva et al. [210] found patients with metabolic syndrome (MetS) appeared to have an altered melatonin profile, with a stronger positive correlation between nocturnal melatonin and insulin levels than seen in controls. In patients with MetS, night-day melatonin variation was positively correlated with diurnal insulin levels and negatively correlated with fasting glucose, an association not found in healthy subjects. The authors suggested that these findings might be indicative of a compensatory mechanism aimed at overcoming insulin resistance and normalising glucose levels in MetS patients. Another study found nocturnal melatonin secretion to be inversely related to insulin resistance in non-diabetic individuals [211]. In addition, a causal link between a single nucleotide polymorphism of MTNR1B in humans, impaired glucose homeostasis, reduced insulin secretion and risk of type 2 diabetes has been identified by several groups [212-214]. A small number of studies have suggested an interaction between melatonin

and insulin sensitivity in specific populations. Reduced glucose tolerance was found in twenty-two postmenopausal women administered 1 mg melatonin compared to a placebo group, in the morning after overnight fasting [89]. A similar single-blind, placebo-controlled study replicated these findings in a group of 21 healthy women [87] given morning and evening melatonin over four consecutive days. Oral glucose tolerance tests showed impaired glucose tolerance was associated with suppressed insulin secretion after morning doses of melatonin, and impaired insulin sensitivity following evening doses. However, contrasting findings were reported by Garfinkel et al. [206] in a placebo-controlled cross-over study of diabetic patients with insomnia in which 2 mg/day prolonged-release melatonin showed no adverse effect on glucose or lipid metabolism during a three-week RCT and five month open-label follow-up. Furthermore, glycaemic control showed improvement over the course of long-term melatonin therapy. The only other RCT including diabetic patients in our survey found no AEs but was not focused on detecting the influence of melatonin on metabolic symptoms [112]. Goyal et al. [93] found that patients with metabolic syndrome treated with melatonin showed modest improvement in most MetS components compared to placebo after 10-weeks, with a tendency towards greater freedom from MetS.

The exact relationship between abnormal endogenous melatonin profiles and metabolic disorders in humans remains to be clarified. Only a small number of RCTs investigating the effect of melatonin therapy on the symptoms of diabetes and metabolic syndrome has been published. In the absence of clear evidence, individuals with pre-existing diabetes, metabolic syndrome or glucose intolerance should be monitored for any possible metabolic effects of melatonin.

4.2.5 Asthma

The observation that levels of inflammatory cytokines increase in the presence of melatonin [5, 159] has led to concerns that melatonin treatment might adversely affect inflammatory conditions such as asthma. An observational study by Sutherland et al. [158] showed a correlation between elevated endogenous melatonin levels and an increased incidence of nocturnal asthma, and an inverse correlation with respiratory function. Evidence of a negative effect of melatonin on asthma symptoms is inconsistent, however, and some studies have indicated the hormone may mitigate certain characteristics of the disease. Earlier research in animal models suggested a relaxant effect in the regulation of bronchial [215] and vascular smooth muscle tone [216]. Further studies have indicated both immunomodulatory [10, 217, 218] and antioxidant properties [11, 13]. Improvements in sleep quality have been observed in patients with asthma treated with melatonin, even where no evidence of a positive effect on asthma severity, use of relief medication or peak expiratory flow rate was found [219].

Asthma was present in subjects in three RCTs included in this review [116, 119, 219]. No evidence of either worsening or improvement in asthma symptoms was reported in any study. Likewise, the long-term open label study by Carr et al. [161] recorded no parental reports of either an exacerbation or improvement in asthma symptoms in affected children. Again, lack of evidence does not exclude possible adverse reactions. Asthma is a common and important condition in childhood; additional studies to determine whether there are any positive or adverse effects of melatonin are recommended.

4.2.6 Other possible effects

A study by Maksoud et al. [220] found an association between exogenous melatonin and worsening of obstructive sleep apnoea (OSA) symptoms in 12 patients receiving continuous positive airway pressure. Apnoea-hypopnea index, mean apnoea duration, and longest apnoea duration were all adversely affected. Other studies have reported no adverse effects in patients with OSA, however [121]. One open-label study of children with treatment-resistant epilepsy and comorbid sleep apnoea found a beneficial effect of melatonin on apnoea symptoms and sleep quality [164].

The apparent immunomodulatory properties of melatonin have led to the suggestion of a potential risk of development of autoimmune-related side effects. A single case study indicating a temporal relationship between melatonin use and the development of autoimmune hepatitis in a patient with insomnia was reported by Hong and Riegler [221].

