BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-065520
Article Type:	Protocol
Date Submitted by the Author:	08-Jun-2022
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Keywords:	SLEEP MEDICINE, Paediatric neurology < NEUROLOGY, Developmental neurology & neurodisability < PAEDIATRICS

Melatonin for sleep disorders in children with neurodevelopmental disorders: a protocol for a systematic review with meta-analysis and Trial Sequential Analysis of randomised clinical trials

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Word count: 4,362

Abstract

Introduction: Neurodevelopmental disorders are a group of disorders thought to be associated with the functioning of the brain and nervous system. Children with neurodevelopmental disorders often have sleep-related comorbidities that may negatively affect quality of life for both the children and their families. Melatonin is one of the most used interventions in children with neurodevelopmental disorders and sleep disorders. Previous reviews have investigated the effects of melatonin for sleep disorders in children with neurodevelopmental disorders, but these had important limitations, such as inadequate analysis of adverse effects, small sample sizes, and short follow-up. Moreover, new trials have been published recently. We aim to conduct this review to include all available evidence.

Methods and analysis: This is a protocol for a systematic review with meta-analysis and Trial Sequential Analysis of randomised clinical trials. The protocol is reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols. We will search for published and unpublished trials in major medical databases and trial registers. We will also request clinical study reports from regulatory authorities and pharmaceutical companies. Review authors working in pairs will screen reports, extract data, and conduct risk of bias assessments using the Cochrane Risk of Bias tool (version 2). We will include randomised clinical trials comparing melatonin versus placebo or no intervention for sleep disorders in children with neurodevelopmental disorders. Primary outcomes will be total sleep time and adverse effects. Secondary outcomes will be quality of life of the child and caregivers and sleep onset latency. Data will be analysed using random-effects and fixed-effect meta-analyses. Certainty of evidence will be assessed with GRADE.

Ethics and dissemination: Ethical approval was not required for this protocol. The results of the systematic review will be published in a peer-reviewed journal to help inform future research and clinical practice.

PROSPERO registration number: CRD42022337530

Keywords: Melatonin; neurodevelopmental disorders; sleep disorders; children; systematic review

Strengths and limitations of this study

- This systematic review will investigate the effects of melatonin for sleep disorders in children with neurodevelopmental disorders. The results will inform future research and clinical practice.
- The predefined methodology is based on the Cochrane Handbook, the eight-step procedure suggested by Jakobsen et al., Trial Sequential Analysis, and GRADE assessment to consider the risks of random errors, systematic errors, publication bias, heterogeneity, and external validity.
- The systematic review will include both published and unpublished trials.
- We assess multiple outcomes and subgroup analyses which will increase the risks of type I errors.

Introduction

Description of the condition

Neurodevelopmental disorders are a group of disorders thought to be associated with the functioning of the brain and nervous system.[1] Neurodevelopmental disorders are usually diagnosed in childhood and include neurological disorders such as cerebral palsy, epilepsy, Angelman syndrome, Down's syndrome, Fragile X syndrome, Prader-Willi syndrome, Rett syndrome, Smith-Magenis syndrome, Williams syndrome, and non-specific intellectual disability, along with some psychiatric disorders including autism spectrum disorder, attention-deficit/hyperactivity disorder (ADHD).[1 2] Children with neurodevelopmental disorders may experience difficulties with learning, attention, behaviour, speech, motor skills, and other neurological functions.[1]

The impact of sleep disturbances was recently ranked as a top 10 research priority within the topics of children with neurodevelopmental disorders by a UK partnership of patients, carers, and clinicians.[3] Children with neurodevelopmental disorders often have sleep-related comorbidities, including sleep disorders such as insomnia disorder, hypersomnolence disorder, narcolepsy, breathing-related sleep disorders, circadian rhythm sleep disorders, non-rapid eye movement (REM) sleep arousal disorders, nightmare disorder, and REM sleep behaviour disorder.[2 4] Studies have shown the prevalence of comorbid neurodevelopmental disorders and sleep disorders is between 25% to 86% compared to 1% to 6% in the general paediatric population.[4-8] Sleep disorders may further enhance problems with learning and behaviour in children with neurodevelopmental disorders,[4-8] and often have a negative effect on quality of life for both the children and their families.[9 10]

Description of the intervention

Melatonin is a naturally occurring hormone in both humans and animals.[11] Previously, melatonin was derived from animal pineal tissue,[11] but it is now developed synthetically and distributed in different forms, including capsules, tablets, gummies, and liquids.[12] Melatonin is available in many countries either sold as prescription-only medicine or as over-the-counter medicine to treat sleep disorders in both children and adults, as it is hypothesised to be associated with few adverse

effects.[11 13] Furthermore, melatonin is one of the most commonly used interventions in children with neurodevelopmental disorders and sleep disorders.[14-18] The dosage recommendations vary according to country, but the UK National Health Service currently recommend treatment up to 13 weeks of 2 mg one to two hours before bedtime for adults with sleep problems.[19] However, there are currently no clear guidelines for prescribing melatonin for children and adolescents with neurodevelopmental disorders.[5 11]

How the intervention might work

The understanding of melatonin's underlying mechanisms has previously been extrapolated from animals to humans, but the exact physiological mechanisms of melatonin in humans remain unclear.[20-22] Melatonin is a neurohormone primarily secreted by the pineal gland.[13] Melatonin mediates dark signals, since the secretion of melatonin is related to darkness, and it is therefore associated with the circadian rhythm in humans.[13 17] The secretion of melatonin is regulated by the suprachiasmatic nucleus in the hypothalamus, and the production of melatonin depends on darkness, as the exposure to light inhibits secretion.[11 23] A decrease in the secretion of melatonin has been associated with aging and different diseases, and synthetic melatonin may theoretically reduce sleep disturbance related to melatonin deficiency.[13 24] Previous studies have shown that melatonin improves total sleep time, sleep onset latency, and sleep quality for adults with sleep disorders, but the effects seem small.[13 25] Furthermore, some studies suggest that children with autistic spectrum disorders have abnormal secretions of melatonin.[6 26 27] For these theoretical reasons, children with neurodevelopmental disorders may benefit from melatonin.

Why it is important to do this review

A systematic review published in 2018 investigated the effects of melatonin for sleep problems in children with neurodevelopmental disorders.[5] The review concluded that melatonin was safe and effective in improving sleep for children with neurodevelopmental disorders.[5] Another systematic review published in 2019 investigated the effects of oral melatonin for non-respiratory sleep disturbances in children with neurodisabilities.[28] This review concluded that there was some evidence of beneficial effects, but the extent of these effects was unclear due to the poor quality of

the evidence.[28] This review also concluded that melatonin was well-tolerated, as comparable adverse effects were found in the melatonin and placebo groups.[28]

These previous reviews had important limitations. The conclusions were affected by a high degree of heterogeneity, high and unclear risk of bias in the included trials, and small sample sizes.[5 28] Furthermore, the duration of treatment was limited to a maximum of 13 weeks, and adverse events were not adequately reported or analysed in either of the reviews.[5 28]

In recent studies, it has been questioned whether higher levels of melatonin are associated with delayed puberty, and other adverse effects of melatonin are also theoretically possible.[29-31] In 2021, a two-year follow-up of a trial investigating the treatment with melatonin in 119 children with autism spectrum disorder was published.[32] This trial concluded that melatonin was safe and effective for long-term treatment in children.[32] Other, new randomised clinical trials might have been published since the last published systematic reviews, and on-going trials have been identified on ClinicalTrials.gov.[33 34] These trials may contribute important information about the use of melatonin in children with neurodevelopmental disorders, including adverse effects. Therefore, there is a need for a systematic review to shed light on this important topic and to assess whether the beneficial effects outweigh any harmful effects. Our systematic review will take risks of systematic errors ('bias'), risks of random errors ('play of chance'), and the certainty of the evidence into consideration when assessing the effects of melatonin for sleep disorders in children with neurodevelopmental disorders.

Methods and analysis

The present protocol has been registered in the PROSPERO database (CRD42022337530) and is reported according to the guidance suggested in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement (please find the checklist in **supplemental material 1**).[35 36]

Criteria for considering studies for this review

Types of studies

We will include randomised clinical trials irrespective of trial design (including crossover trials), setting, publication status, publication year, and language. We will not include quasi-randomised trials, cluster-randomised trials, or observational studies.

Types of participants

We will include trials randomising children and adolescents (below 18 years of age) with neurodevelopmental disorders, such as autism spectrum disorder, ADHD, cerebral palsy, epilepsy, Angelman syndrome, Down's syndrome, Fragile X syndrome, Prader-Willi syndrome, Rett syndrome, Smith-Magenis syndrome, Williams syndrome and non-specific intellectual disability. Trials will be included if the disorders of the participants are diagnosed by standardised diagnostic criteria, such as the Diagnostic and Statistical Manual of Mental Disorders[37] or International Classification of Diseases[38] or where the diagnosis or designation of neurodevelopmental disorder is made by a clinician. The participants also need to have a diagnosis of any type of sleep disorder (as defined by trialists), such as insomnia disorder, hypersomnolence disorder, narcolepsy, breathing-related sleep disorders, circadian rhythm sleep disorders, non-REM sleep arousal disorders, nightmare disorder, and REM sleep behaviour disorder.

We will include participants irrespective of sex, comorbidities, demographic factors, the stage of their condition, and the care setting. If a trial reports data where only a subset of participants is eligible (e.g. a combination of children and adults), we will only include data from those participants that fulfil the inclusion criteria, and we will therefore require subset data for the specific group to be available.

Types of interventions

We will include trials where participants in the experimental group are given melatonin at any dose, form (e.g. tablet, capsules, gummies, liquids), duration of administration, type of administration (e.g. oral), timing of administration, and setting. We will include trials where participants receive a co-intervention (e.g. methylphenidate for participants with ADHD), providing it is delivered equally

(in any aspect, e.g. same dose, equal subset of population receiving co-intervention, etc.) in the experimental group and the control group.

Comparators

As control intervention we will accept placebo or 'no intervention'.

Types of outcome measures

Primary outcomes

1) Total sleep time (in minutes using any type of measurement, e.g. polysomnography, actigraphy, self-report, or parent-report).
2) Adverse effects
   a) The proportion of participants with one or more serious adverse events. We will use the International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use—Good Clinical Practice (ICH-GCP) definition of a serious adverse event, which is any untoward medical occurrence that resulted in death, was life-threatening, required hospitalisation or prolonging of existing hospitalisation, resulted in persistent or significant disability or jeopardised the participant.[39] If the trialists do not use the ICH-GCP definition, we will include the data if the trialists use the term 'serious adverse event'. If the trialists do not use the ICH-GCP definition nor use the term serious adverse event, then we will also include the data provided the event clearly fulfils the ICH-GCP definition for a serious adverse event. We will secondly analyse each type of serious adverse event separately.
   b) The proportion of participants with one or more non-serious adverse events (any adverse event not classified as serious). We will also analyse each type of adverse event separately.

Secondary outcomes

1) Quality of life of the child (any valid continuous scale, e.g. Child Quality of Life Questionnaire).[40]
2) Quality of life of the parents/caregivers (any valid continuous scale, e.g. SF-36).[41]

3) Sleep onset latency (in minutes using any type of measurement, e.g. polysomnography, actigraphy, self-report, or parent-report).

Exploratory outcomes

1) Quality of sleep (any valid continuous scale), such as the Pittsburgh Sleep Quality Index.[42]
2) Delayed puberty or any reports of hormonal changes.
3) Any continuous scale assessing adverse effects (e.g. Pediatric Adverse Event Rating Scale).[43]

Timing of outcome assessment

We will include outcome data recorded at the end of the treatment period primarily and at maximum follow-up secondarily.

Search methods for identification of studies

Electronic searches

We will search the following:

- Cochrane Central Register of Controlled Trials (CENTRAL; current issue) in The Cochrane Library
- MEDLINE Ovid (1946 onwards)
- Embase Ovid (1974 onwards)
- LILACS (Latin American and Caribbean Health Science Information database; 1982 onwards)
- Science Citation Index Expanded (Web of Science; 1964 onwards)
- Conference Proceedings Citation Index-Science (Web of Science; 1990 onwards)
- PsycINFO (1967 onwards)
- ClinicalTrials.gov
- International Clinical Trials Registry Platform (ICTRP)

Please see **supplemental material 2** for the search strategy.

Searching other resources

We will check reference lists of all included trials and any relevant systematic reviews to identify additional trials. We will also search for errata and retraction statements for the included trials. We will search websites of pharmaceutical companies (e.g. Natrol, Neurim Pharmaceuticals, Takeda Pharma), websites of U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) to identify relevant trials. We will request FDA, EMA, and national medicines agencies to provide all publicly releasable information about relevant studies that were submitted for marketing approval, including clinical study reports. We will contact authors of eligible trials and other experts to identify any relevant trials (published or unpublished).

