

This is a repository copy of *Oral Melatonin for Non-Respiratory Sleep Disturbance in Children with Neurodisabilities: Systematic Review and Meta-Analyses*.

White Rose Research Online URL for this paper:
<https://eprints.whiterose.ac.uk/138501/>

Version: Published Version

Article:

Parker, Adwoa orcid.org/0000-0002-2880-3935, Beresford, Bryony Anne orcid.org/0000-0003-0716-2902, Dawson, Vicki et al. (8 more authors) (2019) Oral Melatonin for Non-Respiratory Sleep Disturbance in Children with Neurodisabilities: Systematic Review and Meta-Analyses. *Developmental Medicine and Child Neurology*. pp. 880-890. ISSN 1469-8749

<https://doi.org/10.1111/dmcn.14157>


Reuse

This article is distributed under the terms of the Creative Commons Attribution-NonCommercial (CC BY-NC) licence. This licence allows you to remix, tweak, and build upon this work non-commercially, and any new works must also acknowledge the authors and be non-commercial. You don't have to license any derivative works on the same terms. More information and the full terms of the licence here:
<https://creativecommons.org/licenses/>

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

Oral melatonin for non-respiratory sleep disturbance in children with neurodisabilities: systematic review and meta-analyses

ADWOA PARKER¹  | BRYONY BERESFORD² | VICKI DAWSON³ | HEATHER ELPHICK⁴ | CAROLINE FAIRHURST¹ | CATHERINE HEWITT¹ | ARABELLA SCANTLEBURY¹  | GEMMA SPIERS⁵ | MEGAN THOMAS⁶ | KATH WRIGHT⁷ | CATRIONA MCDAID¹

1 York Trials Unit, Department of Health Sciences, University of York, York; **2** Social Policy Research Unit, University of York, York; **3** The Children's Sleep Charity, Doncaster; **4** Sheffield Children's NHS Foundation Trust, Sheffield; **5** Institute for Health and Society, Newcastle University, Newcastle upon Tyne; **6** Blackpool Teaching Hospitals NHS Foundation Trust, Blackpool; **7** Centre for Reviews and Dissemination, University of York, York, UK.

Correspondence to Catriona McDavid at Department of Health Sciences, ARRC Building, University of York, York YO10 5DD, UK. E-mail: catriona.mcdavid@york.ac.uk

PUBLICATION DATA

Accepted for publication 27th October 2018.

Published online

ABBREVIATIONS

ASD	Autism spectrum disorder
RCT	Randomized controlled trial
SOL	Sleep onset latency
TST	Total sleep time

AIM To evaluate the effectiveness of pharmacological interventions for managing non-respiratory sleep disturbances in children with neurodisabilities.

METHOD We performed a systematic review and meta-analyses of randomized controlled trials (RCTs). We searched 16 databases, grey literature, and reference lists of included papers up to February 2017. Data were extracted and assessed for quality by two researchers (B.B., C.M., G.S., A.S., A.P.).

RESULTS Thirteen trials were included, all evaluating oral melatonin. All except one were at high or unclear risk of bias. There was a statistically significant increase in diary-reported total sleep time for melatonin compared with placebo (pooled mean difference 29.6min, 95% confidence interval [CI] 6.9–52.4, $p=0.01$). Statistical heterogeneity was high (97%). For the single RCT with low risk of bias, the unadjusted mean difference in total sleep time was 13.2 minutes (95% CI –13.3 to 39.7) favouring melatonin, while the mean difference adjusted for baseline total sleep time was statistically significant (22.4min, 95% CI 0.5–44.3, $p=0.04$). Adverse event profile suggested that melatonin was well-tolerated.

INTERPRETATION There is a paucity of evidence on managing sleep disturbances in children with neurodisabilities, and it is mostly of limited scope and poor quality. There is evidence of the benefit and safety of melatonin compared with placebo, although the extent of this benefit is unclear.

Sleep is fundamental to healthy physical and mental functioning and well-being. However, sleep disturbances in children are common. For children with neurodisabilities, sleep disturbances are more common and more severe compared with typically developing children.¹ For children, sleep disturbance can affect educational progress and daytime behaviour.² It can also have a detrimental impact on the physical and emotional well-being of other family members; for example, children's sleep disturbance is associated with heightened levels of parental stress and irritability.^{3,4} These outcomes may create additional support needs and, consequently, increase demands on statutory services, such as respite care.⁵ More widely, the economic consequences of poor sleep are being recognized.^{6,7} Sleep management is a research priority in children with neurodisabilities.⁸ Parents also consistently highlight their need for support with their child's sleep problems.^{9–11}

The clinical and research literature uses numerous alternative phrases to describe sleep disorder in terms of its impact on an individual's sleep, such as 'sleep disturbance', 'sleep problems', and 'sleep difficulties'.¹² Such terms have

all been used to describe difficulties with falling asleep (i.e. sleep initiation) and staying asleep, as opposed to night wakings or very early waking (i.e. sleep maintenance). Regardless of the term used, difficulties with sleep initiation and sleep maintenance result in disturbed sleep and/or sleep deprivation, not only for the individual concerned but often also for other members of the household.

Interventions to address sleep disturbance among children with neurodisabilities include both pharmacological and non-pharmacological approaches. Pharmacological interventions act on the physiological processes of sleep, the timing of the sleep-wake cycle, or both. The most frequently used pharmacological treatment is melatonin, the hormone involved in controlling the sleep-wake cycle.^{13–15} Many paediatricians and general practitioners prescribe melatonin for children, despite it not currently being licensed for children. In 2005, an anonymous survey of 148 paediatricians in the UK suggested that 98% were currently prescribing or had prescribed melatonin in the previous year.¹⁶ Although not currently licensed, melatonin is available over the Internet and over the counter in some countries such as the

USA, where a survey of paediatricians reported that 25% had recommended melatonin for paediatric insomnia in children with and without neurodisabilities.¹⁷ In the UK there are currently more than 6000 children being treated with melatonin.¹⁸ Other pharmacological interventions include medicines that have a sedative effect, such as clonidine and antihistamines. All are prescribed 'off-label'.

Current guidance on the management of sleep disturbance in children advocates that, once clinical or respiratory reasons for sleep disturbance are excluded, parent-directed interventions that seek to change parents' responses to sleep-related problems should be the 'first port of call' for any child,^{13,19–21} with pharmacological intervention (typically melatonin) suggested in cases where such approaches prove ineffective and/or to be used alongside parent-directed approaches.^{12,22} However, current practice in prescribing medicines such as melatonin has been described as haphazard.¹⁸ For melatonin, guidance states that it should be considered for improving sleep onset latency (SOL) in children with neurodisabilities of any form whose sleep problems have not resolved after implementation of behavioural interventions.²⁰ The guidance also states that melatonin should be used in conjunction with behavioural interventions.²³ For children with autism spectrum disorder (ASD) and any type of sleep disorder, current guidance stipulates that parent-directed behavioural interventions should be implemented first before pharmacological interventions; and that where pharmacological interventions are used, this should be in conjunction with behavioural interventions.^{23,24}

Previous systematic reviews of pharmacological interventions for managing sleep disturbance have focused on individual neurodisabilities such as ASD or attention-deficit/hyperactivity disorder.^{25–30} Therefore, a systematic review assessing the effect of pharmacological interventions on sleep disturbance across the neurodisability spectrum is needed, to inform both clinical practice and research.