A recent case-study reported the development of hypothermia in a child with autism after a single 3 mg dose of melatonin for a nighttime sleep disorder. Body temperature decreased to 34°C half an hour after administration and remained below normal for two days [222]. Mild hypothermia was reported in six paediatric patients taking melatonin in the 13 week MENDS study [50] but has not been reported elsewhere in controlled trials of melatonin for sleep disorders.

5. Limitations

The major limitation of this review is the small number of published long-term randomised, placebo-controlled studies of exogenous melatonin in which AEs were a primary or secondary outcome measure, resulting in a scarcity of robust data. The longest placebo-controlled trial was 29 weeks [120]. However, with the exception of one other trial [88], the length of this study was exceptional, and the majority were of much shorter duration. In the available studies, the variability in subject monitoring, the differences in methodologies for collecting AEs, the differences in the level of detail in which AEs were reported, and the generally small sample sizes, limit the power of the current data to reveal subtle, infrequent, and long-term effects. It is important to distinguish between adverse events (AEs) and adverse effects. AEs, as reported in this study, include all treatment-emergent symptoms, which may or may not be attributable to the medication. The frequency figures quoted in this review are those for AEs, where these were stated. In many papers, however, only adverse effects, that is events considered by the authors to be possibly attributable to the study medication, were stated. In open-label studies in particular, reliably differentiating likely adverse effects from background AEs may be difficult. In RCTs, even allowing for the frequency of AEs in placebo groups, some doubt may remain with regard to the events that are actual adverse effects of the hormone. An additional confounding factor is the number of studies involving subjects with serious primary medical, psychological, or behavioural conditions, especially those who are taking additional medication. In some cases, AEs commonly encountered in these studies may be attributable to either the underlying condition itself, or its treatment.

It has come to our attention that there may be a potential conflict of interest involving the authors of some of the studies included in this review. In particular, we understand that Professor Nava Zisapel and Dr Moshe Laudon who co-authored many of the papers on Circadin are employees of Neurim Pharmaceuticals, the manufacturer of this preparation and were involved in the development of the drug. Many of their co-authors on these papers, including lead investigators Dr Thomas Roth and Dr Alan Wade are also either employees or have acted as paid consultants for Neurim Pharmaceuticals [88, 107, 118, 120, 206, 223, 224], as are the authors of the study of Circadin by Gringras et al. [69]. All of the above studies were funded by Neurim Pharmaceuticals.

6. Conclusion

Our review of randomised, placebo-controlled trials found no evidence of serious AEs associated with exogenous melatonin use in the short term. The strongest evidence is for a mild increase in headache and daytime sleepiness. None of the individual studies has revealed a statistically significant difference in the frequency of AEs between melatonin and placebo. Overall, the rate of AEs was not markedly different from that for placebo, and very few AEs were identified uniquely in melatonin-treated patients. In almost half of the studies, no reports of any AEs were recorded. Few studies have included the safety or tolerability of melatonin as a primary or secondary outcome, however, and there remains a lack of high-quality data from long-term RCTs. Systematic investigation of AEs was only rarely undertaken in the studies we considered, and only a small number of studies reported AE frequencies in detail. Study duration was generally no longer than four weeks, and sample sizes were, on the whole, small, which might

have limited any ability to detect subtle effects. The most common AEs were daytime sleepiness, headache, other sleep-related AEs, dizziness, hypothermia and fatigue. Where reported, almost all AEs were considered mild or moderate in severity and tended to resolve either spontaneously within a few days or immediately after discontinuation of treatment. The scarcity of data from long-term RCTs limits the conclusions that can be drawn regarding the safety and tolerability of melatonin in the long-term. In particular, concerns about the possible consequences of exogenous melatonin exposure during pregnancy, and before and during puberty remain. Isolated studies have suggested an adverse effect on seizure control, asthma, and sleep apnoea, and a possible link to metabolic syndrome and diabetes but there is a lack of clear evidence for any such effects. Although there appears to be almost no evidence for clinically significant or serious adverse effects of melatonin, the lack of data imply that further investigation is required.