Data collection and analysis

We will perform and report the review based on the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions. [44] Analyses will be performed using Stata version 17[45] and Trial Sequential Analysis (TSA).[46 47]

Selection of studies

Two review authors will independently screen titles and abstracts using Covidence.[48] We will mark articles that clearly do not meet the eligibility criteria as excludes, while potentially eligible articles will go through to the next phase. We will retrieve all relevant full-text study reports/publications, and two review authors will independently screen the full text to identify and record reasons for exclusion of the ineligible trials. The two review authors will resolve any disagreement through discussion, or, if required, they will consult with a third author (JCJ). We will illustrate the selection process of the trials in a PRISMA flow diagram.[49] If multiple reports are available for a single trial, all reports will be grouped under a single reference ID.

Data extraction and management

Review authors in pairs will independently extract data from the included trials using a pilot tested data extraction form. Disagreements will be resolved through internal discussion or, if required, by discussion with a third author (JCJ). The two review authors will assess all publications of a trial

together to evaluate all available data simultaneously. We will contact trial authors by email to obtain any additional data, which may not have been reported sufficiently in the publication. We will extract the following data:

- Methods: trial setting, trial location, trial design, trial duration, duration of follow-ups, date of the trial, estimation of sample size, inclusion criteria, and exclusion criteria
- Participants: number randomised, number analysed for each outcome, number lost to follow-up, age (mean and standard deviation), sex ratio, and diagnostic criteria
- Interventions: type, dose, timing, and duration of intervention
- Control: type, dose, timing, and duration of comparison
- Co-intervention: type, dose, timing, and duration of co-interventions
- Outcomes: primary, secondary, and exploratory outcomes at the reported time points
- Notes: trial funding and conflicts of interest of the trial authors

One review author will transfer the data to Stata. We will double-check the data by comparing the data presented in the review to the data extraction form.

Assessment of risk of bias in included studies

Our bias risk assessment will be based on the Cochrane Risk of Bias tool—version 2 (RoB 2) as recommended in the Cochrane Handbook of Systematic Reviews of Interventions.[44] We will evaluate the methodology in respect of the following bias domains:

- Bias arising from the randomisation process
- Bias due to deviations from the intended interventions (effect of assignment to intervention).
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

Review authors in pairs will independently assess the risk of bias using a template (available at https://www.riskofbias.info/). Disagreements will be resolved through internal discussion or, if required, by discussion with a third author (JCJ). We will use the signalling questions in the RoB 2 tool to rate each domain at either 'low risk of bias', 'some concerns', or 'high risk of bias'. We will assess all domains of risk of bias for each outcome in each trial. The overall risk of bias of a result

will be judged to be low if all domains are assessed at low risk of bias. If one or more domains are assessed at either some concerns or high risk of bias, the overall risk of bias will be assessed at high. We will assess the risk of bias for the outcomes of the included trials presented in the 'Summary of findings' table (primary and secondary outcomes at end of treatment). The risk of bias assessments will be illustrated in a table (using https://www.riskofbias.info/), and the assessments will be used to conduct subgroup analyses. The risk of bias assessment will also be used to inform GRADE and the 'Summary of findings' table. For trials using crossover design, only data from the first period will be assessed.

Measures of treatment effect

Continuous outcomes

We will calculate mean differences (MDs) and consider calculating standardised mean differences (SMD) with 95% CIs for continuous outcomes. We will enter data presented as a scale with a consistent direction of effect. We will primarily analyse scores assessed at single time points. If only changes from baseline scores are reported, we will analyse the results together with follow-up scores for MD (not for SMD).[44] If standard deviations (SDs) are not reported, we will calculate the SDs using trial data, if possible, or request such data from the authors.

Dichotomous outcomes

We will calculate risk ratios (RRs) with 95% confidence intervals (CI) for dichotomous outcomes.

Unit of analysis issues

We will only include randomised clinical trials. Trials using a crossover design will be treated as parallel trials, since only data from the first period will be included.[44] Where multiple trial arms are reported in a single trial, we will include only the relevant arms. For trials with multiple relevant experimental or control groups, we will combine the groups as appropriate.[44]

If, during the selection of trials, we identify observational studies (i.e. quasi-randomised studies, cohort studies, or patient reports) that report adverse events associated with melatonin, we will review these studies for report on adverse events. We will not specifically search for observational

studies for inclusion in this review, which is a limitation in our review. We will not analyse the extracted data on harms from non-randomised clinical studies together with the data on harms from the randomised clinical trials included in the review; neither will we assess the bias risk in these studies. However, we will refer to the extracted narrative data on harm with a link to a table in an appendix. We are aware that the decision not to search for all observational studies might bias our review towards assessment of benefits and might overlook certain harms such as late or rare harms. If we demonstrate benefits from the use of melatonin in children and adolescents with neurodevelopmental disorders, then a systematic review of harms in observational studies ought to be launched.[50]

Dealing with missing data

We will, as the first option, contact all trial authors to obtain information on missing data (i.e. for data extraction and for assessment of risk of bias, as specified above). We will use intention-to-treat data if provided by the trialists.[51]

Dichotomous outcomes

We will not impute missing values for any outcomes in our primary analysis. In our sensitivity analyses (see below), we will impute data.

Continuous outcomes

We will not impute missing values for any outcomes in our primary analysis. In our sensitivity analysis (see below) for continuous outcomes, we will impute data.

Assessment of heterogeneity

We will investigate forest plots to visually assess for signs of heterogeneity. We will also estimate the presence of statistical heterogeneity by a chi^2 test (threshold $P < 0.05$) and measure the quantities of heterogeneity by the I^2 statistic.[52 53] We will investigate possible heterogeneity through subgroup analyses. We may ultimately decide that a meta-analysis should be avoided.[44] We will interpret I^2 heterogeneity as suggested by the Cochrane Handbook for Systematic Reviews of Interventions.[44] If we identify substantial heterogeneity ($I^2 > 50\%$), we will report it, and explore the

possible causes by prespecified subgroup analyses. We will carefully investigate trial characteristics and report if we find unexpected heterogeneity due to clinical or methodological factors. Ultimately it will be decided if meta-analysis should be avoided.

Assessment of reporting biases

We will use funnel plots to assess reporting bias if ten or more trials are included in an outcome.[44] We will visually inspect funnel plots to assess the risk of small trial effects that could potentially reflect publication bias. We are aware of the limitations of a funnel plot (i.e. a funnel plot assesses bias due to small sample size). From this information, we will assess possible risk of publication bias. For dichotomous outcomes, we will test asymmetry with the Harbord test[54] if τ^2 is less than 0.1 and with the Rücker test if τ^2 is more than 0.1. For continuous outcomes, we will use the regression asymmetry test[55] and the adjusted rank correlation.[56]

Data synthesis

Meta-analysis

We will undertake this meta-analysis according to the recommendations stated in the Cochrane Handbook for Systematic Reviews of Interventions,[44] Keus et al.,[57] and our eight-step procedure suggested by Jakobsen et al.[58] We will assess our intervention effects with both random-effects meta-analyses (Hartung-Knapp-Sidik-Jonkman)[59] and fixed-effect meta-analyses (Mantel-Haenszel for dichotomous outcomes and inverse variance for continuous outcomes),[44 60] and report both meta-analysis results.[58] We will primarily report the most conservative result (widest confidence interval and highest P value), and report the less conservative result as a sensitivity analysis.[58] As two primary outcomes are specified, we will consider a P value of 0.025 or less as the threshold for statistical significance for all outcomes.[58] Our primary analyses will include all trials. Where data are only available from one trial, we will use Fisher's exact test for dichotomous data and Student's t-test for continuous data.[61 62]

Trial Sequential Analysis

Traditional meta-analysis runs the risk of random errors due to sparse data and repetitive testing of accumulating data when updating reviews. We wish to control for the risks of type I and type II

errors. We will therefore perform Trial Sequential Analysis on all outcomes, in order to calculate the required information size (i.e. the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) and the cumulative Z-curve's breach of relevant trial sequential monitoring boundaries.[47 63-68] A more detailed description of Trial Sequential Analysis can be found in the manual[47] and at www.ctu.dk/tsa/. For dichotomous outcomes, we will estimate the required information size based on the observed proportion of patients with an outcome in the control group (the cumulative proportion of patients with an event in the control groups relative to all patients in the control groups), a relative risk reduction or a relative risk increase of 25%, an alpha of 2.5% for all our outcomes, a beta of 10%, and the observed diversity as suggested by the trials in the meta-analysis. For continuous outcomes, we will use the observed standard deviation (SD) in the control group, a mean difference of 30 minutes when assessing total sleep time; otherwise, a mean difference of the observed SD/2, an alpha of 2.5% for all outcomes, a beta of 10%, and the observed diversity of the trials in the meta-analysis. We will only use the diversity-adjusted required information size for random-effects Trial Sequential Analyses.

Subgroup analysis and investigation of heterogeneity

We will perform the following subgroup analyses on the primary outcomes:

1. Type of neurodevelopmental disorder: this subgroup analysis will assess whether the effects of melatonin are different depending on the neurodevelopmental disorder of the child.
2. Age (below 12 years compared to above 12 years and preschool-age children compared to school-age children (as defined by trialists)): this will assess whether the effects of melatonin vary depending on the age of the participants.
3. Type of comparator (placebo or no intervention): this subgroup analysis will assess whether the effects of melatonin vary depending on the comparator.
4. Timing of the melatonin administration. If data are available, we will use the following comparisons: < 2 hours before bedtime, 2-4 hours before bedtime, or 4-8 hours before bedtime. If not, we will use definitions by trialists. This subgroup analysis is relevant, because the timing of administration may affect the outcomes.[69-71]
5. Type of sleep disorder: this subgroup analysis will assess whether the effects of melatonin vary depending on the type of sleep disorder.

6. Trials at high risk of bias compared to trials at low risk of bias: this subgroup analysis will assess whether the effects of melatonin vary depending on the risk of bias of the included trials.
7. Duration of trials: this subgroup analysis will assess whether the effects of melatonin vary depending on the duration of the included trials.

Post-hoc subgroup analyses might be warranted if unexpected clinical or statistical heterogeneity is identified during the analysis of the review results.[58] We will disclose any new subgroup analyses not reported in this protocol in the 'Differences between protocol and review' section of the systematic review.

Sensitivity analysis

To assess the potential impact of the missing data, we will perform the two following sensitivity analyses on the primary outcomes:

'Best-worst-case' scenario: we will assume that all participants lost to follow-up in the experimental group had beneficial outcomes (no serious adverse events/improved quality of sleep defined as the group mean plus two SDs).[58] We will accordingly assume that all participants lost to follow-up in the control group had poor outcomes (serious adverse events/deteriorated quality of sleep defined as the group mean plus two SDs).[58]

'Worst-best-case' scenario: we will assume that all participants lost to follow-up in the experimental group had poor outcomes (serious adverse events/deteriorated quality of sleep defined as the group mean plus two SDs).[58] We will accordingly assume that all participants lost to follow-up in the control group had beneficial outcomes (no serious adverse events/improved quality of sleep defined as the group mean plus two SDs).[58]

We will present the results of both scenarios in our review.

We will assess the potential impact of missing SDs for quality of sleep as follows: when SDs are missing, and it is not possible to calculate them, we will impute SDs from trials with similar

populations and low risk of bias. If we find no such trials, we will impute SDs from trials with a similar population. As the final option, we will impute SDs from all trials. We will present results of this scenario in our review.

Summary of findings and assessment of the certainty of the evidence

Review authors in pairs will use GRADE to assess the certainty of the body of evidence associated with each of the primary and secondary outcomes at end of treatment in our review. We will construct 'Summary of findings' tables using the GRADEpro GDT.[72] The GRADE approach appraises the certainty of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. We will assess the GRADE levels of evidence as either high, moderate, low, or very low certainty on the following quality measures: risk of bias (the overall risk of bias will be used for each outcome), directness of the evidence, heterogeneity of the data, precision of effect estimates (assessed by TSA), and risk of publication bias.[72] We will downgrade the evidence by one or two levels due to serious or very serious issues. We will downgrade imprecision in GRADE by two levels if the accrued number of participants is below 50% of the DARIS, and one level if between 50 and 100% of DARIS. We will not downgrade if the cumulative Z-curve crosses the monitoring boundaries for benefit, harm, or futility, or DARIS is reached. Two review authors will assess the certainty of evidence independently and decide on downgrading. If no agreement can be reached, a third review author (JCJ) will resolve the discussion. We will justify all decisions to downgrade the certainty of evidence using footnotes, and we will make comments to aid the reader's understanding of the review where necessary. The 'Summary of findings' table will also report the anticipated absolute effects, relative effects, number of participants, type of participants, and setting.