This systematic review was commissioned by the Health Technology Assessment programme of the UK National Institute for Health Research (NIHR). The NIHR required the review to focus on the management of 'non-respiratory sleep disturbance' in children with neurodisabilities and that sleep disturbance (affecting the child and/or parent) was a feature of the presenting problem. The commissioning brief was broad and included effectiveness and safety of pharmacological and non-pharmacological interventions to manage sleep disturbances in children with neurodisabilities. In this paper we focus on the effectiveness and safety of pharmacological interventions. Findings with respect to non-pharmacological interventions are reported elsewhere.^{31,32}

We aimed to evaluate and summarize the existing evidence about the effectiveness of pharmacological interventions on sleep disturbances for children with neurodisabilities. Where possible, we planned to undertake subgroup analyses to examine whether intervention effectiveness differed between different types of neurodisability, and whether it was administered in parallel or sequentially to another sleep management intervention.

What this paper adds

- Melatonin for the management of non-respiratory sleep disturbances in children with neurodisabilities was well tolerated with minimal adverse effects.
- The extent of benefit and which children might benefit most from melatonin use is uncertain.
- Benefit may be greatest in those with autism spectrum disorder; however, this finding should be interpreted with caution.

METHOD

This systematic review was undertaken in accordance with the Centre for Reviews and Dissemination's 'Guidance for Undertaking Reviews in Health Care'³³ and is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.³⁴ Data synthesis was undertaken in accordance with the Cochrane handbook.³⁵ The review protocol was prospectively registered with PROSPERO (registration number CRD42016034067).

Inclusion and exclusion criteria

Studies were assessed for eligibility on the basis of the criteria outlined in Table S1 (online supporting information). Concerns have been expressed by others that a crossover design may be inappropriate because of uncertainty about the duration of the effect of interventions on sleep patterns and circadian rhythm and therefore the most appropriate duration for the washout period.¹⁸ We agree with these concerns. However, given that the aim was to undertake a broad review and there were few randomised controlled trials (RCTs) likely to be available, we included crossover studies. In this paper we focus on child-related outcomes.

Information sources

Databases searched included Applied Social Science Abstracts & Indexes (ASSIA); the Cochrane Central Register of Controlled Trials (CENTRAL); Cochrane Database of Systematic Reviews (CDSR); Conference Proceedings Citation Index; Cumulative Index to Nursing & Allied Health (CINAHL); Database of Abstracts of Reviews of Effects (DARE); Embase; Health Management Information Consortium (HMIC); MEDLINE; MEDLINE In-Process; PsycINFO; Science Citation Index; Social Care Online; and Social Policy & Practice. Searches were undertaken in February and March 2016, and updated in February 2017.

The database ClinicalTrials.gov, the World Health Organization's International Clinical Trials Registry Platform (ICTRP), and the UK Clinical Trials Gateway were also searched for ongoing and completed trials. We reviewed the reference lists of relevant systematic reviews and included studies. Searches were not limited by date, language, or study design. The search strategy was broad and aimed to identify both pharmacological and non-pharmacological interventions. Appendix S1 (online supporting information) outlines the search strategy used for Medline, which was adapted for use in other databases.

Selection process

Search results were imported into EndNote (version 17.0.2.7390, Clarivate Analytics [formerly Thomson

Reuters], Philadelphia, PA, USA) and deduplicated. Record titles were initially screened for relevance, independently by two researchers (BB and GS) for 10% of titles, with review of decisions halfway through. The agreement rate was moderate ($K=0.49$), and we discussed and resolved reasons for all disagreements. By the end of this process, only unanimous decisions were made. The remainder were therefore screened by a single researcher. Selection of potentially relevant abstracts and assessment of full-text articles were done independently, by two researchers. A third researcher was consulted where there was disagreement.

Data extraction

Data extraction forms for study details were developed and piloted in Microsoft Excel 2010 and Microsoft Word 2010. All data were extracted by a researcher and checked by a second. Data extracted included study design (setting, aims, inclusion criteria, recruitment method, etc.), intervention and comparator details, evaluation methods (outcomes measured, length of follow-up, etc.) and results at follow-up. Follow-up was defined as the closest assessment time point after the completion of the intervention.

Assessment of risk of bias

The Cochrane Risk of Bias Tool³⁶ was used to assess this aspect of study quality. Risk of bias was independently assessed by two researchers, with disagreements resolved through discussion or with recourse to a third researcher. For crossover trials we also assessed whether an appropriate analysis using paired data was conducted and whether there was a treatment by period interaction.³⁷

A summary risk of bias score was calculated as follows: studies with one or more of the domains on the risk of bias tool classified as 'no' (i.e. high risk) were scored at high risk of bias. Studies with one or more domains on the risk of bias tool scored as 'unclear' were scored at unclear risk of bias. Studies with all domains on the risk of bias tool classified as 'yes' (i.e. low risk) were scored at low risk of bias.³⁶

Data synthesis

A narrative synthesis and meta-analyses were used. First, a narrative and tabular summary of key study characteristics were undertaken to map the population characteristics, in particular the type of neurodisability and the type of sleep disturbance being targeted (e.g. sleep initiation).

Meta-analyses included parallel RCTs, and crossover trials with a washout period of any duration where data from both treatment periods were used. Crossover trials without a washout period were reported separately. The mean difference and its standard error between intervention and comparison groups at the end point were either taken as reported in the article or calculated using standard formulae, following recommendations provided in the Cochrane handbook.³⁵ Data were pooled using a random effects model (for continuous outcomes) using the generic inverse variance method in RevMan.³⁸ For parallel-group RCTs, unadjusted mean differences were primarily used in the

meta-analyses, but sensitivity analyses were conducted including mean differences adjusted for baseline using either estimates reported in the paper from regression techniques or calculated differences in change from baseline.

Sleep efficiency was calculated as a percentage, to represent time spent sleeping as a proportion of total time in bed. Number of night wakings was a count variable. Such variables may not be normally distributed so analysis based on untransformed means may not be appropriate. Individual patient data were not available and only untransformed summaries (e.g. means and standard deviations [SDs]) for these outcomes were given in the original papers. Therefore, following the advice for the meta-analysis of skewed data in the Cochrane handbook,³⁵ a (crude) assessment of skew was made using the untransformed means and SDs. This was possible as we knew the maximum and/or minimum possible values for these outcomes. For sleep efficiency, if the highest possible value (here, 100) minus the observed mean, divided by the SD, was less than 2, then skew was indicated.³⁹ For night wakings, the lowest possible value (0) was subtracted from the mean value before dividing by the SD. Sensitivity analyses were performed to remove trials where significant skew was indicated, and caution in the interpretation of results was included where appropriate.

Heterogeneity was explored using the I^2 statistic.⁴⁰ Two sources of potential clinical and methodological heterogeneity were identified for the included studies, and, where appropriate, subgroup analyses were conducted, stratifying the trials as follows: by type of neurological disorder (whether the population studied primarily had a diagnosis of ASD or not); and by receipt of previous intervention (whether participants were offered an additional intervention [parent-directed or otherwise] immediately before the start of the study or not).

Data preparation was undertaken in Stata 13 (StataCorp, College Station, TX, USA), and data analyses were performed in RevMan 5 (Review Manager, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2014). Where data could not be pooled, summaries of the findings for each trial and outcome are presented with a (estimated unadjusted) mean difference and 95% confidence interval (CI) between the pharmacological intervention and comparison group at follow-up. The risk of publication bias was not formally assessed. Adverse event data were summarized narratively.

RESULTS

Search results

We identified 15 745 records after deduplication, assessed 387 full-text records, and included 13 RCTs, all of which investigated the use of oral melatonin as the pharmacological intervention. We did not identify any eligible trials evaluating another pharmacological intervention, so the remainder of the results therefore only concern trials of melatonin. The study selection process and reasons for exclusion are detailed in Figure S1 (online supporting information). A list of excluded studies is available at

Study characteristics

Study characteristics are outlined in Table SII (online supporting information). The studies were undertaken in the following countries: Canada (four studies);^{41–44} Italy (one study);⁴⁵ the Netherlands (one study);⁴⁶ UK (four studies);^{18,47–49} and the USA (three studies).^{50–52} Ten RCTs compared melatonin with placebo; one compared melatonin, a parent-directed sleep-focused cognitive behavioural therapy, and a combination of the two with placebo; and two compared two regimens of melatonin (5mg vs 10mg; and fast-release versus sustained release). Ten were crossover trials and three were parallel-group RCTs. Sample sizes ranged from six to 160 participants.