Supplementary table 1 – Study characteristics (study design and patient demographics)

Study	Study design	Duration	No. patients		Age (yrs)			Primary medical condition
			MLT	PLB	Min	Max	Mean	
Appleton [50]	Parallel group	12 weeks	70	76	3	15.8		Neurological and/or developmental disorders inc. epilepsy
Baskett [225]	Crossover	4 weeks	40	40	65	84	71.8	Age-related sleep maintenance problems (study included 20 healthy subjects)
Braam [115]	Parallel group	4 weeks	29	22	2	78	23.2	Intellectual disability; ASD; cerebral palsy; epilepsy
Campos [219]	Parallel group	4 weeks	12	10	18	60		Asthma
Chang [226]	Crossover	4 weeks	44	42	1	18		Atopic dermatitis
Coppola [227]	Crossover	4 weeks	25	25	3.6	26	10.5	Mental retardation; epilepsy
Cortesi [228]	Parallel group	12 weeks	69	55	4	10		ASD
Dodge [229]	Crossover	2 weeks	20	20	1	12		Developmental disabilities; ASD; ceerbral palsy; epilepsy
Dolberg [102]	Parallel group	4 weeks	10	9	22	65		Major depressive disorder
Dowling [230]	Crossover	1 week	8	8	56	74	65.6	Parkinson disease
Ellis [117]	Crossover	1 week	15	15	32	67	46	Psychophysiological insomnia
Garfinkel (1995) [223]	Crossover	3 weeks	12	12	68	93	76	Long-term insomnia
Garfinkel (2011) [206]	Crossover	3 weeks	36	36	46	77		Diabetes
Garzon [112]	Crossover	8 weeks	22	22	65			Insomnia or stress-related transient sleep disorder
Gringras [69]	Parallel group	13 weeks	58	61	2	17.5		ASD; ADHD; neurological disorders
Jain [76]	Crossover	4 weeks	10	10	6	11		Epilepsy
Kayumov [231]	Crossover	4 weeks	20	20				Delayed sleep phase disorder
Kunz (2004) [232]	Parallel group	4 weeks	14	14			50	Neuropsychiatric sleep disorders and reduced REM sleep
Kunz (2010) [233]	Crossover	4 weeks	8	8	26	67	54	REM sleep behaviour disorder
Kurdi [142]	Parallel group	2 weeks	24	24				Cancer
Luthringer [107]	Parallel group	3 weeks	20	20	55	68	60.8	Insomnia
McArthur [234]	Crossover	4 weeks	9	9	4	17	10.1	Rett syndrome
Medeiros [121]	Parallel group	4 weeks	8	10	50	71	61.9	Parkinson disease

Study	Study design	Duration	No. patients		Age			Primary medical condition
			MLT	PLB	Min	Max	Mean	
Nunes [122]	Parallel group	3 weeks	12	13				Chronic obstructive pulmonary disease
O'Callaghan [235]	Crossover	2 weeks	7	7	2	28		Tuberous sclerosis
Roth [118]	Parallel group	6 weeks	5	8	37	67	54.4	Blindness
Scheer [123]	Parallel group	3 weeks	8	8	45	64		Hypertension
Serfaty [113]	Parallel group	4 weeks	15	16				Major depressive disorder
Sletten [125]	Parallel group	4 weeks	58	58	17	64	29	Delayed sleep-wake phase disorder
Smits [119]	Parallel group	4 weeks	19	19	6	12	10.3	Childhood sleep onset insomnia
Van Der Heijden [75]	Parallel group	4 weeks	53	52	6	12		ADHD
Van Geijlswijk [101]	Parallel group	1 week	53	17	6	12		Chronic childhood sleep onset insomnia
Wade (2007) [224]	Parallel group	3 weeks	177	177			65.8	Insomnia
Wade (2010) [120]	Parallel group	29 weeks	534	177	18	80		Insomnia
Wade (2014) [88]	Parallel group	24 weeks	39	34	52	85	75.3	Alzheimer disease
Wasdell [116]	Crossover	10 days	50	50	2	18	7.4	Neurodevelopmental disabilities
Wirojinan [236]	Crossover	2 weeks	12	12	2	15.4	6	ASD; fragile x syndrome

Supplementary table 2 – Study characteristics (patient comorbidities, sample characteristics, melatonin formulation and co-medication)