Patient and public involvement

No patient involved.

Ethics and dissemination

Ethical approval was not required for this protocol and systematic review. The results of the systematic review will be published in a peer-reviewed journal to help inform future research and clinical practice.

Acknowledgements

We thank Sarah Louise Klingenberg (Information Specialist, The Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital - Rigshospitalet, Denmark) for the help with developing the search strategy.

Contributors

CKJ, RH, SJ, PF, MH, JM, CG, and JCJ contributed to the conceptualisation and design of the study. CKJ and JCJ wrote the original draft. All authors commented and approved the final manuscript. JCJ is the guarantor of the review.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

None declared.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	22
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	16
Support:			
Sources	5a	Indicate sources of financial or other support for the review	22
Sponsor	5b	Provide name for the review funder and/or sponsor	22
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7-8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	9-10
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplementary material 2

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	10
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10-11
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	10-11
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8-9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	11-12
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	12-15
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	12-15
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	15-17
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	12-13
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	14
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	17

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Search strategies for
Melatonin for neurodevelopmental disorders and non-respiratory sleep disorders
Preliminary searches prepared 3 June 2022

Cochrane Central Register of Controlled Trials (latest issue) in the Cochrane Library

#1 MeSH descriptor: [Neurodevelopmental Disorders] explode all trees
#2 MeSH descriptor: [Central Nervous System Diseases] explode all trees
#3 MeSH descriptor: [Intellectual Disability] explode all trees
#4 (((neurodevelopment* or neurotic* or development* or mental* or central nervous system or cns or intellectual* or ((disruptive or child) and behavio*) or Communicati* or speech* or language or Learning or Motor* or psychomotor or Reactive Attachment* or Stereotypic Movement*) and (disease* or disorder* or disabilit* or syndrom* or dysfunc* or impair* or deficienc* or retardation*)) or neurodisabilit* or neuro-disabilit* or idiocy or dyslexia or dyscalculia or autis* or kaunner* or ASD or Asperger* or attention deficit* or ADHD* or ADDH or hyperactivity* or impulsiv* cerebral pals* or spastic displeg* or epilep* or mutism* or tic* or Tourette* or ((happy or child*) and puppet*) or fragile x or Frax* or angelman* or prader-willi* or rett* or smith-magenis or williams or Cri-du-Chat or De Lange or down* or Coffin-Lowry or Lesch-Nyhan or Menkes Kinky Hair or Rubinstein-Taybi or WAGR or schizophreni* or Adrenoleukodystrophy or Mucopolysaccharidosis)
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Melatonin] explode all trees
#7 (melatonin* or Circadin* or Slenyto* or (Methoxy near Acetyl near tryptamin*))
#8 #6 or #7
#9 #5 and #8
#10 MeSH descriptor: [Adolescent] explode all trees
#11 MeSH descriptor: [Child] explode all trees
#12 MeSH descriptor: [Infant] explode all trees
#13 MeSH descriptor: [Pediatrics] explode all trees
#14 (baby or babies or infan* or child* or toddler* or pre-school* or preschool* or adolescen* or teen* or schoolchild* or schoolage* or pediatric* or paediatric*)
#15 #10 or #11 or #12 or #13 or #14
#16 #9 and #15

MEDLINE Ovid (1946 to the date of the search)

1. exp Neurodevelopmental Disorders/
2. exp Central Nervous System Diseases/
3. exp Intellectual Disability/
4. (((neurodevelopment* or neurotic* or development* or mental* or central nervous system or cns or intellectual* or ((disruptive or child) and behavio*) or Communicati* or speech* or language or Learning or Motor* or psychomotor or Reactive Attachment* or Stereotypic Movement*) and (disease* or disorder* or disabilit* or syndrom* or dysfunc* or impair* or deficienc* or retardation*)) or neurodisabilit* or neuro-disabilit* or idiocy or dyslexia or dyscalculia or autis* or kanner* or ASD or Asperger* or attention deficit* or ADHD* or ADDH or hyperactivity* or impulsiv* cerebral pals* or spastic displeg* or epilep* or mutism* or tic* or Tourette* or ((happy or child*) and puppet*) or fragile x or Frax* or angelman* or prader-willi* or rett* or smith-magenis or williams or Cri-du-Chat or De Lange or down* or Coffin-Lowry or Lesch-Nyhan or Menkes Kinky Hair or Rubinstein-Taybi or WAGR or schizophreni* or Adrenoleukodystrophy or Mucopolysaccharidosis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
5. 1 or 2 or 3 or 4
6. exp Melatonin/
7. (melatonin* or Circadin* or Slenyto* or 5-Methoxy-N-Acetyltryptamin* or N-Acetyl-5-Methoxytryptamin*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
8. 6 or 7
9. 5 and 8
10. exp adolescent/ or exp child/ or exp infant/
11. exp Pediatrics/
12. (baby or babies or infan* or child* or toddler* or pre-school* or preschool* or adolescen* or teen* or schoolchild* or schoolage* or pediatric* or paediatric*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

13. 10 or 11 or 12
14. 9 and 13
15. (randomized controlled trial or controlled clinical trial or retracted publication or retraction of publication).pt. or clinical trials as topic.sh. or trial.ti.
16. (random* or blind* or placebo*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
17. 14 and (15 or 16)

Embase Ovid (1974 to the date of the search)

1. exp mental disease/
2. exp central nervous system disease/
3. exp intellectual impairment/
4. (((neurodevelopment* or neurotic* or development* or mental* or central nervous system or cns or intellectual* or ((disruptive or child) and behavio*) or Communicati* or speech* or language or Learning or Motor* or psychomotor or Reactive Attachment* or Stereotypic Movement*) and (disease* or disorder* or disabilit* or syndrom* or dysfunc* or impair* or deficienc* or retardation*)) or neurodisabilit* or neuro-disabilit* or idiocy or dyslexia or dyscalculia or autis* or kanner* or ASD or Asperger* or attention deficit* or ADHD* or ADDH or hyperactivity* or impulsiv* cerebral pals* or spastic displeg* or epilep* or mutism* or tic* or Tourette* or ((happy or child*) and puppet*) or fragile x or Frax* or angelman* or prader-willi* or rett* or smith-magenis or williams or Cri-du-Chat or De Lange or down* or Coffin-Lowry or Lesch-Nyhan or Menkes Kinky Hair or Rubinstein-Taybi or WAGR or schizophreni* or Adrenoleukodystrophy or Mucopolysaccharidosis).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
5. 1 or 2 or 3 or 4
6. exp melatonin/
7. (melatonin* or Circadin* or Slenyto* or 5-Methoxy-N-Acetyltryptamin* or N-Acetyl-5-Methoxytryptamin*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
8. 6 or 7
9. 5 and 8
10. exp adolescent/ or exp child/
11. exp pediatrics/
12. (baby or babies or infan* or child* or toddler* or pre-school* or preschool* or adolescen* or teen* or schoolchild* or schoolage* or pediatric* or paediatric*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
13. 10 or 11 or 12
14. 9 and 13
15. Randomized controlled trial/ or Controlled clinical trial/ or retracted article/ or (erratum or tombstone).pt. or trial.ti. or yes.ne.
16. (random* or blind* or placebo*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
17. 14 and (15 or 16)

LILACS (Bireme; 1982 to the date of the search)

(((neurodevelopment$ or neurotic$ or development$ or mental$ or central nervous system or cns or intellectual$ or ((disruptive or child) and behavio$) or Communicati$ or speech$ or language or Learning or Motor$ or psychomotor or Reactive Attachment$ or Stereotypic Movement$) and (disease$ or disorder$ or disabilit$ or syndrom$ or dysfunc$ or impair$ or deficienc$ or retardation$)) or neurodisabilit$ or neuro-disabilit$ or idiocy or dyslexia or dyscalculia or autis$ or kanner$ or ASD or Asperger$ or attention deficit$ or ADHD$ or ADDH or hyperactivity$ or impulsiv$ cerebral pals$ or spastic displeg$ or epilep$ or mutism$ or tic$ or Tourette$ or ((happy or child$) and puppet$) or fragile x or Frax$ or angelman$ or prader-willi$ or rett$ or smith-magenis or williams or Cri-du-Chat or De Lange or down$ or Coffin-Lowry or Lesch-Nyhan or Menkes Kinky Hair or Rubinstein-Taybi or WAGR or schizophreni$ or Adrenoleukodystrophy or Mucopolysaccharidosis) [Words] and (melatonin$ or Circadin$ or Slenyto$ or 5-Methoxy-N-Acetyltryptamin$ or N-Acetyl-5-Methoxytryptamin$) [Words] and (baby or babies or infan$ or child$ or toddler$ or pre-school$ or preschool$ or adolescen$ or teen$ or schoolchild$ or schoolage$ or pediatric$ or paediatric$) [Words]

PsycINFO (EBSCO Host; date will be given at review stage)

S11 S9 AND S10

S10 TX (random* or blind* or placebo* or trial*)
S9 S5 AND S8
S8 S6 OR S7
S7 TX (melatonin* or Circadin* or Slenyto* or 5-Methoxy-N-Acetyltryptamin* or N-Acetyl-5-Methoxytryptamin*)
S6 MA Melatonin
S5 S1 OR S2 OR S3 OR S4
S4 TX (((neurodevelopment* or neurotic* or development* or mental* or central nervous system or cns or intellectual* or ((disruptive or child) and behavio*) or Communicati* or speech* or language or Learning or Motor* or psychomotor or Reactive Attachment* or Stereotypic Movement*) and (disease* or disorder* or disabilit* or syndrom* or dysfunc* or impair* or deficienc* or retardation*)) or neurodisabilit* or neuro-disabilit* or idiocy or dyslexia or dyscalculia or autis* or kanner* or ASD or Asperger* or attention deficit* or ADHD* or ADDH or hyperactivity* or impulsiv* cerebral pals* or spastic displeg* or epilep* or mutism* or tic* or Tourette* or ((happy or child*) and puppet*) or fragile x or Frax* or angelman* or prader-willi* or rett* or smith-magenis or williams or Cri-du-Chat or De Lange or down* or Coffin-Lowry or Lesch-Nyhan or Menkes Kinky Hair or Rubinstein-Taybi or WAGR or schizophreni* or Adrenoleukodystrophy or Mucopolysaccharidosis)
S3 MA Intellectual Disability
S2 MA Central Nervous System Diseases
S1 MA Neurodevelopmental Disorders

Science Citation Index Expanded (1900 to the date of the search) and Conference Proceedings Citation Index – Science (1990 to the date of the search) (Web of Science)
#5 #4 AND #3 AND #2 AND #1
#4 TI=(random* or blind* or placebo* or trial*) OR TS=(random* or blind* or placebo*)
#3 TS=(baby or babies or infan* or child* or toddler* or pre-school* or preschool* or adolescen* or teen* or schoolchild* or schoolage* or pediatric* or paediatric*)
#2 TS=(melatonin* or Circadin* or Slenyto* or 5-Methoxy-N-Acetyltryptamin* or N-Acetyl-5-Methoxytryptamin*)
#1 TS=(((neurodevelopment* or neurotic* or development* or mental* or central nervous system or cns or intellectual* or ((disruptive or child) and behavio*) or Communicati* or speech* or language or Learning or Motor* or psychomotor or Reactive Attachment* or Stereotypic Movement*) and (disease* or disorder* or disabilit* or syndrom* or dysfunc* or impair* or deficienc* or retardation*)) or neurodisabilit* or neuro-disabilit* or idiocy or dyslexia or dyscalculia or autis* or kanner* or ASD or Asperger* or attention deficit* or ADHD* or ADDH or hyperactivity* or impulsiv* cerebral pals* or spastic displeg* or epilep* or mutism* or tic* or Tourette* or ((happy or child*) and puppet*) or fragile x or Frax* or angelman* or prader-willi* or rett* or smith-magenis or williams or Cri-du-Chat or De Lange or down* or Coffin-Lowry or Lesch-Nyhan or Menkes Kinky Hair or Rubinstein-Taybi or WAGR or schizophreni* or Adrenoleukodystrophy or Mucopolysaccharidosis)

BMJ Open

Melatonin for sleep disorders in children with neurodevelopmental disorders: protocol for a systematic review with meta-analysis and Trial Sequential Analysis of randomised clinical trials

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-065520.R1
Article Type:	Protocol
Date Submitted by the Author:	13-Sep-2022
Complete List of Authors:	Jørgensen, Caroline Kamp; Rigshospitalet Copenhagen Trial Unit; Syddansk Universitet Det Sundhedsvidenskabelige Fakultet, Department of Regional Health Research Hermann, Rikke; Centre for children, youth, and families Juul, Sophie ; Rigshospitalet Copenhagen Trial Unit Faltermeier, Pascal; MSH Medical School Hamburg Horowitz, Mark; University College London Division of Psychiatry; North East London NHS Foundation Trust, Research and Development Department Moncrieff, Joanna; University College London Division of Psychiatry; North East London NHS Foundation Trust, Research and Development Department Gluud, Christian; Rigshospitalet Copenhagen Trial Unit; Syddansk Universitet Det Sundhedsvidenskabelige Fakultet, Department of Regional Health Research Jakobsen, Janus; Rigshospitalet Copenhagen Trial Unit; Syddansk Universitet Det Sundhedsvidenskabelige Fakultet, Department of Regional Health Research
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Neurology
Keywords:	SLEEP MEDICINE, Paediatric neurology < NEUROLOGY, Developmental neurology & neurodisability < PAEDIATRICS

Melatonin for sleep disorders in children with neurodevelopmental disorders: protocol for a systematic review with meta-analysis and Trial Sequential Analysis of randomised clinical trials

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Word count: 4,440

Abstract

Introduction: Neurodevelopmental disorders are a group of disorders thought to be associated with the functioning of the brain and nervous system. Children with neurodevelopmental disorders often have sleep-related comorbidities that may negatively affect quality of life for both the children and their families. Melatonin is one of the most used interventions in children with neurodevelopmental disorders and sleep disorders. Previous reviews have investigated the effects of melatonin for sleep disorders in children with neurodevelopmental disorders, but these had important limitations, such as inadequate analysis of adverse effects, small sample sizes, and short follow-up.