Owing to the different terminology used to describe sleep disturbances in the included studies, we classified assessment of sleep outcomes under the following headings: global sleep outcomes and composite scores; sleep initiation (e.g. sleep latency, sleep association, settling, bedtime resistance); sleep maintenance (e.g. night waking, waking time, parasomnia, cosleeping to manage night waking, sleep fragmentation), and sleep scheduling (e.g. daytime sleepiness).

Risk of bias within studies

Only one RCT was assessed as having a low risk of bias across all domains,¹⁸ with the remaining RCTs having high or unclear risk of bias (Table SII). We could not locate a prospective registration of 11 studies in order to check planned outcome measures, meaning they were at unclear risk of selective reporting.^{41–43,45–48,50–52} All of the studies were described by their authors as being randomized; however, seven studies failed to provide details of the method of random allocation;^{41–43,46,48,50,52} and four studies provided little or no detail about allocation concealment.^{41,45,50,52} Similarly, it was unclear in three studies whether and how blinding was undertaken.^{41,43,47} Missing data were not adequately addressed in the analysis for three studies.^{45,47,50}

Melatonin versus placebo

Eleven trials ($n=589$ randomized participants) compared melatonin against placebo: eight crossover trials;^{41–43,47,48,50–52} two two-armed, parallel-group trials;^{18,46} and one four-armed parallel-group trial of oral melatonin, parent-directed sleep management intervention (on the basis of cognitive behavioural principles), oral melatonin plus parent-directed intervention and oral placebo.⁴⁵

The age of participants ranged from 1 to 18 years old and the mean age ranged from 5 years 6 months to 10 years 4 months. Four RCTs included children with a mix of neurodisabilities,^{18,41,42,50} three RCTs only included children with ASD,^{45,47,48} two trials included only children with attention-deficit/hyperactivity disorder,^{43,46} one trial included children with ASD and/or fragile X syndrome,⁵² and one RCT included children with epilepsy.⁵¹

Two trials used ‘controlled-release’ melatonin.^{42,45} One trial each described the formulation as ‘immediate-release’,¹⁸ ‘fast-release’,⁴⁶ ‘standard-release’,⁴⁸ ‘short-acting’,⁴³ and ‘sustained-release’ melatonin.⁵¹ Four trials did not report formulation.^{41,47,50,52} Six trials varied dosage on the basis of the child’s age and/or weight and response, from 0.5mg to 10mg (Table SII).^{18,41,46,48} Fixed dosages ranged from 3mg to 9mg.^{42,44,45,47,50–52} Matched placebos were used except for one RCT where details of the placebo were not specified.⁴³ The duration of treatment was between 10 days and 12 weeks. Two crossover RCTs had no washout period.^{41,52} The remaining crossover RCTs had a washout period of between 3 days and 1 month.^{42,43,47,48,50,51}

Seven RCTs required that an immediately preceding parent-directed sleep management intervention had been ineffective for children to be included in the trial.^{18,41–43,47,48,50} Two of these trials did not report the specific nature of the intervention.^{41,50} In two trials, guidance on sleep was provided in the form of an advice booklet;^{18,47} and in three trials, advice about sleep hygiene and behaviour management was provided face-to-face.^{43,48,52}

The most commonly measured sleep-related outcomes, measured by actigraphy and/or parent-reported diaries/questionnaires, were total sleep time (TST) ($n=11$ trials); SOL ($n=10$); number of night wakings ($n=6$); and sleep efficiency ($n=5$). Other sleep outcomes assessed in fewer than two studies included bedtime,^{45,51} wake up time,^{46,51} the Child Sleep Habits Questionnaire,⁴⁵ difficulty falling asleep,⁴⁶ sleep onset,⁴⁸ longest sleep episode,⁴² the Sleep Behaviour Questionnaire,⁵¹ percentage of sleep stages,⁵¹ wake after sleep onset,^{45,51} nights without awakening,⁴¹ naptime,⁴⁵ moving time,⁴⁶ and arousal.⁵¹

In terms of outcomes that were not child sleep-focused, the following additional child outcomes were reported, but only by single RCTs: child-related quality of life (Paediatric Quality of Life Questionnaire); Quality of Life in Childhood Epilepsy; Netherlands Organisation for Applied Scientific Research Academic Medical Centre Children’s Quality Of Life Questionnaire (TNO-AZL);^{18,46,51} child daytime behaviour and cognition (Aberrant Behaviour Checklist; Behaviour Assessment System for Children; Conner’s Attention Deficit Scale-Parent; Child Behaviour Checklist; teacher’s report form; sustained attention dots—task completion time and task inaccuracy; Erikson’s task);^{18,43,46,51} adherence to treatment (parent-report; medication counts);^{45,46} and core problems.⁴⁶ One further study assessed daytime sleepiness in caregivers.¹⁸

All RCTs had follow-up immediately after the completion of the intervention, which ranged from 10 days to 12 weeks after randomization.

Global measures and composite scores

TST

All 11 RCTs ($n=589$ randomized participants) measured TST. Four measured TST using parent-reported sleep diaries only;^{41,47,48,50} three solely reported actigraphy-

measured TST data;^{45,46,52} and four reported TST derived from both parent-completed sleep diaries and actigraphy data^{18,42,43,51} (one of which additionally used polysomnography, which was measured in a sleep laboratory setting).⁵¹

Parent-reported TST using sleep diaries

Data from seven RCTs using sleep diary-reported TST were pooled in a meta-analysis: six crossover trials with a washout period ($n=122$ analysed participants)^{42,43,47,48,50,51} and one parallel-group trial ($n=110$).¹⁸ Note that in the forest plot (Fig. 1) the sample sizes count participants in crossover trials twice (as being in the melatonin and placebo groups), so the total figures reported in the text and in the figures may not match. There was a statistically significant increase in sleep diary-reported TST with melatonin compared with placebo (pooled mean difference 29.6min, 95% CI 6.9–52.4, $p=0.01$).

Statistical heterogeneity was high ($I^2=97%$) and this treatment effect is unlikely to be generalizable; however, the effect estimates were all in the direction of benefit with melatonin. Heterogeneity was reduced when studies were stratified on the basis of whether the study population had ASD exclusively or not (Fig. 1; test for subgroup differences: $p<0.001$; $I^2=99%$): there was a pooled mean difference of 64.7 minutes (95% CI 58.8–70.7, $I^2=0%$) for the studies of ASD ($n=24$) and a smaller pooled mean difference of 15.9 minutes (95% CI 9.2–22.6, $I^2=31%$) for the studies of mixed or other populations ($n=208$). There was a single study ($n=9$)⁵¹ where participants had no previous parent-directed sleep management intervention, limiting the usefulness of this subgroup analysis; the overall results did not substantially change with removal of this study (Fig. S2, online supporting information; pooled mean difference 33.0min, 95% CI 8.6–57.4, $I^2=95%$). When the single trial with a low risk of bias was considered alone, the unadjusted mean difference in sleep time at follow-up was

13.2 minutes (95% CI –13.3 to 39.7) favouring melatonin. This was the difference used in the meta-analysis. The paper, however, additionally reported a mean difference adjusted for baseline TST of 22.43 minutes favouring melatonin (95% CI 0.52–44.34, $p=0.045$).¹⁸ When the adjusted mean difference was used in place of the unadjusted mean difference in the meta-analysis, the pooled mean difference increased to 30.8 minutes (95% CI 8.3–53.2, $p=0.01$). Either way, while both pooled mean differences between the treatment groups were statistically significant, neither 95% CI contained the minimum clinically important difference of 60 minutes, which was specified at the start of that trial.¹⁸

One RCT of six ‘*n-of-1*’ trials also reported sleep diary TST but, owing to the design, could not be included in the meta-analysis.⁴¹ We calculated the mean difference between melatonin and placebo for parent-reported TST to be 13.9 minutes in favour of the melatonin group (95% CI –6.8 to 34.6, $p=0.14$).