Study	Other patient details and comorbidites	Melatonin		Co-medication
		Dose (mg/d)	Formulation	
Appleton [50]		0.5 - 12	Immediate release	
Baskett [225]	Sample included 20 'problem' and 20 'normal' sleepers	5	Immediate release	
Braam [115]	Idiopathic sleep disturbance for > 1 year	5	Immediate release	
Campos [219]	Female subjects only	3	Not specified	Beclomethasone; salbutamol; metidopa
Chang [226]		3	Not specified	
Coppola [227]		9	Immediate release	
Cortesi [228]		3	Controlled relase	
Dodge [229]	IQ or development quotient ≤ 50. 15 subjects with seizure disorders	5	Immediate relase	
Dolberg [102]			Controlled release	Fluoxetine
Dowling [230]	Male subjects only	5	Not specified	
Ellis [117]		5	Not specified	
Garfinkel (1995) [223]	Hypertension (n = 6); ischaemic heart disease (n = 5); spondyloarthrosis (n = 3); Parkinson disease (n = 3); diabetes (n = 2)	2	Controlled release	
Garfinkel (2011) [206]		2	Controlled release	Metformin; sulfonylureas; glucosidase inhibitors; glitazones; insulin; statins; fibrates; angiotensin-converting enzyme inhibitors
Garzon [112]	Patients discontinuing other hypnotic drugs. Type 2 diabetes (n = 5); hypertension (n = 12)	5	Not specified	Benzodiazepines
Gringras [69]		5	Controlled release	
Jain [76]		9	Controlled release	Anti-epileptic medications
Kayumov [231]		5	Not specified	
Kunz (2004) [232]	Idiopathic insomnia (n = 5); restless leg syndrome (n = 4); periodic limb movement disorder (n = 7); REM sleep behaviour disorder (n = 6); narcolepsy (n = 2)	3	Not specified	Captopril; nifedepine/furosemide; lithium
Kunz (2010) [233]	Male subjects only. Narcolepsy (n = 2); Parkinson disease (n = 1)	3	Not specified	L-dopa

Study	Other patient details and comorbidites	Melatonin		Co-medication
		Dose (mg/d)	Formulation	
Kurdi [142]		3	Not specified	
Luthringer [107]		2	Controlled release	
McArthur [234]		2.5 - 7.5	Immediate release	Phenobarbital; carbamazepine; ethosuximide; sodium valproate; gabapentin; felbamate
Medeiros [121]	Severe sleep apnea	3	Not specified	L-dopa; amantadine; biperiden; pramipexol; selegiline
Nunes [122]		3	Immediate release	
O'Callaghan [235]	All patients had epilepsy and learning disabilities	5	Not specified	Anti-convulsants
Roth [118]	Non 24-hour sleep-wake disorder	2	Controlled release	
Scheer [123]		2.5	Not specified	Beta-blockers (atenolol or metoprolol)
Serfaty [113]		6	Controlled release	Antidepressants
Sletten [125]		0.5	Immediate release	
Smits [119]	Asthma; ADHD	5	Immediate release	Salbutamol; methylphenidate; lacticil
Van Der Heijden [75]	Chronic sleep onset insomnia	3 - 6	Immediate release	
Van Geijlswijk [101]		0.15 - 6.3	Not specified	Antihistamines; methylphenidate; fluticason; salbutamol; valproic acid; trimethoprim; lactitol
Wade (2007) [224]		2	Controlled release	
Wade (2010) [120]		2	Controlled release	
Wade (2014) [88]	Patients with and without insomnia	2	Controlled release	Acetylcholinesterase inhibitors
Wasdell [116]	Severe intellectual impairment (n = 32); cerebral palsy (n = 26); epilepsy (n = 23); visual impairment (n = 20); lack of mobility (n = 18); ASD (n = 16)	5	Controlled release	
Wirojinan [236]		3	Not specified	

Supplementary table 3 – Study characteristics (reporting of adverse events)