Methods and analysis: This is a protocol for a systematic review with meta-analysis and Trial Sequential Analysis of randomised clinical trials. The protocol is reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols. We will search for published and unpublished trials in the Cochrane Central Register of Controlled Trials, MEDLINE Ovid, Embase Ovid, LILACS, Science Citation Index Expanded, Conference Proceedings Citation Index-Science, PsycINFO, ClinicalTrials.gov, and the International Clinical Trials Registry Platform. We will search the databases from their inception without language restrictions. We will also request clinical study reports from regulatory authorities and pharmaceutical companies. Review authors working in pairs will screen reports, extract data, and conduct risk of bias assessments using the Cochrane Risk of Bias tool. We will include randomised clinical trials comparing melatonin versus placebo or no intervention for sleep disorders in children with neurodevelopmental disorders. Primary outcomes will be total sleep time and adverse effects. Secondary outcomes will be quality of life of the child and caregivers and sleep onset latency. Data will be analysed using random-effects and fixed-effect meta-analyses. Certainty of evidence will be assessed with GRADE.

Ethics and dissemination: Ethical approval was not required for this protocol. The systematic review will be published in a peer-reviewed journal.

PROSPERO registration number: CRD42022337530

Keywords: Melatonin; neurodevelopmental disorders; sleep disorders; children; systematic review

Strengths and limitations of this study

- The methodology of our systematic review is predefined in detail to avoid data-driven biased results.
- The protocol is based on the Cochrane Handbook, the eight-step procedure suggested by Jakobsen et al., Trial Sequential Analysis, and the Grading of Recommendations, Assessment, Development and Evaluation approach.
- The systematic review will consider the risks of random errors, systematic errors, publication bias, heterogeneity, and external validity.
- The systematic review will include both published and unpublished trials.
- We assess multiple outcomes and subgroup analyses which increases the risks of type I errors.

Introduction

Description of the condition

Neurodevelopmental disorders are a group of disorders thought to be associated with the functioning of the brain and nervous system.[1] Neurodevelopmental disorders are usually diagnosed in childhood and include neurological disorders such as cerebral palsy, epilepsy, Angelman syndrome, Down's syndrome, Fragile X syndrome, Prader-Willi syndrome, Rett syndrome, Smith-Magenis syndrome, Williams syndrome, and non-specific intellectual disability, along with some psychiatric disorders including autism spectrum disorder, attention deficit hyperactivity disorder (ADHD), and attention deficit disorder (ADD).[1, 2] Children with neurodevelopmental disorders may experience difficulties with learning, attention, behaviour, speech, motor skills, and other neurological functions.[1]

The impact of sleep disturbances was recently ranked as a top 10 research priority within the topics of children with neurodevelopmental disorders by a UK partnership of patients, carers, and clinicians.[3] Children with neurodevelopmental disorders often have sleep-related comorbidities, including sleep disorders such as insomnia disorder, hypersomnolence disorder, narcolepsy, breathing-related sleep disorders, circadian rhythm sleep disorders, rapid eye movement (REM) sleep arousal disorders, non-REM sleep arousal disorders, and nightmare disorders.[2, 4] Studies have shown the prevalence of comorbid neurodevelopmental disorders and sleep disorders is between 25% to 86% compared to 1% to 6% in the general paediatric population.[4-8] Sleep disorders may further enhance problems with learning and behaviour in children with neurodevelopmental disorders,[4-8] and often have a negative effect on quality of life for both the children and their families.[9, 10]

Description of the intervention

Melatonin is a naturally occurring hormone in both humans and animals.[11] Previously, melatonin was derived from animal pineal tissue,[11] but it is now developed synthetically and distributed in different forms, including capsules, tablets, gummies, and liquids.[12] Melatonin is available in many countries either sold as prescription-only medicine or as over-the-counter medicine to treat

sleep disorders in both children and adults, as it is hypothesised to be associated with few adverse effects.[11, 13] Furthermore, melatonin is one of the most commonly used interventions in children with neurodevelopmental disorders and sleep disorders.[14-18] The dosage recommendations vary according to country, but the UK National Health Service currently recommend treatment up to 13 weeks of 2 mg one to two hours before bedtime for adults with sleep problems.[19] However, there are currently no clear guidelines for prescribing melatonin for children and adolescents with neurodevelopmental disorders.[5, 11]

How the intervention might work

The understanding of melatonin's underlying mechanisms has previously been extrapolated from animals to humans, but the exact physiological mechanisms of melatonin in humans remain unclear.[20-22] Melatonin is a neurohormone primarily secreted by the pineal gland.[13] Melatonin mediates dark signals, since the secretion of melatonin is related to darkness, and it is therefore associated with the circadian rhythm in humans.[13, 17] The secretion of melatonin is regulated by the suprachiasmatic nucleus in the hypothalamus, and the production of melatonin depends on darkness, as the exposure to light inhibits secretion.[11, 23] A decrease in the secretion of melatonin has been associated with aging and different diseases, and synthetic melatonin may theoretically reduce sleep disturbance related to melatonin deficiency.[13, 24] Previous studies have shown that melatonin improves total sleep time, sleep onset latency, and sleep quality for adults with sleep disorders, but the effects seem small.[13, 25] Furthermore, some studies suggest that children with autistic spectrum disorders have abnormal secretions of melatonin.[6, 26, 27] For these theoretical reasons, children with neurodevelopmental disorders may benefit from melatonin.

Why it is important to do this review

A systematic review published in 2018 investigated the effects of melatonin for sleep problems in children with neurodevelopmental disorders.[5] The review concluded that melatonin was safe and effective in improving sleep for children with neurodevelopmental disorders.[5] Another systematic review published in 2019 investigated the effects of oral melatonin for non-respiratory sleep disturbances in children with neurodisabilities.[28] The review concluded that there was some evidence of beneficial effects, but the extent of these effects was unclear due to the poor quality of

the evidence.[28] The review also concluded that melatonin was well-tolerated, as comparable adverse effects were found in the melatonin and placebo groups.[28]

These previous reviews had important limitations. The conclusions were affected by a high degree of heterogeneity, high and unclear risk of bias in the included trials, and small sample sizes.[5, 28] Furthermore, the duration of treatment was limited to a maximum of 13 weeks, and adverse events were not adequately reported or analysed in either of the reviews.[5, 28]

In recent studies, it has been questioned whether higher levels of melatonin are associated with delayed puberty, and other adverse effects of melatonin are also theoretically possible.[29-31] In 2021, a two-year follow-up of a trial investigating the treatment with melatonin in 119 children with autism spectrum disorder was published.[32] This trial concluded that melatonin was safe and effective for long-term treatment in children.[32] Other, new randomised clinical trials might have been published since the last published systematic reviews, and on-going trials have been identified on ClinicalTrials.gov.[33, 34] These trials may contribute important information about the use of melatonin in children with neurodevelopmental disorders, including adverse effects. Therefore, there is a need for a systematic review to shed light on this important topic and to assess whether the beneficial effects outweigh any harmful effects. Our systematic review will take risks of systematic errors ('bias'), risks of random errors ('play of chance'), and the certainty of the evidence into consideration when assessing the effects of melatonin for sleep disorders in children with neurodevelopmental disorders.

Methods and analysis

The present protocol has been registered in the PROSPERO database (CRD42022337530) and is reported according to the guidance suggested in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement (please find the checklist in **supplemental material 1**).[35, 36]

Criteria for considering studies for this review

Types of studies

We will include randomised clinical trials irrespective of trial design (including crossover trials), setting, publication status, publication year, and language. We will use online translation services to translate foreign abstracts and reach out to our international colleagues (who will be thanked in the acknowledgements) for help with data extraction of relevant trials. We will not include quasi-randomised trials, cluster-randomised trials, or observational studies.

Types of participants

We will include trials randomising children and adolescents (below 18 years of age) with neurodevelopmental disorders, such as cerebral palsy, epilepsy, Angelman syndrome, Down's syndrome, Fragile X syndrome, Prader-Willi syndrome, Rett syndrome, Smith-Magenis syndrome, Williams syndrome, non-specific intellectual disability, autism spectrum disorder, ADHD, and ADD.[1, 2] Trials will be included if the disorders of the participants are diagnosed by standardised diagnostic criteria, such as the Diagnostic and Statistical Manual of Mental Disorders[37] or International Classification of Diseases[38] or where the diagnosis or designation of neurodevelopmental disorder is made by a clinician. The participants also need to have a diagnosis of any type of sleep disorder (as defined by trialists), such as insomnia disorder, hypersomnolence disorder, narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorders, REM sleep arousal disorder, non-REM sleep arousal disorder, and nightmare disorders.

We will include participants irrespective of sex, comorbidities, demographic factors, the stage of their condition, and the care setting. If a trial reports data where only a subset of participants is eligible (e.g. a combination of children and adults), we will only include data from those participants that fulfil the inclusion criteria, and we will therefore require subset data for the specific group to be available.

Types of interventions

We will include trials where participants in the experimental group are given melatonin at any dose, form (e.g. tablet, capsules, gummies, liquids), duration of administration, type of administration (e.g. oral), timing of administration, and setting. We will include trials where participants receive a

co-intervention (e.g. pharmacological interventions, such as methylphenidate, or non-pharmacological interventions, such as exercise), providing it is delivered equally (in any aspect, e.g. same dose, equal subset of population receiving co-intervention, etc.) in the experimental group and the control group.

Comparators

As control intervention we will accept placebo or 'no intervention'.

Types of outcome measures

Primary outcomes

1) Total sleep time (in minutes using any type of measurement, e.g. polysomnography, actigraphy, self-report, or parent-report).
2) Adverse effects
   a) The proportion of participants with one or more serious adverse events. We will use the International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use—Good Clinical Practice (ICH-GCP) definition of a serious adverse event, which is any untoward medical occurrence that resulted in death, was life-threatening, required hospitalisation or prolonging of existing hospitalisation, resulted in persistent or significant disability or jeopardised the participant.[39] If the trialists do not use the ICH-GCP definition, we will include the data if the trialists use the term 'serious adverse event'. If the trialists do not use the ICH-GCP definition nor use the term serious adverse event, then we will also include the data provided the event clearly fulfils the ICH-GCP definition for a serious adverse event. We will secondly analyse each type of serious adverse event separately.
   b) The proportion of participants with one or more non-serious adverse events (any adverse event not classified as serious). We will also analyse each type of adverse event separately.

Secondary outcomes

1) Quality of life of the child (any valid continuous scale, e.g. Child Quality of Life Questionnaire).[40]
2) Quality of life of the parents/caregivers (any valid continuous scale, e.g. SF-36).[41]
3) Sleep onset latency (in minutes using any type of measurement, e.g. polysomnography, actigraphy, self-report, or parent-report).

Exploratory outcomes

1) Quality of sleep (any valid continuous scale), such as the Pittsburgh Sleep Quality Index.[42]
2) Delayed puberty or any reports of hormonal changes.
3) Any continuous scale assessing adverse effects (e.g. Pediatric Adverse Event Rating Scale).[43]

Timing of outcome assessment

We will include outcome data recorded at the end of the treatment period primarily and at maximum follow-up secondarily.