Actigraphy-measured TST

Five trials ($n=265$ analysed participants) were pooled for actigraphy-measured TST, comprising two crossover trials with a washout period ($n=60$)^{42,51} and three parallel-group trials ($n=205$).^{18,45,46} One further RCT reported that there was no significant difference between melatonin and placebo; however, it did not provide data, so it was not included in the meta-analysis.⁴³

There was a statistically significant increase in actigraphy-measured TST with melatonin compared with placebo (Fig. 2; pooled mean difference 31.9min, 95% CI 14.8–49.1, $p<0.001$). Heterogeneity was high ($I^2=76%$) and this treatment effect is unlikely to be generalizable, although the effect estimates were all in the direction of benefit with melatonin. There was no statistically significant difference in effect between the studies where participants received or

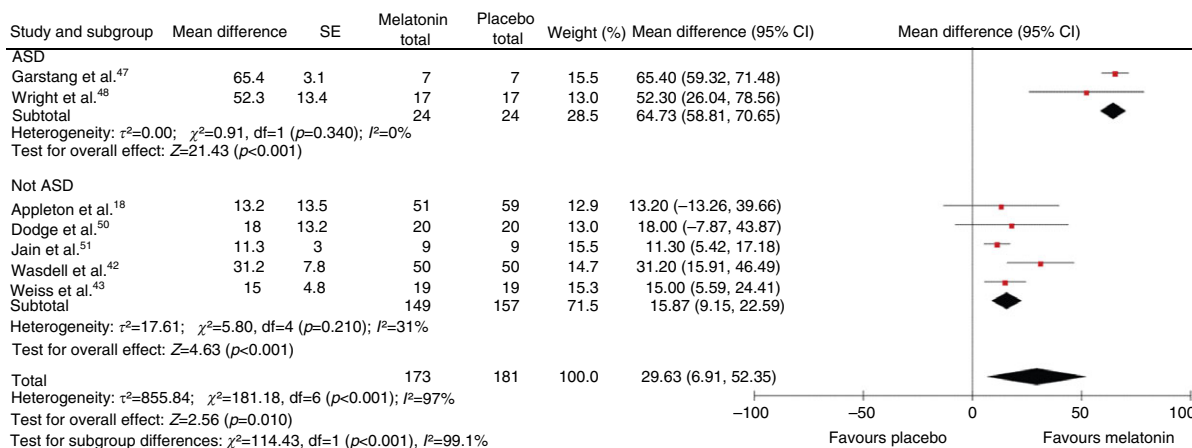


Figure 1: Sleep diary-reported total sleep time: melatonin versus placebo and autism spectrum disorder (ASD) subgroup analysis. Squares represent the point estimate of the individual study result. The squares also give a representation of the size of the study. Larger squares indicate more participants in the study. SE, standard error; CI, confidence interval; df, degrees of freedom. [Colour figure can be viewed at wileyonlinelibrary.com]

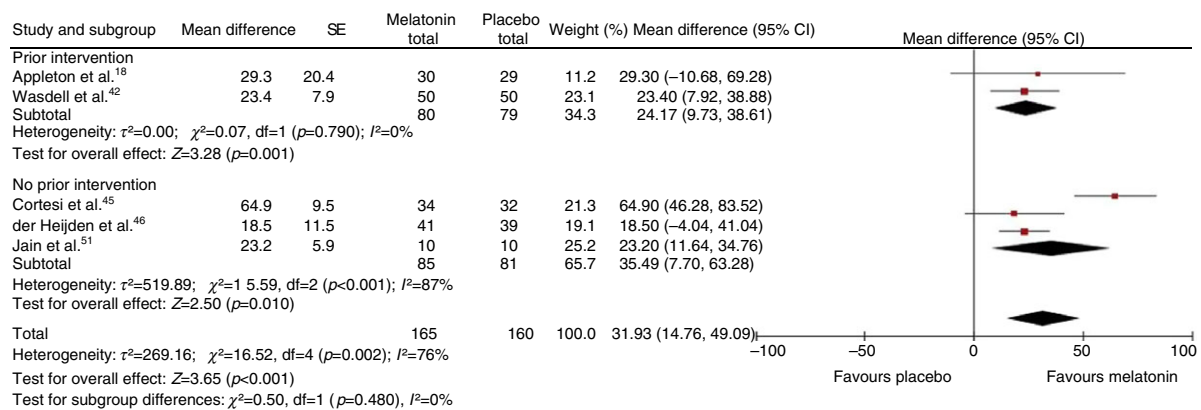


Figure 2: Actigraphy-measured total sleep time: melatonin versus placebo. Squares represent the point estimate of the individual study result. The squares also give a representation of the size of the study. Larger squares indicate more participants in the study. SE, standard error; CI, confidence interval; df, degrees of freedom. [Colour figure can be viewed at wileyonlinelibrary.com]

did not receive a previous parent-directed sleep management intervention (test for subgroup differences: $p=0.48$; $I^2=0\%$). There was a single included trial where the study population primarily had ASD;⁴⁵ the overall mean difference reduced with removal of this study (pooled mean difference 22.9min, 95% CI 14.5–31.3, $p<0.001$). When mean differences (adjusted for baseline values; Appleton: mean difference 13.3 [SE 14.7]; Cortesi: 67.6 [10.4]; van der Heijden: 33.4 [12.7]) were included in the meta-analysis for the parallel-group RCTs, the overall pooled mean difference increased marginally to 32.3 minutes (95% CI 15.3–49.3, $p<0.001$).

One RCT without a washout period⁵² ($n=12$ analysed participants) reported a mean difference in actigraphy-measured TST of 21 minutes between melatonin and placebo favouring melatonin. The authors reported p -values of 0.0019 and 0.02 for this outcome on the basis of datasets produced using two different approaches for dealing with missing data (complete case and last observation carried forward respectively). This outcome was also analysed by the trial authors using a paired t -test, which produced a p -value of 0.057. On the basis of this, we estimated the 95% CI for the mean difference of 21 minutes as -0.7 to 42.7.

For TST based on polysomnography,⁵¹ which was not pooled with the actigraphy-based measures, there was no statistically significant difference ($p=0.26$) between melatonin and placebo, with a reported mean difference of 39.3 minutes (favouring placebo, estimated 95% CI -34.7 to 113.3, $n=10$).

Sleep efficiency

Five RCTs ($n=475$ randomized participants) reported sleep efficiency: that is, the ratio of TST to total time in bed. One RCT used both actigraphy and parent-report,⁴² three used actigraphy data only,^{18,45,46} and one trial used polysomnography.⁵¹ One RCT additionally measured the percentage of children who achieved sleep efficiency in the normative level of more than 85% at the 12-week assessment.⁴⁵

The four RCTs ($n=254$ analysed participants) reporting actigraphy-measured sleep efficiency were pooled in a meta-analysis. There was no statistically significant difference in sleep efficiency with melatonin compared with placebo (Fig. S3, online supporting information; pooled mean difference 4.76% favouring melatonin, 95% CI -0.95 to 10.47, $p=0.10$). Heterogeneity was high ($I^2=94\%$) and this treatment effect is unlikely to be generalizable. The trials did consistently report very small differences between groups in sleep efficiency, favouring melatonin, and these differences are unlikely to be clinically meaningful. A sensitivity analysis removing the results of Wasdell et al.⁴² was performed because the means and SDs of the outcome for this trial indicated that the data may have been non-normally distributed; the pooled mean difference increased slightly to 6.32% (95% CI 0.14–12.51, $p=0.05$). When mean differences adjusted for baseline (Appleton: mean difference 4.0 [SE 2.37]; Cortesi: 10.8 [1.15]; van der Heijden: 4.7 [1.81]) were included in the meta-analysis for the parallel-group RCTs, the overall pooled mean difference was 5.03% (95% CI -0.46 to 10.52, $p=0.07$).