	Reporting of adverse events		
Study	AE outcome measure	Methodology	Analysis and reporting
Appleton [50]	Secondary outcome	Weekly reviews by interview of predefined treatment-emergent signs and symptoms (TESS)	No formal analysis. MLT and PLB AE frequencies compared
Baskett [225]	Not specified as outcome	Not specified (assumed patient self-report)	No analysis. AEs reported only if resulting in withdrawal
Braam [115]	Secondary outcome	Not specified (assumed patient self-report). Change in seizures considered separately	No analysis. Brief narrative reporting
Campos [219]	Not specified as outcome	Not specified (assumed patient self-report)	No analysis. Brief narrative reporting
Chang [226]	Not specified as outcome	Not specified (assumed patient self-report)	No analysis. Brief narrative reporting
Coppola [227]	Not specified as outcome	Not specified (assumed patient self-report)	No analysis. Brief narrative reporting
Cortesi [228]	Not specified as outcome	Not specified (assumed patient self-report)	No analysis. Brief narrative reporting
Dodge [229]	Not specified as outcome	Not specified (assumed patient self-report)	No analysis. Brief narrative reporting
Dolberg [102]	Not specified as outcome	Not specified (assumed patient self-report)	No analysis. Brief narrative reporting
Dowling [230]	Not specified as outcome	Not specified (assumed patient self-report)	No analysis. Brief narrative reporting
Ellis [117]	Secondary outcome	Patient-completed questionnaire checklist with predefined symptoms	No analysis. Brief narrative reporting
Garfinkel (1995) [223]	Not specified as outcome	Not specified (assumed patient self-report)	No analysis. Brief narrative reporting
Garfinkel (2011) [206]	Not specified as outcome	Not specified (assumed patient self-report)	No analysis. Brief narrative reporting
Garzon [112]	Not specified as outcome	Ongoing monitoring by trial personnel	No analysis. Brief narrative reporting
Gringras [69]	Secondary outcome	Ongoing monitoring by trial personnel (TESS, AEs, vital signs, physical examination)	Narrative report. Data available as supplementary material
Jain [76]	Not specified as outcome[†]	AEs elicited at patient visit or via phone call. Seizures monitored by seizure diary	No analysis. Brief narrative reporting
Kayumov [231]	Not specified as outcome	Not specified (assumed patient self-report)	No analysis. Brief narrative reporting
Kunz (2004) [232]	Not specified as outcome	Not specified (assumed patient self-report)	No analysis. Brief narrative reporting
Kunz (2010) [233]	Not specified as outcome	Not specified (assumed patient self-report)	No analysis. Brief narrative reporting
Kurdi [142]	Not specified as outcome	Not specified (assumed patient self-report)	No analysis. Brief narrative reporting
Luthringer [107]	Secondary outcome	Not specified (assumed patient self-report)	No detailed analysis. Only most common AEs reported
McArthur [234]	Not specified as outcome	Not specified (assumed patient self-report)	No analysis. Brief narrative reporting
Medeiros [121]	Not specified as outcome	AEs elicited via weekly phone call with patient. Daytime somnolence assessed via the Epworth Sleepiness Scale (ESS)	No analysis. Brief narrative reporting

Study	Reporting of adverse events		
	AE outcome measure	Methodology	Analysis and reporting
Nunes [122]	Not specified as outcome	AEs elicited via weekly phone call with patient. Daytime somnolence assessed via the ESS	No analysis. Brief narrative reporting
O'Callaghan [235]	Not specified as outcome	Not specified (assumed patient self-report)	No analysis. Brief narrative reporting
Roth [118]	Safety specified as outcome	Physical examination (vital signs, laboratory tests, electrocardiogram) and AE assessment	Descriptive statistics for AEs, physical parameters and vital signs
Scheer [123]	Not specified as outcome	Patient-completed questionnaire checklist with predefined symptoms	No analysis. Brief narrative reporting
Serfaty [113]	Secondary outcome	AEs recorded by patients on sleep diary charts	No analysis. Brief narrative reporting
Sletten [125]	Not specified as outcome‡	Not specified (assumed patient self-report)	No analysis. Brief narrative reporting
Smits [119]	Secondary outcome	Parents asked to report suspected AEs in sleep diary charts	No analysis. Brief narrative reporting
Van Der Heijden [75]	Secondary outcome	AEs elicited in unstructured interviews with parents 3 weeks after treatment initiation	Basic analysis. Comparison between MLT and PLB groups with p-values stated
Van Geijlswijk [101]	Secondary outcome	Not specified (assumed patient self-report)	No analysis. Brief narrative reporting. Comparison of overall AE frequencies between MLT dosage regimes
Wade (2007) [224]	Not specified as outcome‡	Not specified (assumed patient self-report)	No detailed analysis. Only most frequent AEs reported
Wade (2010) [120]	Secondary outcome	Safety variables and vital signs assessed at each clinic visit. AEs via spontaneous report.	AEs reported by affected organ class. Withdrawal rates due to AEs and severe AEs reported
Wade (2014) [88]	Secondary outcome	Safety variables and vital signs assessed at each clinic visit. AEs via spontaneous report.	Statistical analysis of difference in overall AE frequency between MLT and PLB groups. AEs in ≥ 2 patients reported
Wasdell [116]	Secondary outcome	Safety variables assessed at each clinic visit. AEs elicited via patient interview	No analysis. Only most common AEs reported
Wirojanan [236]	Not specified as outcome	Not specified (assumed patient self-report)	No analysis. Brief narrative reporting