Search methods for identification of studies

Electronic searches

We will search the following:

- Cochrane Central Register of Controlled Trials (CENTRAL; current issue) in The Cochrane Library
- MEDLINE Ovid (1946 onwards)
- Embase Ovid (1974 onwards)
- LILACS (Latin American and Caribbean Health Science Information database; 1982 onwards)
- Science Citation Index Expanded (Web of Science; 1964 onwards)
- Conference Proceedings Citation Index-Science (Web of Science; 1990 onwards)
- PsycINFO (1967 onwards)
- ClinicalTrials.gov
- International Clinical Trials Registry Platform (ICTRP)

Please see **supplemental material 2** for the search strategy.

Searching other resources

We will check reference lists of all included trials and any relevant systematic reviews to identify additional trials. We will also search for errata and retraction statements for the included trials. We will search websites of pharmaceutical companies (e.g. Natrol, Neurim Pharmaceuticals, Takeda Pharma), websites of U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) to identify relevant trials. We will request FDA, EMA, and national medicines agencies to provide all publicly releasable information about relevant studies that were submitted for marketing approval, including clinical study reports. We will contact authors of eligible trials and other experts to identify any relevant trials (published or unpublished).

Data collection and analysis

We will perform and report the review based on the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions. [44] Analyses will be performed using Stata version 17[45] and Trial Sequential Analysis.[46, 47]

Selection of studies

Two review authors will independently screen titles and abstracts using Covidence.[48] We will mark articles that clearly do not meet the eligibility criteria as excludes, while potentially eligible articles will go through to the next phase. We will retrieve all relevant full-text study reports/publications, and two review authors will independently screen the full text to identify and record reasons for exclusion of the ineligible trials. The two review authors will resolve any disagreement through discussion, or, if required, they will consult with a third author (JCJ). We will illustrate the selection process of the trials in a PRISMA flow diagram.[49] If multiple reports are available for a single trial, all reports will be grouped under a single reference ID.

Data extraction and management

Review authors in pairs will independently extract data from the included trials using a pilot tested data extraction form. Disagreements will be resolved through internal discussion or, if required, by discussion with a third author (JCJ). The two review authors will assess all publications of a trial together to evaluate all available data simultaneously. We will contact trial authors by email to obtain any additional data, which may not have been reported sufficiently in the publication. We will extract the following data:

- Methods: trial setting, trial location, trial design, trial duration, duration of follow-ups, date of the trial, estimation of sample size, inclusion criteria, and exclusion criteria
- Participants: number randomised, number analysed for each outcome, number lost to follow-up, age (mean and standard deviation), sex ratio, and diagnostic criteria
- Interventions: type, dose, timing, and duration of intervention
- Control: type, dose, timing, and duration of comparison
- Co-intervention: type, dose, timing, and duration of co-interventions
- Outcomes: primary, secondary, and exploratory outcomes at the reported time points
- Notes: trial funding and conflicts of interest of the trial authors

One review author will transfer the data to Stata. We will double-check the data by comparing the data presented in the review to the data extraction form.

Assessment of risk of bias in included studies

Our bias risk assessment will be based on the Cochrane Risk of Bias tool—version 2 (RoB 2) as recommended in the Cochrane Handbook of Systematic Reviews of Interventions.[44] We will evaluate the methodology in respect of the following bias domains:

- Bias arising from the randomisation process
- Bias due to deviations from the intended interventions (effect of assignment to intervention).
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

Review authors in pairs will independently assess the risk of bias using a template (available at https://www.riskofbias.info/). Disagreements will be resolved through internal discussion or, if required, by discussion with a third author (JCJ). We will use the signalling questions in the RoB 2 tool to rate each domain at either 'low risk of bias', 'some concerns', or 'high risk of bias'. We will assess all domains of risk of bias for each outcome in each trial. The overall risk of bias of a result will be judged to be low if all domains are assessed at low risk of bias. If one or more domains are assessed at either some concerns or high risk of bias, the overall risk of bias will be assessed at high. We will assess the risk of bias for the outcomes of the included trials presented in the 'Summary of findings' table (primary and secondary outcomes at end of treatment). The risk of bias assessments will be illustrated in a table (using https://www.riskofbias.info/), and the assessments will be used to conduct subgroup analyses. The risk of bias assessment will also be used to inform the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) and the 'Summary of findings' table. For trials using crossover design, only data from the first period will be assessed.

Measures of treatment effect

Continuous outcomes

We will calculate mean differences (MDs) and consider calculating standardised mean differences (SMD) with 95% CIs for continuous outcomes. We will enter data presented as a scale with a consistent direction of effect. We will primarily analyse scores assessed at single time points. If only changes from baseline scores are reported, we will analyse the results together with follow-up scores for MD (not for SMD).[44] If standard deviations (SDs) are not reported, we will calculate the SDs using trial data, if possible, or request such data from the authors.

Dichotomous outcomes

We will calculate risk ratios (RRs) with 95% confidence intervals (CI) for dichotomous outcomes.

Unit of analysis issues

We will only include randomised clinical trials. Trials using a crossover design will be treated as parallel trials, since only data from the first period will be included.[44] Where multiple trial arms

are reported in a single trial, we will include only the relevant arms. For trials with multiple relevant experimental or control groups, we will combine the groups as appropriate.[44]

If, during the selection of trials, we identify observational studies (i.e. quasi-randomised studies, cohort studies, or patient reports) that report adverse events associated with melatonin, we will review these studies for report on adverse events. We will not specifically search for observational studies for inclusion in this review, which is a limitation in our review. We will not analyse the extracted data on harms from non-randomised clinical studies together with the data on harms from the randomised clinical trials included in the review; neither will we assess the bias risk in these studies. However, we will refer to the extracted narrative data on harm with a link to a table in an appendix. We are aware that the decision not to search for all observational studies might bias our review towards assessment of benefits and might overlook certain harms such as late or rare harms. If we demonstrate benefits from the use of melatonin in children and adolescents with neurodevelopmental disorders, then a systematic review of harms in observational studies ought to be launched.[50]

Dealing with missing data

We will, as the first option, contact all trial authors to obtain information on missing data (i.e. for data extraction and for assessment of risk of bias, as specified above). We will use intention-to-treat data if provided by the trialists.[51]

Dichotomous outcomes

We will not impute missing values for any outcomes in our primary analysis. In our sensitivity analyses (see below), we will impute data.

Continuous outcomes

We will not impute missing values for any outcomes in our primary analysis. In our sensitivity analysis (see below) for continuous outcomes, we will impute data.

Assessment of heterogeneity

We will investigate forest plots to visually assess for signs of heterogeneity. We will also estimate the presence of statistical heterogeneity by a chi^2 test (threshold $P < 0.05$) and measure the quantities of heterogeneity by the I^2 statistic.[52, 53] We will investigate possible heterogeneity through subgroup analyses. We may ultimately decide that a meta-analysis should be avoided.[44] We will interpret I^2 heterogeneity as suggested by the Cochrane Handbook for Systematic Reviews of Interventions.[44] If we identify substantial heterogeneity ($I^2 > 50\%$), we will report it, and explore the possible causes by prespecified subgroup analyses. We will carefully investigate trial characteristics and report if we find unexpected heterogeneity due to clinical or methodological factors. Ultimately it will be decided if meta-analysis should be avoided.

Assessment of reporting biases

We will use funnel plots to assess reporting bias if ten or more trials are included in an outcome.[44] We will visually inspect funnel plots to assess the risk of small trial effects that could potentially reflect publication bias. We are aware of the limitations of a funnel plot (i.e. a funnel plot assesses bias due to small sample size). From this information, we will assess possible risk of publication bias. For dichotomous outcomes, we will test asymmetry with the Harbord test[54] if τ^2 is less than 0.1 and with the Rücker test if τ^2 is more than 0.1. For continuous outcomes, we will use the regression asymmetry test[55] and the adjusted rank correlation.[56]

Data synthesis

Meta-analysis

We will undertake this meta-analysis according to the recommendations stated in the Cochrane Handbook for Systematic Reviews of Interventions,[44] Keus et al.,[57] and our eight-step procedure suggested by Jakobsen et al.[58] We will assess our intervention effects with both random-effects meta-analyses (Hartung-Knapp-Sidik-Jonkman)[59] and fixed-effect meta-analyses (Mantel-Haenszel for dichotomous outcomes and inverse variance for continuous outcomes),[44, 60] and report both meta-analysis results.[58] We will primarily report the most conservative result (widest confidence interval and highest P value), and report the less conservative result as a sensitivity analysis.[58] As two primary outcomes are specified, we will consider a P value of 0.025 or less as the threshold for statistical significance for all outcomes.[58] Our primary analyses will

include all trials. Where data are only available from one trial, we will use Fisher's exact test for dichotomous data and Student's t-test for continuous data.[61, 62]

Trial Sequential Analysis

Traditional meta-analysis runs the risk of random errors due to sparse data and repetitive testing of accumulating data when updating reviews. We wish to control for the risks of type I and type II errors. We will therefore perform Trial Sequential Analysis on all outcomes, in order to calculate the required information size (i.e. the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) and the cumulative Z-curve's breach of relevant trial sequential monitoring boundaries.[47, 63-68] A more detailed description of Trial Sequential Analysis can be found in the manual[47] and at www.ctu.dk/tsa/. For dichotomous outcomes, we will estimate the required information size based on the observed proportion of patients with an outcome in the control group (the cumulative proportion of patients with an event in the control groups relative to all patients in the control groups), a relative risk reduction or a relative risk increase of 25%, an alpha of 2.5% for all our outcomes, a beta of 10%, and the observed diversity as suggested by the trials in the meta-analysis. For continuous outcomes, we will use the observed standard deviation (SD) in the control group, a mean difference of 30 minutes when assessing total sleep time; otherwise, a mean difference of the observed SD/2, an alpha of 2.5% for all outcomes, a beta of 10%, and the observed diversity of the trials in the meta-analysis. We will only use the diversity-adjusted required information size (DARIS) for random-effects Trial Sequential Analyses.

Subgroup analysis and investigation of heterogeneity

We will perform the following subgroup analyses on the primary outcomes:

1. Type of neurodevelopmental disorder: this subgroup analysis will assess whether the effects of melatonin are different depending on the neurodevelopmental disorder of the child.
2. Age (below 12 years compared to above 12 years and preschool-age children compared to school-age children (as defined by trialists)): this will assess whether the effects of melatonin vary depending on the age of the participants.
3. Type of comparator (placebo or no intervention): this subgroup analysis will assess whether the effects of melatonin vary depending on the comparator.

4. Timing of the melatonin administration. If data are available, we will use the following comparisons: < 2 hours before bedtime, 2-4 hours before bedtime, or 4-8 hours before bedtime. If not, we will use definitions by trialists. This subgroup analysis is relevant, because the timing of administration may affect the outcomes.[69-71]
5. Formulation of medication: this subgroup analysis will assess whether the effects of melatonin vary depending on the formulation of melatonin.
6. Type of sleep disorder: this subgroup analysis will assess whether the effects of melatonin vary depending on the type of sleep disorder.
7. Trials at high risk of bias compared to trials at low risk of bias: this subgroup analysis will assess whether the effects of melatonin vary depending on the risk of bias of the included trials.
8. Duration of trials: this subgroup analysis will assess whether the effects of melatonin vary depending on the duration of the included trials.

Post-hoc subgroup analyses might be warranted if unexpected clinical or statistical heterogeneity is identified during the analysis of the review results.[58] We will disclose any new subgroup analyses not reported in this protocol in the 'Differences between protocol and review' section of the systematic review.

Sensitivity analysis

To assess the potential impact of the missing data, we will perform the two following sensitivity analyses on the primary outcomes:

'Best-worst-case' scenario: we will assume that all participants lost to follow-up in the experimental group had beneficial outcomes (no serious adverse events/improved quality of sleep defined as the group mean plus two SDs).[58] We will accordingly assume that all participants lost to follow-up in the control group had poor outcomes (serious adverse events/deteriorated quality of sleep defined as the group mean plus two SDs).[58]

'Worst-best-case' scenario: we will assume that all participants lost to follow-up in the experimental group had poor outcomes (serious adverse events/deteriorated quality of sleep defined as the group

mean plus two SDs).[58] We will accordingly assume that all participants lost to follow-up in the control group had beneficial outcomes (no serious adverse events/improved quality of sleep defined as the group mean plus two SDs).[58]

We will present the results of both scenarios in our review.