There was no statistically significant difference in effect between the studies where participants received or did not receive a previous parent-directed sleep management intervention (test for subgroup differences: $p=0.34$; $I^2=0\%$). There was a single included trial where the study population primarily had ASD;⁴⁵ the overall mean difference reduced with removal of this study (pooled mean difference 1.75%, 95% CI -0.43 to 3.92, $p=0.12$).

The single RCT reporting parent-reported sleep efficiency ($n=50$ analysed participants) described no statistically significant difference between the groups (mean difference 0.30% favouring melatonin, estimated 95% CI -0.90 to 1.49, $p=0.62$).⁴² However, the means and SDs reported for each arm of the crossover trial in the original paper indicated significant skew and there was no evidence that data were transformed (e.g. log-transformed) to correct for this before analysis; thus the comparison of

unadjusted means is likely to be inappropriate and therefore the results invalid.

One RCT⁴⁵ reported the percentage of children who achieved sleep efficiency in the normative range (>85%) as 46.4% of the melatonin group compared with 0% of the placebo group.

Another RCT⁵¹ reported no statistically significant difference ($p=0.17$) in polysomnography-measured sleep efficiency (mean difference 3.8% favouring melatonin, estimated 95% CI -2.5 to 10.1 , $n=10$). Again, assessment of the means and SDs suggest data may have been skewed, so the results should be treated with caution.

Sleep initiation

Ten RCTs ($n=583$ randomized participants) measured SOL, defined as the time in minutes from the child being placed in bed to sleep onset. Three RCTs reported parent-reported SOL data only;^{47,48,50} two reported actigraphy-measured SOL data only;^{45,52} four reported both actigraphy and parent-reported SOL;^{18,42,43,46} and one reported outcomes using polysomnography.⁵¹ One RCT additionally calculated the percentage of children who either met a standard sleep criterion for SOL of 30 minutes or less, or a reduction of SOL by 50%.⁴⁵ Another RCT used another measure of SOL, defined as the duration of time between taking the medication and falling asleep.⁴⁸

For sleep diary SOL, six trials ($n=223$ analysed participants) were pooled, comprising five crossover trials with a washout period ($n=110$)^{42,43,47,48,50} and one parallel-group trial ($n=113$).¹⁸ There was a statistically significant decrease (favouring melatonin) in SOL (Fig. S4, online supporting information; pooled mean difference -35.6 min, 95% CI -50.9 to -20.3 , $p<0.001$). Heterogeneity was high ($I^2=89%$) and the treatment effect is unlikely to be generalizable, although the individual effect estimates were all in the direction of benefit with melatonin. When mean differences adjusted for baseline (Appleton: mean difference -37.5 [SE 9.1]) were included in the meta-analysis for the parallel-group RCTs, the overall pooled mean difference barely changed (-35.6 min, 95% CI -50.6 to -20.6 , $p<0.001$).

There was a statistically significant difference in effect between the studies of children with ASD and those with mixed and other populations (test for subgroup differences: $p<0.001$; $I^2=93%$). There was a larger difference in the ASD group between melatonin and placebo with a mean reduction in favour of melatonin of 50.9 minutes (95% CI -55.5 to -46.2) compared with 27.4 minutes (95% CI -39.1 to -15.7) in the other group (Fig. S4). A subgroup analysis based on receipt of previous intervention could not be conducted since all of the included trials offered participants an additional intervention before the start of the study.

Five RCTs ($n=264$ analysed participants) reporting actigraphy-measured SOL were pooled, comprising three parallel-group trials ($n=195$)^{18,45,46} and two crossover trials with a washout period ($n=69$).^{42,43} There was a statistically

significant decrease (favouring melatonin) in actigraphy-reported SOL (Fig. S5, online supporting information; pooled mean difference -23.4 , 95% CI -30.9 to -15.8 , $p<0.001$). There was moderate heterogeneity ($I^2=48%$). When mean differences adjusted for baseline (Appleton: mean difference -45.3 [SE 11.9]; Cortesi: -37.4 [7.6]; van der Heijden: -24.3 [5.2]) were included in the meta-analysis for the parallel-group RCTs, the overall pooled mean difference increased to -26.5 minutes (95% CI -35.3 to -17.8 , $p<0.001$). For both sleep diary-reported and actigraphy-measured SOL, the single study with a low risk of bias¹⁸ reported a statistically significant improvement (adjusted and unadjusted) with melatonin compared with placebo.

On the basis of the subgroup analysis there was no statistically significant difference between studies by whether participants had or did not have a previous parent-directed intervention (Fig. S5, online supporting information; test for subgroup differences: $p=0.55$; $I^2=0%$). There was a single included trial where the study population primarily had ASD;⁴⁵ the overall mean difference reduced with removal of this study (pooled mean difference -19.7 min, 95% CI -25.5 to -13.9 , $p<0.001$).

A statistically significant decrease in mean SOL was reported for the crossover RCT without a washout period ($n=12$ analysed participants). However, the mean difference with the comparator group was not reported. When analysed using a paired t -test, the result was not statistically significant (mean difference -28.08 min, estimated 95% CI -2.5 to 58.7 , $p=0.10$).⁵²

For the RCTs that could not be pooled in the meta-analyses, one used an additional indicator of SOL (the percentage of children who met a criterion of SOL of 30min or less, or a reduction of SOL by 50% after intervention), and reported that 39% of the melatonin group versus 0% of the placebo group achieved one of these changes ($n=66$ analysed participants).⁴⁵ The RCT using polysomnography ($n=10$) reported that melatonin significantly reduced the mean SOL compared with placebo (mean difference -11.4 min, estimated 95% CI -17.2 to -5.6 , $p=0.02$).⁵¹

The RCT that measured the duration of time between taking the medication and falling asleep ($n=17$) reported a significant decrease in SOL with melatonin compared with placebo (mean difference 51.7min, estimated 95% CI 16.5 – 86.9 , $p=0.01$).⁴⁸

Sleep maintenance

Six RCTs ($n=142$ randomized participants) reported the number of night wakings.^{41,42,47,48,50,52} Four crossover RCTs with a washout period were pooled ($n=94$ analysed participants).^{42,47,48,50} There was no difference in the mean number of night wakings with melatonin compared with placebo (Fig. S6, online supporting information; pooled mean difference -0.04 , 95% CI -0.22 to 0.13 , $p=0.61$). Heterogeneity was high ($I^2=84%$), although the results consistently favoured melatonin with the exception of the results of Dodge and Wilson.⁵⁰ On the basis of the

subgroup analysis, there was no statistically significant difference in effect between studies for type of neurodisability (test for subgroup differences: $p=0.06$; $I^2=72\%$). A subgroup analysis based on receipt of previous parent-directed sleep management intervention could not be conducted since all of the included trials offered participants such an additional intervention before the start of the study. However, for all included trials, skew for this variable was detected using the summary statistics so the validity of the meta-analysis based on means is questionable and results should be treated with caution.