† Seizure frequency included as secondary outcome measure

‡ Next day alertness included included as outcome measure

Supplementary table 4 - CONSORT quality of reporting checklist

	CONSORT item																																			
Study	1a	1b	2a	2b	3a	3b	4a	4b	5	6a	6b	7a	7b	8a	8b	9	10	11a	11b	12a	12b	13a	13b	14a	14b	15	16	17a	17b	18	19	20	21	22	23	24	25
Appleton [50]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0.5	0.5	1	1	1	1	1	1	NA	1	1	1	0.5	1	1	1	0.5	1	1	1	1
Baskett [225]	1	1	1	1	0.5	NA	1	0.5	0.5	1	NA	1	NA	1	1	0	0	0.5	0	1	1	1	1	0	NA	1	1	1	NA	1	0	0.5	0.5	1	0	0	0
Braam [115]	1	1	1	0	0	NA	1	0	1	1	NA	0	NA	0	1	0	0	1	1	1	NA	1	1	0	NA	0.5	1	0.5	0.5	NA	0.5	1	0.5	1	0	0	0
Campos [219]	1	0.5	1	1	1	NA	1	0	1	1	NA	0	NA	0	0	0	0	0	1	1	NA	1	1	0	NA	0	0.5	1	NA	NA	1	0	0	0.5	0	0	0
Chang [226]	1	1	1	1	1	NA	1	1	1	1	NA	1	NA	1	1	1	1	1	1	1	1	1	1	1	NA	1	1	1	0	1	1	1	0.5	1	1	1	1
Coppola [227]	1	0.5	1	1	0	NA	1	0	0.5	1	NA	NA	NA	0	0	0	0	0	0	1	0	0	0	0	NA	1	1	1	NA	NA	1	0	0	1	0	0	0
Cortesi [228]	1	0.5	1	1	0.5	NA	1	1	1	1	NA	1	NA	1	0	0	1	1	1	1	1	1	1	0	NA	1	1	1	NA	1	1	1	1	1	0	0	0
Dodge [229]	0	0.5	1	1	0.5	NA	1	0	0.5	1	NA	0	NA	0	0	0	0	1	1	1	NA	1	1	0	NA	1	1	1	NA	NA	1	1	0	1	0	0	1
Dolberg [102]	0	0.5	1	1	0	NA	1	1	1	1	NA	0	NA	0	0	0	0	1	0	1	NA	0	0	0	NA	0	0	1	NA	NA	1	0	0	0.5	0	0	0
Dowling [230]	0	0.5	1	1	1	NA	0.5	0	1	0	NA	0	NA	0	0	0	0	0	0	1	NA	0	0	0	NA	0	0	1	NA	NA	1	0	0	1	0	0	1
Ellis [117]	0	0.5	1	0	0	NA	1	1	1	1	NA	0	NA	0	0	0	0	0	0	1	NA	0	0	0	NA	0	1	1	NA	NA	1	0	0	1	0	0	1
Garfinkel [223]	0	0.5	1	1	1	NA	0.5	0.5	1	1	NA	0	NA	0	0	0.5	0	1	1	1	NA	1	1	0	NA	0	1	0.5	NA	NA	1	0	0.5	1	0	0	0
Garfinkel [206]	1	1	1	1	1	NA	1	0	1	1	NA	0	NA	0	0	0	0	1	0	1	1	1	1	0	NA	0	1	0	NA	NA	1	1	0	1	0	0	1
Garzon [112]	1	1	1	1	1	NA	1	1	1	1	NA	0	NA	0	0	0	0	0	1	1	NA	1	1	0	NA	1	1	1	NA	NA	1	0.5	0	1	0	0	0
Gringras [69]	0	1	1	1	1	NA	1	1	1	NA	NA	1	NA	1	1	1	0	0	1	1	1	1	1	0	NA	1	1	1	1	1	1	1	1	1	0	1
Jain [76]	1	1	1	1	1	NA	1	1	1	1	NA	1	NA	1	0	0	1	1	1	1	1	1	1	1	NA	1	1	1	NA	1	1	1	0	1	1	0	1
Kayumov [231]	1	1	1	1	0	NA	1	1	1	1	NA	0	NA	0	0	0	0	0	0	1	NA	0	0	0	NA	0	0	1	NA	NA	1	1	0	1	0	0	0
Kunz (2004) [232]	1	0.5	1	1	1	NA	1	0	1	1	NA	1	NA	1	0	0	1	0.5	1	1	1	1	1	0	NA	0.5	1	1	NA	1	1	0	0	1	0	0	0
Kunz (2010) [233]	1	0.5	1	1	1	NA	1	0	1	1	NA	1	NA	1	0	0	1	0.5	1	1	1	1	1	0	NA	0.5	1	1	NA	1	1	0	0	1	0	0	0
Kurdi [142]	1	0	1	1	1	NA	1	0	1	1	NA	1	NA	1	1	1	1	1	0	0	NA	0	0	1	NA	1	0	1	NA	NA	1	1	0	1	0	0	0
Luthringer [107]	0	0.5	1	1	1	NA	1	1	1	0.5	NA	0	NA	0	0	0	0	0	0	1	1	1	1	0	NA	1	1	1	NA	1	1	0	0.5	1	0	0	1
McArthur [234]	0	0.5	1	1	0	NA	0	1	1	1	NA	0	NA	0	0	0	0	0	1	0	NA	1	0	0	NA	1	0	0	NA	NA	1	0	0	1	0	0	0
Medeiros [121]	0	0.5	1	1	1	NA	1	0.5	1	1	NA	0	NA	0	0	0	0	0	0	1	NA	1	0	0	NA	1	1	1	NA	NA	1	0	0	1	0	0	0
Nunes [122]	0	0.5	1	1	1	NA	1	1	1	1	NA	0	NA	0	0	0	0	1	0	1	1	1	1	0	NA	1	1	0	0	0	1	0	0	1	0	0	0
O'Callaghan [235]	0	0.5	1	0	1	NA	1	1	1	1	NA	0	NA	0	0	0	0	0	1	1	NA	1	0	0	NA	0.5	1	1	NA	NA	0	0	0	0	0	0	0