We will assess the potential impact of missing SDs for quality of sleep as follows: when SDs are missing, and it is not possible to calculate them, we will impute SDs from trials with similar populations and low risk of bias. If we find no such trials, we will impute SDs from trials with a similar population. As the final option, we will impute SDs from all trials. We will present results of this scenario in our review.

Summary of findings and assessment of the certainty of the evidence

Review authors in pairs will use GRADE to assess the certainty of the body of evidence associated with each of the primary and secondary outcomes at end of treatment in our review. We will construct 'Summary of findings' tables using the GRADEpro GDT.[72] The GRADE approach appraises the certainty of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. We will assess the GRADE levels of evidence as either high, moderate, low, or very low certainty on the following quality measures: risk of bias (the overall risk of bias will be used for each outcome), directness of the evidence, heterogeneity of the data, precision of effect estimates (assessed by Trial Sequential Analysis), and risk of publication bias.[72] We will downgrade the evidence by one or two levels due to serious or very serious issues. We will downgrade imprecision in GRADE by two levels if the accrued number of participants is below 50% of the DARIS, and one level if between 50 and 100% of DARIS. We will not downgrade if the cumulative Z-curve crosses the monitoring boundaries for benefit, harm, or futility, or DARIS is reached. Two review authors will assess the certainty of evidence independently and decide on downgrading. If no agreement can be reached, a third review author (JCJ) will resolve the discussion. We will justify all decisions to downgrade the certainty of evidence using footnotes, and we will make comments to aid the reader's understanding of the review where necessary. The 'Summary of findings' table will also report the anticipated absolute effects, relative effects, number of participants, type of participants, and setting.

Differences between the protocol and the review

We will conduct the review according to this published protocol and report any deviations from it in the "differences between the protocol and the review" section of the systematic review.

Patient and public involvement

None.

Ethics and dissemination

Ethical approval was not required for this protocol and systematic review. The results of the systematic review will be published in a peer-reviewed journal to help inform future research and clinical practice.

Acknowledgements

We thank Sarah Louise Klingenberg (Information Specialist, The Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital - Rigshospitalet, Denmark) for the help with developing the search strategy.

Contributors

CKJ, RH, SJ, PF, MH, JM, CG, and JCJ contributed to the conceptualisation and design of the study. CKJ and JCJ wrote the original draft. All authors commented and approved the final manuscript. JCJ is the guarantor of the review.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

None declared.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Section
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Title
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Abstract
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title page
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Contributors
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Differences between the protocol and the review
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Funding
Sponsor	5b	Provide name for the review funder and/or sponsor	Funding
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Why it is important to do this review
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Why it is important to do this review
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Criteria for considering studies for this review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Search methods for identification of studies
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that	Supplementary material 2

		it could be repeated	
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Data collection and analysis
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Selection of studies
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Data extraction and management
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Data extraction and management
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Types of outcomes measures
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Assessment of risk of bias in included studies
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Data synthesis
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Dealing with missing data, Assessment of heterogeneity
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Subgroup analysis and investigation of heterogeneity, Sensitivity analysis
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Unit of analysis issues
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Assessment of reporting biases
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Summary of findings and assessment of the certainty of the evidence

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Search strategies for
Melatonin for neurodevelopmental disorders and non-respiratory sleep disorders
Preliminary searches prepared 3 June 2022

Cochrane Central Register of Controlled Trials (latest issue) in the Cochrane Library

#1 MeSH descriptor: [Neurodevelopmental Disorders] explode all trees
#2 MeSH descriptor: [Central Nervous System Diseases] explode all trees
#3 MeSH descriptor: [Intellectual Disability] explode all trees
#4 (((neurodevelopment* or neurotic* or development* or mental* or central nervous system or cns or intellectual* or ((disruptive or child) and behavio*) or Communicati* or speech* or language or Learning or Motor* or psychomotor or Reactive Attachment* or Stereotypic Movement*) and (disease* or disorder* or disabilit* or syndrom* or dysfunc* or impair* or deficienc* or retardation*)) or neurodisabilit* or neuro-disabilit* or idiocy or dyslexia or dyscalculia or autis* or kaunner* or ASD or Asperger* or attention deficit* or ADHD* or ADDH or hyperactivity* or impulsiv* cerebral pals* or spastic displeg* or epilep* or mutism* or tic* or Tourette* or ((happy or child*) and puppet*) or fragile x or Frax* or angelman* or prader-willi* or rett* or smith-magenis or williams or Cri-du-Chat or De Lange or down* or Coffin-Lowry or Lesch-Nyhan or Menkes Kinky Hair or Rubinstein-Taybi or WAGR or schizophreni* or Adrenoleukodystrophy or Mucopolysaccharidosis)
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Melatonin] explode all trees
#7 (melatonin* or Circadin* or Slenyto* or (Methoxy near Acetyl near tryptamin*))
#8 #6 or #7
#9 #5 and #8
#10 MeSH descriptor: [Adolescent] explode all trees
#11 MeSH descriptor: [Child] explode all trees
#12 MeSH descriptor: [Infant] explode all trees
#13 MeSH descriptor: [Pediatrics] explode all trees
#14 (baby or babies or infan* or child* or toddler* or pre-school* or preschool* or adolescen* or teen* or schoolchild* or schoolage* or pediatric* or paediatric*)
#15 #10 or #11 or #12 or #13 or #14
#16 #9 and #15

MEDLINE Ovid (1946 to the date of the search)

1. exp Neurodevelopmental Disorders/
2. exp Central Nervous System Diseases/
3. exp Intellectual Disability/
4. (((neurodevelopment* or neurotic* or development* or mental* or central nervous system or cns or intellectual* or ((disruptive or child) and behavio*) or Communicati* or speech* or language or Learning or Motor* or psychomotor or Reactive Attachment* or Stereotypic Movement*) and (disease* or disorder* or disabilit* or syndrom* or dysfunc* or impair* or deficienc* or retardation*)) or neurodisabilit* or neuro-disabilit* or idiocy or dyslexia or dyscalculia or autis* or kanner* or ASD or Asperger* or attention deficit* or ADHD* or ADDH or hyperactivity* or impulsiv* cerebral pals* or spastic displeg* or epilep* or mutism* or tic* or Tourette* or ((happy or child*) and puppet*) or fragile x or Frax* or angelman* or prader-willi* or rett* or smith-magenis or williams or Cri-du-Chat or De Lange or down* or Coffin-Lowry or Lesch-Nyhan or Menkes Kinky Hair or Rubinstein-Taybi or WAGR or schizophreni* or Adrenoleukodystrophy or Mucopolysaccharidosis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
5. 1 or 2 or 3 or 4
6. exp Melatonin/
7. (melatonin* or Circadin* or Slenyto* or 5-Methoxy-N-Acetyltryptamin* or N-Acetyl-5-Methoxytryptamin*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
8. 6 or 7
9. 5 and 8
10. exp adolescent/ or exp child/ or exp infant/
11. exp Pediatrics/
12. (baby or babies or infan* or child* or toddler* or pre-school* or preschool* or adolescen* or teen* or schoolchild* or schoolage* or pediatric* or paediatric*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

13. 10 or 11 or 12
14. 9 and 13
15. (randomized controlled trial or controlled clinical trial or retracted publication or retraction of publication).pt. or clinical trials as topic.sh. or trial.ti.
16. (random* or blind* or placebo*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
17. 14 and (15 or 16)

Embase Ovid (1974 to the date of the search)

1. exp mental disease/
2. exp central nervous system disease/
3. exp intellectual impairment/
4. (((neurodevelopment* or neurotic* or development* or mental* or central nervous system or cns or intellectual* or ((disruptive or child) and behavio*) or Communicati* or speech* or language or Learning or Motor* or psychomotor or Reactive Attachment* or Stereotypic Movement*) and (disease* or disorder* or disabilit* or syndrom* or dysfunc* or impair* or deficienc* or retardation*)) or neurodisabilit* or neuro-disabilit* or idiocy or dyslexia or dyscalculia or autis* or kanner* or ASD or Asperger* or attention deficit* or ADHD* or ADDH or hyperactivity* or impulsiv* cerebral pals* or spastic displeg* or epilep* or mutism* or tic* or Tourette* or ((happy or child*) and puppet*) or fragile x or Frax* or angelman* or prader-willi* or rett* or smith-magenis or williams or Cri-du-Chat or De Lange or down* or Coffin-Lowry or Lesch-Nyhan or Menkes Kinky Hair or Rubinstein-Taybi or WAGR or schizophreni* or Adrenoleukodystrophy or Mucopolysaccharidosis).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
5. 1 or 2 or 3 or 4
6. exp melatonin/
7. (melatonin* or Circadin* or Slenyto* or 5-Methoxy-N-Acetyltryptamin* or N-Acetyl-5-Methoxytryptamin*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
8. 6 or 7
9. 5 and 8
10. exp adolescent/ or exp child/
11. exp pediatrics/
12. (baby or babies or infan* or child* or toddler* or pre-school* or preschool* or adolescen* or teen* or schoolchild* or schoolage* or pediatric* or paediatric*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
13. 10 or 11 or 12
14. 9 and 13
15. Randomized controlled trial/ or Controlled clinical trial/ or retracted article/ or (erratum or tombstone).pt. or trial.ti. or yes.ne.
16. (random* or blind* or placebo*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
17. 14 and (15 or 16)

LILACS (Bireme; 1982 to the date of the search)

(((neurodevelopment$ or neurotic$ or development$ or mental$ or central nervous system or cns or intellectual$ or ((disruptive or child) and behavio$) or Communicati$ or speech$ or language or Learning or Motor$ or psychomotor or Reactive Attachment$ or Stereotypic Movement$) and (disease$ or disorder$ or disabilit$ or syndrom$ or dysfunc$ or impair$ or deficienc$ or retardation$)) or neurodisabilit$ or neuro-disabilit$ or idiocy or dyslexia or dyscalculia or autis$ or kanner$ or ASD or Asperger$ or attention deficit$ or ADHD$ or ADDH or hyperactivity$ or impulsiv$ cerebral pals$ or spastic displeg$ or epilep$ or mutism$ or tic$ or Tourette$ or ((happy or child$) and puppet$) or fragile x or Frax$ or angelman$ or prader-willi$ or rett$ or smith-magenis or williams or Cri-du-Chat or De Lange or down$ or Coffin-Lowry or Lesch-Nyhan or Menkes Kinky Hair or Rubinstein-Taybi or WAGR or schizophreni$ or Adrenoleukodystrophy or Mucopolysaccharidosis) [Words] and (melatonin$ or Circadin$ or Slenyto$ or 5-Methoxy-N-Acetyltryptamin$ or N-Acetyl-5-Methoxytryptamin$) [Words] and (baby or babies or infan$ or child$ or toddler$ or pre-school$ or preschool$ or adolescen$ or teen$ or schoolchild$ or schoolage$ or pediatric$ or paediatric$) [Words]

PsycINFO (EBSCO Host; date will be given at review stage)

S11 S9 AND S10

S10 TX (random* or blind* or placebo* or trial*)
S9 S5 AND S8
S8 S6 OR S7
S7 TX (melatonin* or Circadin* or Slenyto* or 5-Methoxy-N-Acetyltryptamin* or N-Acetyl-5-Methoxytryptamin*)
S6 MA Melatonin
S5 S1 OR S2 OR S3 OR S4
S4 TX (((neurodevelopment* or neurotic* or development* or mental* or central nervous system or cns or intellectual* or ((disruptive or child) and behavio*) or Communicati* or speech* or language or Learning or Motor* or psychomotor or Reactive Attachment* or Stereotypic Movement*) and (disease* or disorder* or disabilit* or syndrom* or dysfunc* or impair* or deficienc* or retardation*)) or neurodisabilit* or neuro-disabilit* or idiocy or dyslexia or dyscalculia or autis* or kanner* or ASD or Asperger* or attention deficit* or ADHD* or ADDH or hyperactivity* or impulsiv* cerebral pals* or spastic displeg* or epilep* or mutism* or tic* or Tourette* or ((happy or child*) and puppet*) or fragile x or Frax* or angelman* or prader-willi* or rett* or smith-magenis or williams or Cri-du-Chat or De Lange or down* or Coffin-Lowry or Lesch-Nyhan or Menkes Kinky Hair or Rubinstein-Taybi or WAGR or schizophreni* or Adrenoleukodystrophy or Mucopolysaccharidosis)
S3 MA Intellectual Disability
S2 MA Central Nervous System Diseases
S1 MA Neurodevelopmental Disorders