The crossover study without a washout period reported no significant difference for the melatonin period compared with the placebo period either by the non-parametric analyses or by the paired t -test (reported paired t -test mean difference -0.07 favouring melatonin, $p=0.73$, estimated 95% CI -0.44 to 0.30).⁵² Another RCT reported no statistically significant difference ($p=0.48$) for melatonin compared with placebo (mean difference -0.41 favouring melatonin, 95% CI -1.47 to 0.66) for actigraphy-measured number of waking episodes; however, these data are likely to have a non-normal distribution so analyses based on means, which were conducted by the original authors, may not be appropriate.⁴²

Other outcomes

Six of the 11 RCTs reported other outcomes.^{41,42,45,46,51,52} With the exception of waking after sleep onset (night waking duration and/or frequency after the child falls asleep), which was reported by two studies,^{45,51} each outcome measure was only reported by a single study. These are summarized in Table SIII (online supporting information).

Melatonin regimes

Two crossover RCTs involving a total of 24 randomized participants each compared two different regimens of melatonin. One,⁴⁴ with no washout period, compared controlled-release with fast-release melatonin; the other,⁴⁹ with a 2-week washout period, compared a dose regimen of 5mg with 10mg of melatonin (in this trial the formulation of melatonin was not reported).⁴⁹ The durations of the interventions were 11 days and 2 weeks for Jan et al.⁴⁴ and Hancock et al.⁴⁹ respectively.

The mean ages of participants were 6 years 11 months⁴⁹ and 9 years 4 months.⁴⁴ Children in one RCT⁴⁹ were described as having a variety of severe neurodevelopmental difficulties, whereas in the other⁴⁴ all were diagnosed with tuberous sclerosis complex. Sleep disturbance in both studies was sleep initiation and maintenance.

In one RCT⁴⁴ the inclusion criterion was that children had already been treated with fast-release melatonin for more than 3 months, but slept for fewer than 5 to 6 hours a night. No guidance on sleep management was provided to parents before or during either of the RCTs.

The two RCTs measured four sleep-related outcomes: one⁴⁹ measured TST, SOL, and number of night wakings, whereas the other⁴⁴ measured 'changes in sleep pattern' as

the only outcome. The results of these outcomes are summarized in Table SIV (online supporting information). There was no evidence of benefit in terms of the formulation of melatonin on any of the sleep-related outcomes in the RCT comparing controlled-release and fast-release formulations; the authors reported that possible reasons for the lack of improvement in five children may have included their inability to swallow the controlled-release tablets whole (which was required to enable the coating to provide the controlled-release effect). There was also no evidence of differences in benefit for the RCT that compared a dose of 5mg of melatonin with 10mg of melatonin.

Adverse events

Adverse event data were reported in 11 of the 13 RCTs.^{18,42-46,48-52} However, these data were collected and reported in different ways across the RCTs and no meta-analysis was possible (Table SV, online supporting information). Many adverse event data were collected, including abdominal pain, agitation, anxiety, behaviour change/problems, breathlessness, cold/flu/infection, confusion, constipation, diarrhoea, cough, daytime laziness, decreased mood, dizziness, drowsiness, gastro intestinal illness, impaired appetite, increased activity, increased excitability, mood swings, seizures, rash, hypothermia, fatigue, headache/migraine, 'hung-over feeling', tremor, nausea, vomiting, nightmares, rash, mood swings, hypothermia, irritation to skin hyperactivity, itching or painful lumps on the skin, sleep maintenance insomnia, somnolence skin pigment changes, perspiration, regression of development, and visual disturbance.

Three trials reported that no adverse events were observed or reported.^{44,45,52} The adverse event profile seemed to be similar between the melatonin and placebo groups, suggesting that melatonin was tolerated well.

DISCUSSION

Main findings

We set out to undertake a systematic review of existing literature to identify trials that evaluated the effectiveness of pharmacological intervention(s) for managing sleep disturbance in children with neurodisabilities. Thirteen eligible RCTs were identified, all of which studied melatonin. The quality of the evidence was poor, with only one RCT assessed as having a low risk of bias. Just three child sleep outcomes – variously measured using parent-report and actigraphy – were reported by more than half of the studies, with many other sleep outcomes assessed by individual studies. Eleven trials assessed the effectiveness of melatonin compared with placebo, while two evaluated different regimens of melatonin (controlled-release vs fast-release; and 5mg vs 10mg). We found evidence of benefit for melatonin compared with placebo for TST and SOL; however, the exact extent of the benefit, which children might benefit the most, and the clinical significance of the benefit remain uncertain. There was a lack of evidence around the clinical significance of study findings, with only one trial assigning

clinical significance.¹⁸ There was no statistically significant evidence of benefit for sleep maintenance outcomes, such as number of night wakings; however, some studies may not have been sufficiently powered to detect an effect. In addition, analyses of the comparison of means may not be appropriate for such an outcome as it is likely to be non-normally distributed; authors should take care to assess the normality of their data and consider whether a log-transformation (or other) is required to correct the skew before data are summarized and analysed.³⁹ The same applies to sleep efficiency, which is expressed as a percentage. The single trial comparing controlled-release and fast-release melatonin found no difference in outcomes (although the study authors noted that compliance was compromised in the controlled-release arm). No evidence in difference of benefit for any outcome was found in the single trial comparing 5mg and 10mg of melatonin. On the whole, the studies identified did not assess parent or other child outcomes. All included studies only evaluated follow-up outcomes immediately after completion of the melatonin treatment, meaning we were unable to determine its longer-term effects.

Strengths and limitations

The review design and conduct were partly informed by a public and patient involvement committee comprising professionals and parents of children with neurodisabilities. This has strengthened the findings reported here and enabled the perspectives of parents during the design and conduct of this review to be represented, and provided useful contextual information for the review team.

We undertook thorough and systematic searches of 16 databases, without language restrictions, and included grey literature. To minimize reviewer error and bias, two researchers independently undertook key study processes such as study selection and risk of bias assessment of studies.

Where possible, the synthesis grouped studies by type of neurodisability, and whether the participants received a previous parent-directed sleep management intervention. However, subgroup analyses were restricted by the small number of studies and the likelihood of confounding with other study characteristics. The results of the subgroup analyses should, therefore, be interpreted with caution. Additionally, subgroup analyses are based on summary data and are therefore observational rather than randomized comparisons.

Owing to the nature of the outcomes measured, robust, blinded outcome assessment is often unlikely to be feasible. Although actigraphy-based child sleep outcomes are more objective than parent-reported measures, we did not consider these to be true objective outcomes, with non-blinding unlikely to introduce bias.

Comparison with existing literature

In a recent national research prioritization exercise for children with neurodisability, the management of sleep disturbance was ranked in the top ten research priorities.⁸ Our review was undertaken as part of a larger systematic review

funded by the Health Technology Assessment programme of the UK National Institute for Health Research,³¹ which assessed the effectiveness of pharmacological and non-pharmacological interventions for non-respiratory sleep disturbance in children with neurodisabilities. We did not identify any trials of pharmacological interventions other than melatonin that met our inclusion criteria.

This review includes children with neurodisabilities, with some having comorbidities (e.g. epilepsy). This is a heterogeneous population; and coupled with the small numbers of studies identified, this hindered our ability to accurately estimate the relative impact of melatonin for specific groups of children. This is similar to the conclusion reached by Appleton et al.¹⁸

Implications of findings for clinical practice and research

Owing to uncertainty in the evidence, it is not appropriate to make definitive conclusions about the role of melatonin in the treatment of non-respiratory sleep disturbances in children with neurodisabilities. The meta-analyses found substantial heterogeneity when all the studies were pooled, but subgroup analysis based on whether the population had a diagnosis of ASD or not suggested that the treatment effect, at least with respect to some sleep outcomes, may vary across diagnostic groups with the effect greatest in children with ASD. This might reflect differences in the aetiology of the sleep disturbance in children with ASD compared with children with other neurodisabilities, with relatively low levels of melatonin reported in children with ASD.⁵³⁻⁵⁵

Our findings also indicate that melatonin is one option for the management of sleep initiation in this population. However, given that there was no greater benefit of melatonin in children whose parents had not previously received a parent-directed sleep management intervention, our findings support existing recommendations that melatonin should only be used where sleep problems persist after such an intervention has been implemented.^{20,24} Future research directly comparing the two interventions, or evaluating their parallel use, with respect to the management of sleep initiation would be useful.