Study	CONSORT item																																			
	1a	1b	2a	2b	3a	3b	4a	4b	5	6a	6b	7a	7b	8a	8b	9	10	11a	11b	12a	12b	13a	13b	14a	14b	15	16	17a	17b	18	19	20	21	22	23	24	25
Roth [118]	1	1	1	1	1	NA	1	0	1	1	NA	1	NA	0	0	0	0	0	0	1	1	1	1	0	NA	1	0	1	NA	1	1	1	0	1	1	0	1
Scheer [123]	1	1	1	1	1	NA	1	0	1	1	NA	0	NA	1	1	0	1	1	0	1	NA	1	1	0	NA	0.5	0	0	NA	NA	1	1	0	1	1	0	0
Serfaty [113]	1	0.5	1	1	1	NA	1	1	1	1	NA	1	NA	0	0	0	1	1	1	1	1	1	1	1	NA	1	1	1	NA	1	1	0	0	1	0	0	1
Sletten [125]	1	1	1	1	1	NA	1	1	1	1	NA	1	NA	1	1	1	1	1	1	1	1	1	1	1	NA	1	1	1	1	NA	1	1	0.5	1	1	1	1
Smits [119]	1	0.5	1	1	0	NA	1	0	1	1	NA	1	NA	0	1	0	0	1	1	1	1	1	1	1	NA	0.5	0	0.5	NA	1	1	0	0	1	0	0	0
van der Heijden [75]	0	1	1	1	1	NA	1	1	1	1	NA	1	NA	1	1	0	1	1	1	1	1	1	1	1	NA	1	1	1	1	1	1	1	1	1	1	0	0
van Geijlswijk [101]	0	1	1	1	1	NA	1	1	1	1	NA	1	0	1	1	1	1	1	1	1	NA	1	1	1	1	1	1	1	NA	NA	1	1	0	1	1	0	0
Wade (2007) [224]	0	1	1	1	1	NA	1	1	1	1	NA	0	NA	0	1	1	0	0	0	1	NA	1	1	0	NA	1	1	1	1	NA	1	0	0	1	0	0	0
Wade (2010) [120]	1	1	1	1	1	NA	1	1	1	1	NA	1	NA	1	1	1	0	1	1	1	1	1	1	0	NA	1	1	1	1	1	1	1	0	1	1	0	1
Wade (2014) [88]	1	1	1	1	1	NA	1	1	1	1	NA	0	0	1	1	0	0	0	1	1	1	1	1	0	1	1	1	1	NA	1	1	0	0	1	0	0	1
Wasdell [116]	1	0.5	1	0	1	NA	1	1	1	1	NA	1	NA	0	1	0	1	1	1	1	1	0.5	0	1	NA	0.5	0	1	NA	1	1	1	0	1	0	0	0
Wirojanan [236]	0	1	1	0	1	NA	1	1	1	1	NA	0	NA	0	0	0	0	0	0	1	NA	1	1	0	NA	1	1	1	NA	NA	1	0.5	0	1	0	0	0