Science Citation Index Expanded (1900 to the date of the search) and Conference Proceedings Citation Index – Science (1990 to the date of the search) (Web of Science)
#5 #4 AND #3 AND #2 AND #1
#4 TI=(random* or blind* or placebo* or trial*) OR TS=(random* or blind* or placebo*)
#3 TS=(baby or babies or infan* or child* or toddler* or pre-school* or preschool* or adolescen* or teen* or schoolchild* or schoolage* or pediatric* or paediatric*)
#2 TS=(melatonin* or Circadin* or Slenyto* or 5-Methoxy-N-Acetyltryptamin* or N-Acetyl-5-Methoxytryptamin*)
#1 TS=(((neurodevelopment* or neurotic* or development* or mental* or central nervous system or cns or intellectual* or ((disruptive or child) and behavio*) or Communicati* or speech* or language or Learning or Motor* or psychomotor or Reactive Attachment* or Stereotypic Movement*) and (disease* or disorder* or disabilit* or syndrom* or dysfunc* or impair* or deficienc* or retardation*)) or neurodisabilit* or neuro-disabilit* or idiocy or dyslexia or dyscalculia or autis* or kanner* or ASD or Asperger* or attention deficit* or ADHD* or ADDH or hyperactivity* or impulsiv* cerebral pals* or spastic displeg* or epilep* or mutism* or tic* or Tourette* or ((happy or child*) and puppet*) or fragile x or Frax* or angelman* or prader-willi* or rett* or smith-magenis or williams or Cri-du-Chat or De Lange or down* or Coffin-Lowry or Lesch-Nyhan or Menkes Kinky Hair or Rubinstein-Taybi or WAGR or schizophreni* or Adrenoleukodystrophy or Mucopolysaccharidosis)

BMJ Open

Melatonin for sleep disorders in children with neurodevelopmental disorders: protocol for a systematic review with meta-analysis and Trial Sequential Analysis of randomised clinical trials

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-065520.R2
Article Type:	Protocol
Date Submitted by the Author:	14-Nov-2022
Complete List of Authors:	Jørgensen, Caroline Kamp; Rigshospitalet Copenhagen Trial Unit; Syddansk Universitet Det Sundhedsvidenskabelige Fakultet, Department of Regional Health Research Hermann, Rikke; Centre for children, youth, and families Juul, Sophie ; Rigshospitalet Copenhagen Trial Unit Faltermeier, Pascal; MSH Medical School Hamburg Horowitz, Mark; University College London Division of Psychiatry; North East London NHS Foundation Trust, Research and Development Department Moncrieff, Joanna; University College London Division of Psychiatry; North East London NHS Foundation Trust, Research and Development Department Gluud, Christian; Rigshospitalet Copenhagen Trial Unit; Syddansk Universitet Det Sundhedsvidenskabelige Fakultet, Department of Regional Health Research Jakobsen, Janus; Rigshospitalet Copenhagen Trial Unit; Syddansk Universitet Det Sundhedsvidenskabelige Fakultet, Department of Regional Health Research
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Neurology
Keywords:	SLEEP MEDICINE, Paediatric neurology < NEUROLOGY, Developmental neurology & neurodisability < PAEDIATRICS

Melatonin for sleep disorders in children with neurodevelopmental disorders: protocol for a systematic review with meta-analysis and Trial Sequential Analysis of randomised clinical trials

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Word count: 4,266

Abstract

Introduction: Neurodevelopmental disorders are a group of disorders thought to be associated with the functioning of the brain and nervous system. Children with neurodevelopmental disorders often have sleep-related comorbidities that may negatively affect quality of life for both the children and their families. Melatonin is one of the most used interventions in children with neurodevelopmental disorders and sleep disorders. Previous reviews have investigated the effects of melatonin for sleep disorders in children with neurodevelopmental disorders, but these had important limitations, such as inadequate analysis of adverse effects, small sample sizes, and short follow-up.

Methods and analysis: This is a protocol for a systematic review with meta-analysis and Trial Sequential Analysis of randomised clinical trials. The protocol is reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols. We will search for published and unpublished trials in the Cochrane Central Register of Controlled Trials, MEDLINE Ovid, Embase Ovid, LILACS, Science Citation Index Expanded, Conference Proceedings Citation Index-Science, PsycINFO, ClinicalTrials.gov, and the International Clinical Trials Registry Platform. We will search the databases from their inception without language restrictions. We will also request clinical study reports from regulatory authorities and pharmaceutical companies. Review authors working in pairs will screen reports, extract data, and conduct risk of bias assessments using the Cochrane Risk of Bias tool. We will include randomised clinical trials comparing melatonin versus placebo or no intervention for sleep disorders in children with neurodevelopmental disorders. Primary outcomes will be total sleep time and adverse effects. Secondary outcomes will be quality of life of the child and caregivers and sleep onset latency. Data will be analysed using random-effects and fixed-effect meta-analyses. Certainty of evidence will be assessed with GRADE.

Ethics and dissemination: Ethical approval was not required for this protocol. The systematic review will be published in a peer-reviewed journal.

PROSPERO registration number: CRD42022337530

Keywords: Melatonin; neurodevelopmental disorders; sleep disorders; children; systematic review

Strengths and limitations of this study

- The methodology of our systematic review is predefined in detail to avoid data-driven biased results.
- The protocol is based on the Cochrane Handbook, the eight-step procedure suggested by Jakobsen et al., Trial Sequential Analysis, and the Grading of Recommendations, Assessment, Development and Evaluation approach.
- The systematic review will consider the risks of random errors, systematic errors, publication bias, heterogeneity, and external validity.
- The systematic review will include both published and unpublished trials.
- We assess multiple outcomes and subgroup analyses which increases the risks of type I errors.

Introduction

Description of the condition

Neurodevelopmental disorders are a group of disorders thought to be associated with the functioning of the brain and nervous system.[1] Neurodevelopmental disorders are usually diagnosed in childhood and include neurological disorders such as cerebral palsy, epilepsy, Angelman syndrome, Down's syndrome, Fragile X syndrome, Prader-Willi syndrome, Rett syndrome, Smith-Magenis syndrome, Williams syndrome, and non-specific intellectual disability, along with some psychiatric disorders including autism spectrum disorder, attention deficit hyperactivity disorder (ADHD), and attention deficit disorder (ADD).[1, 2] Children with neurodevelopmental disorders may experience difficulties with learning, attention, behaviour, speech, motor skills, and other neurological functions.[1]

The impact of sleep disturbances was recently ranked as a top 10 research priority within the topics of children with neurodevelopmental disorders by a UK partnership of patients, carers, and clinicians.[3] Children with neurodevelopmental disorders often have sleep-related comorbidities, including sleep disorders such as insomnia disorder, hypersomnolence disorder, narcolepsy, breathing-related sleep disorders, circadian rhythm sleep disorders, rapid eye movement (REM) sleep arousal disorders, non-REM sleep arousal disorders, and nightmare disorders.[2, 4] Studies have shown the prevalence of comorbid neurodevelopmental disorders and sleep disorders is between 25% to 86% compared to 1% to 6% in the general paediatric population.[4-8] Sleep disorders may further enhance problems with learning and behaviour in children with neurodevelopmental disorders,[4-8] and often have a negative effect on quality of life for both the children and their families.[9, 10]

Description of the intervention

Melatonin is a naturally occurring hormone in both humans and animals.[11] Previously, melatonin was derived from animal pineal tissue,[11] but it is now developed synthetically and distributed in different forms, including capsules, tablets, gummies, and liquids.[12] Melatonin is available in many countries either sold as prescription-only medicine or as over-the-counter medicine to treat

sleep disorders in both children and adults, as it is hypothesised to be associated with few adverse effects.[11, 13] Furthermore, melatonin is one of the most commonly used interventions in children with neurodevelopmental disorders and sleep disorders.[14-18] The dosage recommendations vary according to country, but the UK National Health Service currently recommend treatment up to 13 weeks of 2 mg one to two hours before bedtime for adults with sleep problems.[19] However, there are currently no clear guidelines for prescribing melatonin for children and adolescents with neurodevelopmental disorders.[5, 11]

How the intervention might work

The understanding of melatonin's underlying mechanisms has previously been extrapolated from animals to humans, but the exact physiological mechanisms of melatonin in humans remain unclear.[20-22] Melatonin is a neurohormone primarily secreted by the pineal gland.[13] Melatonin mediates dark signals, since the secretion of melatonin is related to darkness, and it is therefore associated with the circadian rhythm in humans.[13, 17] The secretion of melatonin is regulated by the suprachiasmatic nucleus in the hypothalamus, and the production of melatonin depends on darkness, as the exposure to light inhibits secretion.[11, 23] A decrease in the secretion of melatonin has been associated with aging and different diseases, and synthetic melatonin may theoretically reduce sleep disturbance related to melatonin deficiency.[13, 24] Previous studies have shown that melatonin improves total sleep time, sleep onset latency, and sleep quality for adults with sleep disorders, but the effects seem small.[13, 25] Furthermore, some studies suggest that children with autistic spectrum disorders have abnormal secretions of melatonin.[6, 26, 27] For these theoretical reasons, children with neurodevelopmental disorders may benefit from melatonin.

Why it is important to do this review

A systematic review published in 2018 investigated the effects of melatonin for sleep problems in children with neurodevelopmental disorders.[5] The review concluded that melatonin was safe and effective in improving sleep for children with neurodevelopmental disorders.[5] Another systematic review published in 2019 investigated the effects of oral melatonin for non-respiratory sleep disturbances in children with neurodisabilities.[28] The review concluded that there was some evidence of beneficial effects, but the extent of these effects was unclear due to the poor quality of

the evidence.[28] The review also concluded that melatonin was well-tolerated, as comparable adverse effects were found in the melatonin and placebo groups.[28]

These previous reviews had important limitations. The conclusions were affected by a high degree of heterogeneity, high and unclear risk of bias in the included trials, and small sample sizes.[5, 28] Furthermore, the duration of treatment was limited to a maximum of 13 weeks, and adverse events were not adequately reported or analysed in either of the reviews.[5, 28]

In recent studies, it has been questioned whether higher levels of melatonin are associated with delayed puberty, and other adverse effects of melatonin are also theoretically possible.[29-31] In 2021, a two-year follow-up of a trial investigating the treatment with melatonin in 119 children with autism spectrum disorder was published.[32] This trial concluded that melatonin was safe and effective for long-term treatment in children.[32] Other, new randomised clinical trials might have been published since the last published systematic reviews, and on-going trials have been identified on ClinicalTrials.gov.[33, 34] These trials may contribute important information about the use of melatonin in children with neurodevelopmental disorders, including adverse effects. Therefore, there is a need for a systematic review to shed light on this important topic and to assess whether the beneficial effects outweigh any harmful effects. Our systematic review will take risks of systematic errors ('bias'), risks of random errors ('play of chance'), and the certainty of the evidence into consideration when assessing the effects of melatonin for sleep disorders in children with neurodevelopmental disorders.

Methods and analysis

The present protocol has been registered in the PROSPERO database (CRD42022337530) and is reported according to the guidance suggested in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement (please find the checklist in **supplemental material 1**).[35, 36]

Criteria for considering studies for this review

Types of studies

We will include randomised clinical trials irrespective of trial design (including crossover trials), setting, publication status, publication year, and language. We will use online translation services to translate foreign abstracts and reach out to our international colleagues (who will be thanked in the acknowledgements) for help with data extraction of relevant trials. We will not include quasi-randomised trials, cluster-randomised trials, or observational studies.

Types of participants

We will include trials randomising children and adolescents (below 18 years of age) with neurodevelopmental disorders, such as cerebral palsy, epilepsy, Angelman syndrome, Down's syndrome, Fragile X syndrome, Prader-Willi syndrome, Rett syndrome, Smith-Magenis syndrome, Williams syndrome, non-specific intellectual disability, autism spectrum disorder, ADHD, and ADD.[1, 2] Trials will be included if the disorders of the participants are diagnosed by standardised diagnostic criteria, such as the Diagnostic and Statistical Manual of Mental Disorders[37] or International Classification of Diseases[38] or where the diagnosis or designation of neurodevelopmental disorder is made by a clinician. The participants also need to have a diagnosis of any type of sleep disorder (as defined by trialists), such as insomnia disorder, hypersomnolence disorder, narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorders, REM sleep arousal disorder, non-REM sleep arousal disorder, and nightmare disorders.

We will include participants irrespective of sex, comorbidities, demographic factors, the stage of their condition, and the care setting. If a trial reports data where only a subset of participants is eligible (e.g. a combination of children and adults), we will only include data from those participants that fulfil the inclusion criteria, and we will therefore require subset data for the specific group to be available.