Studies included in this review used a wide variety of different outcomes and measurement tools. This limited our ability to undertake effective syntheses of the studies. For example, the only outcome measured by most studies and assessed in similar ways was TST. There was also variability in the outcome domains of interest: for instance, sleep maintenance outcomes were assessed in some studies but not others. Poor reporting by many studies of the specific nature of the children's sleep disturbance meant it was not possible to judge whether this variability in choice of outcome domains was due to differences in sleep disturbance. Furthermore, there was variability in the measure used to assess specific outcome domains. For adverse events there was also variability in the type of adverse event reported, data collection methods used, and reporting.

Thus there is a need for standardization of measures used in future trials, and in terms used to define sleep problems. A

core outcome set would enable comparison between studies and ensure outcomes that are assessed are of relevance to key stakeholders. Future work with families to identify minimally important differences in these outcome measures is also essential. There is also a need to identify other relevant child and parent outcomes as well as the time-points at which outcomes should be measured. In particular, the effect of melatonin on longer-term outcomes, after the cessation of the medication, needs to be assessed. Furthermore, to improve clinical relevance, future studies of melatonin should specifically consider breaking down their included populations according to children's ages, and whether they were recruited from community or clinical cohorts. No other types of pharmacological intervention were identified that met the inclusion criteria for this review. Thus there is a need to evaluate alternative pharmacological treatments that have a different mechanism of action to melatonin as the evidence suggests uncertainty about the magnitude of any benefit of melatonin, and that some populations may benefit less than others. It would also be helpful to compare the effectiveness of melatonin with alternative pharmacological interventions that act on neurophysiological sleep mechanisms, such as sedation. None of the studies on clonidine – a sedative known to be used with children⁵⁶ – met our eligibility criteria; therefore further research is needed to clarify any possible role clonidine may have. Further research is also needed on different formulations and dosages of pharmacological interventions.

CONCLUSIONS

There is some evidence of benefit for melatonin compared with placebo on the management of sleep disturbances in children with neurodisabilities, but the degree and duration of benefit, which children might benefit most, and the significance of the benefit to the well-being of the child/family remain uncertain because of the diverse populations in the studies and the predominantly poor-quality evidence. The adverse event profile suggested that melatonin was well-tolerated. Subgroup analysis suggested that benefit may be greatest for populations with ASD; however, this should be interpreted with caution and further research is required before definitive recommendations can be made.

REFERENCES

1. Tietze AL, Blankenburg M, Hechler T, et al. Sleep disturbances in children with multiple disabilities. *Sleep Med Rev* 2012; **16**: 117–27.
2. Simola P. Sleep problems and their implications from pre-school to school age. PhD thesis. Helsinki, Finland: University of Helsinki, Faculty of Behavioural Sciences, 2014.
3. Wiggs L, Stores G. A randomised controlled trial of behavioural intervention for sleeplessness in children with autism spectrum disorders. *J Sleep Res* 2006; **15**: S83.
4. Doo S, Wing YK. Sleep problems of children with pervasive developmental disorders: correlation with parental stress. *Dev Med Child Neurol* 2006; **48**: 650–5.
5. McConkey R, Kelly F, Craig S. Access to respite breaks for families who have a relative with intellectual disabilities: a national survey. *J Adv Nurs* 2011; **67**: 1349–57.
6. Colten H. Functional and economic impact of sleep loss and sleep-related disorders. In Colten HR, Altevogt BM, editors. *Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem*. Washington, DC: National Academies Press, 2006: 137–72.
7. Hillman DR, Murphy AS, Pezzullo L. The economic cost of sleep disorders. *Sleep* 2006; **29**: 299–305.
8. Morris C, Simkiss D, Busk M, et al. Setting research priorities to improve the health of children and young people with neurodisability: a British Academy of Childhood Disability-James Lind Alliance Research Priority Setting Partnership. *BMJ Open* 2015; **5**: e006233.
9. Beresford B, Stuttard L, Clarke S, Maddison J, Beecham J. Interventions E and F: individually delivered sleep management interventions. In: *Managing behaviour and sleep problems in disabled children: an investigation into the effectiveness and costs of parent-training interventions*. Department for Education Research Report C4EO/DfE 2494. London: Department for Education, 2012: 189–208.
10. Beresford B. *Expert Opinions: A National Survey of Parents Caring for a Severely Disabled Child*. Bristol, UK: Policy Press, 1995.

ACKNOWLEDGEMENTS

We thank our parent advisors for their interest and enthusiasm in the project and their contributions at project meetings. We thank Kate Baxter for her contribution to the quality appraisal work. We also thank Katherine Chatterton for her assistance with sourcing full-text articles. This project was funded by the Health Technology Assessment (HTA) programme of the UK National Institute for Health Research (NIHR) (project number 14/212/02). Further information is available at <https://www.journalslibrary.nihr.ac.uk/programmes/hta/1421202/>. The views expressed are those of the author(s) and not necessarily those of the National Health Service, the NIHR, or the Department of Health and Social Care. BB and MT were authors on studies included in the review. Neither were involved in quality assessment or data extraction of studies. CM is a member of the NIHR Health Technology Assessment and Efficacy and Mechanism Evaluation Editorial Board. CH is a member of the HTA commissioning board. All other authors have stated that they had no interests that might be perceived as posing a conflict or bias.

SUPPORTING INFORMATION

The following additional material may be found online:

Table S1: Inclusion and exclusion criteria

Table SII: Characteristics of studies of melatonin interventions

Table SIII: Other outcome results from studies of pharmacological interventions

Table SIV: Outcome results from trials comparing melatonin doses

Table SV: Adverse events in studies evaluating melatonin

Appendix S1: Search strategy in Medline.

Figure S1: Flow chart of the study selection process.

Figure S2: Sleep diary-reported total sleep time: melatonin versus placebo and prior intervention subgroup analysis.

Figure S3: Actigraphy-measured sleep efficiency: melatonin versus placebo.

Figure S4: Sleep diary-reported sleep onset latency: melatonin versus placebo.

Figure S5: Actigraphy-measured sleep onset latency: melatonin versus placebo.

Figure S6: Parent-reported number of night wakings: melatonin versus placebo.