Each item is scored 1, 0.5, 0 or NA. 1 = criterion met; 0.5 = criterion partially met; 0 = criterion not met; NA = item not applicable

Supplementary table 5 - Cochrane risk of bias

Study	Cochrane risk of bias item							
	Random sequence generation	Allocation concealment	Selective reporting	Other bias	Binding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	AHRQ standard
Appleton [50]	Low	Low	Low	Low	Low	Low	Low	Good
Baskett [225]	Low	High	Unclear	Low	Unclear	Low	Low	Fair
Braam [115]	Unclear	Unclear	Unclear	Low	High	High	Low	Poor
Campos [219]	Unclear	Unclear	Unclear	Low	Unclear	Unclear	High	Poor
Chang [226]	Low	Low	Low	Low	Low	Low	Low	Good
Coppola [227]	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low	Fair
Cortesi [228]	Low	Unclear	Unclear	Low	Low	Unclear	Low	Fair
Dodge [229]	Unclear	Unclear	Unclear	Low	Low	Unclear	Low	Fair
Dolberg [102]	Unclear	Unclear	Unclear	Low	Low	Low	High	Poor
Dowling [230]	Unclear	Unclear	Unclear	Low	Unclear	Unclear	High	Poor
Ellis [117]	Unclear	Unclear	Unclear	Low	Unclear	Unclear	High	Poor
Garfinkel (1995) [223]	Unclear	Low	Unclear	Low	Low	Low	Low	Fair
Garfinkel (2011) [206]	Unclear	Unclear	Unclear	Low	Unclear	Unclear	High	Poor
Garzon [112]	Unclear	Unclear	Unclear	Low	Unclear	Unclear	High	Poor
Gringras [69]	Low	Low	Low	Low	Low	Low	Low	Good
Jain [76]	Low	Low	Low	Low	Low	Low	Low	Good
Kayumov [231]	Unclear	Unclear	Unclear	Low	Unclear	Unclear	High	Poor
Kunz (2004) [232]	Low	Low	Unclear	Low	Unclear	Unclear	Low	Fair
Kunz (2010) [233]	Low	Low	Unclear	Low	Unclear	Unclear	Low	Fair
Kurdi [142]	Low	Low	Unclear	Low	Unclear	Unclear	High	Poor
Luthringer [107]	Unclear	Unclear	Unclear	Low	Unclear	Low	Low	Poor
McArthur [234]	Unclear	Unclear	Unclear	Low	Unclear	Unclear	High	Poor
Medeiros [121]	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Fair

Study	Cochrane risk of bias item							
	Random sequence generation	Allocation concealment	Selective reporting	Other bias	Binding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	AHRQ standard
Nunes [122]	Unclear	Unclear	Unclear	Low	Unclear	Unclear	High	Poor
O'Callaghan [235]	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Fair
Roth [118]	Unclear	Unclear	Low	Low	Unclear	Unclear	Low	Fair
Scheer [123]	Low	Low	Low	Low	Unclear	Unclear	High	Poor
Serfaty [113]	Unclear	Unclear	Unclear	Low	Low	Low	Low	Fair
Sletten [125]	Low	Low	Low	Low	Low	Low	Low	Good
Smits [119]	Unclear	Unclear	Unclear	Low	Low	Low	Unclear	Fair
Van Der Heijden [75]	Low	Low	Low	Low	Low	Low	Low	Good
Van Geijlswijk [101]	Low	Low	Low	Low	Low	Low	Low	Good
Wade (2007) [224]	Unclear	Low	Unclear	Low	Unclear	Unclear	Low	Fair
Wade (2010) [120]	Low	Low	Low	Low	Low	Low	Low	Good
Wade (2014) [88]	Low	Unclear	Unclear	Low	Unclear	Unclear	Low	Fair
Wasdell [116]	Low	Low	Unclear	Low	Low	Low	Low	Fair
Wirojanan [236]	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low	Fair

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