11. Allard A, Fellowes A, Shilling V, Janssens A, Beresford B, Morris C. Key health outcomes for children and young people with neurodisability: qualitative research with young people and parents. *BMJ Open* 2014; **4**: e004611.
12. Stores G. Multifactorial influences, including comorbidities, contributing to sleep disturbance in children with a neurodevelopmental disorder. *CNS Neurosci Ther* 2016; **22**: 875–9.
13. Appleton RE, Gringras P. Melatonin: helping to MEND impaired sleep. *Arch Dis Child* 2013; **98**: 216–17.
14. MacLeod RL, Keen DV. Innovations in practice: ‘off-label’ clonidine: UK paediatric and child and adolescent psychiatry prescribing practice for sleep problems. *Child Adolesc Psychiatr Ment Health* 2014; **19**: 147–50.
15. Heussler H, Chan P, Price AM, Waters K, Davey MJ, Hiscock H. Pharmacological and non-pharmacological management of sleep disturbance in children: an Australian Paediatric Research Network survey. *Sleep Med* 2013; **14**: 189–94.
16. Waldron D, Bramble D, Gringras P. Melatonin: prescribing practices and adverse events. *Arch Dis Child* 2005; **90**: 1206–7.
17. Owens JA, Rosen CL, Mindell JA. Medication use in the treatment of pediatric insomnia: results of a survey of community-based pediatricians. *Pediatrics* 2003; **111**: e628–35.
18. Appleton RE, Jones AP, Gamble C, et al. The use of melatonin in children with neurodevelopmental disorders and impaired sleep: a randomised, double-blind, placebo-controlled, parallel study (MENDS). *Health Technol Assess* 2012; **16**: i–239.
19. Galland BC, Mitchell EA. Helping children sleep. *Arch Dis Child* 2010; **95**: 850–3.
20. Bruni O, Novelli L. Sleep disorders in children. *BMJ Clin Evid* 2010; **2010**: 2304.
21. National Institute for Health and Care Excellence. Autism: The Management and Support of Children and Young People on the Autism Spectrum. CG 170. London, UK: National Institute for Health and Care Excellence, 2013.
22. Owens JA, Moturi S. Pharmacologic treatment of pediatric insomnia. *Child Adolesc Psychiatr Clin N Am* 2009; **18**: 1001–16.
23. Scottish Intercollegiate Guidelines Network (SIGN). Assessment, Diagnosis and Interventions for Autism Spectrum Disorders. Edinburgh: SIGN; 2016. (SIGN publication no. 145). Available from: <http://www.sign.ac.uk> (accessed 1 June 2016).
24. NICE. Autism: The Management and Support of Children and Young People on the Autism Spectrum. Clinical Guideline 170. London: NICE; 2013.
25. Barrett JR, Tracy DK, Giaroli G. To sleep or not to sleep: a systematic review of the literature of pharmacological treatments of insomnia in children and adolescents with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol* 2013; **23**: 640–7.
26. Cortese S, Brown TE, Corkum P, et al. Assessment and management of sleep problems in youths with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2013; **52**: 784–96.
27. Malow BA, Byars K, Johnson K, et al. A practice pathway for the identification, evaluation, and management of insomnia in children and adolescents with autism spectrum disorders. *Pediatrics* 2012; **130**(Suppl. 2): S106–24.
28. Guérolé F, Godbout R, Nicolas A, Franco P, Claustrat B, Baleyte JM. Melatonin for disordered sleep in individuals with autism spectrum disorders: systematic review and discussion. *Sleep Med Rev* 2011; **15**: 379–87.
29. Bendz LM, Scates AC. Melatonin treatment for insomnia in pediatric patients with attention-deficit/hyperactivity disorder. *Ann Pharmacother* 2010; **44**: 185–91.
30. Cohen-Zion M, Ancoli-Israel S. Sleep in children with attention-deficit hyperactivity disorder (ADHD): a review of naturalistic and stimulant intervention studies. *Sleep Med Rev* 2004; **8**: 379–402.
31. Beresford B, McDaid C, Parker A, et al. Pharmacological and non-pharmacological interventions for non-respiratory sleep disturbance in children with neurodisabilities: a systematic review. *Health Technol Assess* 2018; **22**(60): 17–21.
32. Scantlebury A, McDaid C, Dawson V, et al. Non-pharmacological interventions for non-respiratory sleep disturbance in children with neurodisabilities: a systematic review. *Dev Med Child Neurol* 2018; **60**: 1076–92.
33. Centre for Reviews and Dissemination. Systematic Reviews: CRD’s Guidance for Undertaking Reviews in Health Care. York, UK: Centre for Reviews and Dissemination, University of York, 2009.
34. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e1000097.
35. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. London: Cochrane; 2011. Available from: <http://handbook.cochrane.org> (accessed 1 September 2018)
36. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**: d5928.
37. McDaid C, Griffin S, Weatherley H, et al. Continuous positive airway pressure devices for the treatment of obstructive sleep apnoea-hypopnoea syndrome: a systematic review and economic analysis. *Health Technol Assess* 2009; **13**: 1–162.
38. Curtin F, Elbourne D, Altman DG. Meta-analysis combining parallel and cross-over clinical trials. III: the issue of carry-over. *Statist Med* 2002; **21**: 2161–73.
39. Altman DG, Bland JM. Detecting skewness from summary information. *BMJ* 1996; **313**: 1200.
40. Higgins J, Thompson S, Deeks J, Altman D. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–60.
41. Camfield P, Gordon K, Dooley J, Camfield C. Melatonin appears ineffective in children with intellectual deficits and fragmented sleep: six “N of 1” trials. *J Child Neurol* 1996; **11**: 341–3.
42. Wasdell MB, Jan JE, Bomben MM, et al. A randomized, placebo-controlled trial of controlled release melatonin treatment of delayed sleep phase syndrome and impaired sleep maintenance in children with neurodevelopmental disabilities. *J Pineal Res* 2008; **44**: 57–64.
43. Weiss MD, Wasdell MB, Bomben MM, Rea KJ, Freeman RD. Sleep hygiene and melatonin treatment for children and adolescents with ADHD and initial insomnia. *J Am Acad Child Adolesc Psychiatry* 2006; **45**: 512–19.
44. Jan JE, Hamilton D, Seward N, Fast DK, Freeman RD, Laudon M. Clinical trials of controlled-release melatonin in children with sleep-wake cycle disorders. *J Pineal Res* 2000; **29**: 34–9.
45. Cortesi F, Giannotti F, Sebastiani T, Panunzi S, Valente D. Controlled-release melatonin, singly and combined with cognitive behavioural therapy, for persistent insomnia in children with autism spectrum disorders: a randomized placebo-controlled trial. *J Sleep Res* 2012; **21**: 700–9.
46. Van der Heijden KB, Smits MG, Van Someren EJW, Ridderinkhof KR, Gunning WB. Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia. *J Am Acad Child Adolesc Psychiatry* 2007; **46**: 233–41.
47. Garstang J, Wallis M. Randomized controlled trial of melatonin for children with autistic spectrum disorders and sleep problems. *Child Care Health Dev* 2006; **32**: 585–9.
48. Wright B, Sims D, Smart S, et al. Melatonin versus placebo in children with autism spectrum conditions and severe sleep problems not amenable to behaviour management strategies: a randomised controlled crossover trial. *J Autism Dev Disord* 2011; **41**: 175–84.
49. Hancock E, O’Callaghan F, Osborne JP. Effect of melatonin dosage on sleep disorder in tuberous sclerosis complex. *J Child Neurol* 2005; **20**: 78–80.
50. Dodge NN, Wilson GA. Melatonin for treatment of sleep disorders in children with developmental disabilities. *J Child Neurol* 2001; **16**: 581–4.
51. Jain SV, Horn PS, Simakajornboon N, et al. Melatonin improves sleep in children with epilepsy: a randomized, double-blind, crossover study. *Sleep Med* 2015; **16**: 637–44.
52. Wirojanan J, Jacquemont S, Diaz R, et al. The efficacy of melatonin for sleep problems in children with autism, fragile X syndrome, or autism and fragile X syndrome. *J Clin Sleep Med* 2009; **5**: 145–50.
53. Melke J, Goubran Botros H, Chaste P, et al. Abnormal melatonin synthesis in autism spectrum disorders. *Mol Psychiatry* 2008; **13**: 90–8.
54. Kulman G, Lissoni P, Rovelli F, Roselli MG, Brivio F, Sequeri P. Evidence of pineal endocrine hypofunction in autistic children. *Neuroendocrinol Lett* 2000; **21**: 31–4.
55. Tordjman S, Anderson GM, Pichard N, Charbuy H, Touitou Y. Nocturnal excretion of 6-sulphatoxymelatonin in children and adolescents with autistic disorder. *Biol Psychiatry* 2005; **57**: 134–8.
56. Nguyen M, Tharani S, Rahmani M, Shapiro M. A review of the use of clonidine as a sleep aid in the child and adolescent population. *Clin Pediatr* 2014; **53**: 211–16.