Types of interventions

We will include trials where participants in the experimental group are given melatonin at any dose, form (e.g. tablet, capsules, gummies, liquids), duration of administration, type of administration (e.g. oral), timing of administration, and setting. We will include trials where participants receive a

co-intervention (e.g. pharmacological interventions, such as methylphenidate, or non-pharmacological interventions, such as exercise), providing it is delivered equally (in any aspect, e.g. same dose, equal subset of population receiving co-intervention, etc.) in the experimental group and the control group.

Comparators

As control intervention we will accept placebo or 'no intervention'.

Types of outcome measures

Primary outcomes

1) Total sleep time (in minutes using any type of measurement, e.g. polysomnography, actigraphy, self-report, or parent-report).
2) Adverse effects
   a) The proportion of participants with one or more serious adverse events. We will use the International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use—Good Clinical Practice (ICH-GCP) definition of a serious adverse event, which is any untoward medical occurrence that resulted in death, was life-threatening, required hospitalisation or prolonging of existing hospitalisation, resulted in persistent or significant disability or jeopardised the participant.[39] If the trialists do not use the ICH-GCP definition, we will include the data if the trialists use the term 'serious adverse event'. If the trialists do not use the ICH-GCP definition nor use the term serious adverse event, then we will also include the data provided the event clearly fulfils the ICH-GCP definition for a serious adverse event. We will secondly analyse each type of serious adverse event separately.
   b) The proportion of participants with one or more non-serious adverse events (any adverse event not classified as serious). We will also analyse each type of adverse event separately.

Secondary outcomes

1) Quality of life of the child (any valid continuous scale, e.g. Child Quality of Life Questionnaire).[40]
2) Quality of life of the parents/caregivers (any valid continuous scale, e.g. SF-36).[41]
3) Sleep onset latency (in minutes using any type of measurement, e.g. polysomnography, actigraphy, self-report, or parent-report).

Exploratory outcomes

1) Quality of sleep (any valid continuous scale), such as the Pittsburgh Sleep Quality Index.[42]
2) Delayed puberty or any reports of hormonal changes.
3) Any continuous scale assessing adverse effects (e.g. Pediatric Adverse Event Rating Scale).[43]

Timing of outcome assessment

We will include outcome data recorded at the end of the treatment period primarily and at maximum follow-up secondarily.

Search methods for identification of studies

Electronic searches

We will search the following:

- Cochrane Central Register of Controlled Trials (CENTRAL; current issue) in The Cochrane Library
- MEDLINE Ovid (1946 onwards)
- Embase Ovid (1974 onwards)
- LILACS (Latin American and Caribbean Health Science Information database; 1982 onwards)
- Science Citation Index Expanded (Web of Science; 1964 onwards)
- Conference Proceedings Citation Index-Science (Web of Science; 1990 onwards)
- PsycINFO (1967 onwards)
- ClinicalTrials.gov
- International Clinical Trials Registry Platform (ICTRP)

Please see **supplemental material 2** for the search strategy.

Searching other resources

We will check reference lists of all included trials and any relevant systematic reviews to identify additional trials. We will also search for errata and retraction statements for the included trials. We will search websites of pharmaceutical companies (e.g. Natrol, Neurim Pharmaceuticals, Takeda Pharma), websites of U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) to identify relevant trials. We will request FDA, EMA, and national medicines agencies to provide all publicly releasable information about relevant studies that were submitted for marketing approval, including clinical study reports. We will contact authors of eligible trials and other experts to identify any relevant trials (published or unpublished).

Data collection and analysis

We will perform and report the review based on the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions. [44] Analyses will be performed using Stata version 17[45] and Trial Sequential Analysis.[46, 47]

Selection of studies

Two review authors will independently screen titles and abstracts using Covidence.[48] We will mark articles that clearly do not meet the eligibility criteria as excludes, while potentially eligible articles will go through to the next phase. We will retrieve all relevant full-text study reports/publications, and two review authors will independently screen the full text to identify and record reasons for exclusion of the ineligible trials. The two review authors will resolve any disagreement through discussion, or, if required, they will consult with a third author (JCJ). We will illustrate the selection process of the trials in a PRISMA flow diagram.[49] If multiple reports are available for a single trial, all reports will be grouped under a single reference ID.

Data extraction and management

Review authors in pairs will independently extract data from the included trials using a pilot tested data extraction form. Disagreements will be resolved through internal discussion or, if required, by discussion with a third author (JCJ). The two review authors will assess all publications of a trial together to evaluate all available data simultaneously. We will contact trial authors by email to obtain any additional data, which may not have been reported sufficiently in the publication. We will extract the following data:

- Methods: trial setting, trial location, trial design, trial duration, duration of follow-ups, date of the trial, estimation of sample size, inclusion criteria, and exclusion criteria
- Participants: number randomised, number analysed for each outcome, number lost to follow-up, age (mean and standard deviation), sex ratio, and diagnostic criteria
- Interventions: type, dose, timing, and duration of intervention
- Control: type, dose, timing, and duration of comparison
- Co-intervention: type, dose, timing, and duration of co-interventions
- Outcomes: primary, secondary, and exploratory outcomes at the reported time points
- Notes: trial funding and conflicts of interest of the trial authors

One review author will transfer the data to Stata. We will double-check the data by comparing the data presented in the review to the data extraction form.

Assessment of risk of bias in included studies

Our bias risk assessment will be based on the Cochrane Risk of Bias tool—version 2 (RoB 2) as recommended in the Cochrane Handbook of Systematic Reviews of Interventions.[44] We will evaluate the methodology in respect of the following bias domains:

- Bias arising from the randomisation process
- Bias due to deviations from the intended interventions (effect of assignment to intervention).
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

Review authors in pairs will independently assess the risk of bias using a template (available at https://www.riskofbias.info/). Disagreements will be resolved through internal discussion or, if required, by discussion with a third author (JCJ). We will use the signalling questions in the RoB 2 tool to rate each domain at either 'low risk of bias', 'some concerns', or 'high risk of bias'. We will assess all domains of risk of bias for each outcome in each trial. The overall risk of bias of a result will be judged to be low if all domains are assessed at low risk of bias. If one or more domains are assessed at either some concerns or high risk of bias, the overall risk of bias will be assessed at high. We will assess the risk of bias for the outcomes of the included trials presented in the 'Summary of findings' table (primary and secondary outcomes at end of treatment). The risk of bias assessments will be illustrated in a table (using https://www.riskofbias.info/), and the assessments will be used to conduct subgroup analyses. The risk of bias assessment will also be used to inform the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) and the 'Summary of findings' table. For trials using crossover design, only data from the first period will be assessed.

Measures of treatment effect

Continuous outcomes

We will calculate mean differences (MDs) and consider calculating standardised mean differences (SMD) with 95% CIs for continuous outcomes. We will enter data presented as a scale with a consistent direction of effect. We will primarily analyse scores assessed at single time points. If only changes from baseline scores are reported, we will analyse the results together with follow-up scores for MD (not for SMD).[44] If standard deviations (SDs) are not reported, we will calculate the SDs using trial data, if possible, or request such data from the authors.

Dichotomous outcomes

We will calculate risk ratios (RRs) with 95% confidence intervals (CI) for dichotomous outcomes.

Unit of analysis issues

We will only include randomised clinical trials. Trials using a crossover design will be treated as parallel trials, since only data from the first period will be included.[44] Where multiple trial arms

are reported in a single trial, we will include only the relevant arms. For trials with multiple relevant experimental or control groups, we will combine the groups as appropriate.[44]

Dealing with missing data

We will, as the first option, contact all trial authors to obtain information on missing data (i.e. for data extraction and for assessment of risk of bias, as specified above). We will use intention-to-treat data if provided by the trialists.[50]

Dichotomous outcomes

We will not impute missing values for any outcomes in our primary analysis. In our sensitivity analyses (see below), we will impute data.

Continuous outcomes

We will not impute missing values for any outcomes in our primary analysis. In our sensitivity analysis (see below) for continuous outcomes, we will impute data.

Assessment of heterogeneity

We will investigate forest plots to visually assess for signs of heterogeneity. We will also estimate the presence of statistical heterogeneity by a chi^2 test (threshold $P < 0.05$) and measure the quantities of heterogeneity by the I^2 statistic.[51, 52] We will investigate possible heterogeneity through subgroup analyses. We may ultimately decide that a meta-analysis should be avoided.[44] We will interpret I^2 heterogeneity as suggested by the Cochrane Handbook for Systematic Reviews of Interventions.[44] If we identify substantial heterogeneity ($I^2 > 50\%$), we will report it, and explore the possible causes by prespecified subgroup analyses. We will carefully investigate trial characteristics and report if we find unexpected heterogeneity due to clinical or methodological factors. Ultimately it will be decided if meta-analysis should be avoided.

Assessment of reporting biases

We will use funnel plots to assess reporting bias if ten or more trials are included in an outcome.[44] We will visually inspect funnel plots to assess the risk of small trial effects that could potentially reflect publication bias. We are aware of the limitations of a funnel plot (i.e. a funnel plot assesses bias due to small sample size). From this information, we will assess possible risk of publication bias. For dichotomous outcomes, we will test asymmetry with the Harbord test[53] if τ^2 is less than 0.1 and with the Rücker test if τ^2 is more than 0.1. For continuous outcomes, we will use the regression asymmetry test[54] and the adjusted rank correlation.[55]

Data synthesis

Meta-analysis

We will undertake this meta-analysis according to the recommendations stated in the Cochrane Handbook for Systematic Reviews of Interventions,[44] Keus et al.,[56] and our eight-step procedure suggested by Jakobsen et al.[57] We will assess our intervention effects with both random-effects meta-analyses (Hartung-Knapp-Sidik-Jonkman)[58] and fixed-effect meta-analyses (Mantel-Haenszel for dichotomous outcomes and inverse variance for continuous outcomes),[44, 59] and report both meta-analysis results.[57] We will primarily report the most conservative result (widest confidence interval and highest P value), and report the less conservative result as a sensitivity analysis.[57] As two primary outcomes are specified, we will consider a P value of 0.025 or less as the threshold for statistical significance for all outcomes.[57] Our primary analyses will include all trials. Where data are only available from one trial, we will use Fisher's exact test for dichotomous data and Student's t-test for continuous data.[60, 61]

Trial Sequential Analysis

Traditional meta-analysis runs the risk of random errors due to sparse data and repetitive testing of accumulating data when updating reviews. We wish to control for the risks of type I and type II errors. We will therefore perform Trial Sequential Analysis on all outcomes, in order to calculate the required information size (i.e. the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) and the cumulative Z-curve's breach of relevant trial sequential monitoring boundaries.[47, 62-67] A more detailed description of Trial Sequential Analysis can be found in the manual[47] and at www.ctu.dk/tsa/. For dichotomous outcomes, we will estimate the required information size based on the observed proportion of patients with an outcome in the

control group (the cumulative proportion of patients with an event in the control groups relative to all patients in the control groups), a relative risk reduction or a relative risk increase of 25%, an alpha of 2.5% for all our outcomes, a beta of 10%, and the observed diversity as suggested by the trials in the meta-analysis. For continuous outcomes, we will use the observed standard deviation (SD) in the control group, a mean difference of 30 minutes when assessing total sleep time; otherwise, a mean difference of the observed SD/2, an alpha of 2.5% for all outcomes, a beta of 10%, and the observed diversity of the trials in the meta-analysis. We will only use the diversity-adjusted required information size (DARIS) for random-effects Trial Sequential Analyses.

Subgroup analysis and investigation of heterogeneity

We will perform the following subgroup analyses on the primary outcomes:

1. Type of neurodevelopmental disorder: this subgroup analysis will assess whether the effects of melatonin are different depending on the neurodevelopmental disorder of the child.
2. Age (below 12 years compared to above 12 years and preschool-age children compared to school-age children (as defined by trialists)): this will assess whether the effects of melatonin vary depending on the age of the participants.
3. Type of comparator (placebo or no intervention): this subgroup analysis will assess whether the effects of melatonin vary depending on the comparator.
4. Timing of the melatonin administration. If data are available, we will use the following comparisons: < 2 hours before bedtime, 2-4 hours before bedtime, or 4-8 hours before bedtime. If not, we will use definitions by trialists. This subgroup analysis is relevant, because the timing of administration may affect the outcomes.[68-70]
5. Formulation of medication: this subgroup analysis will assess whether the effects of melatonin vary depending on the formulation of melatonin.
6. Type of sleep disorder: this subgroup analysis will assess whether the effects of melatonin vary depending on the type of sleep disorder.
7. Trials at high risk of bias compared to trials at low risk of bias: this subgroup analysis will assess whether the effects of melatonin vary depending on the risk of bias of the included trials.
8. Duration of trials: this subgroup analysis will assess whether the effects of melatonin vary depending on the duration of the included trials.

Post-hoc subgroup analyses might be warranted if unexpected clinical or statistical heterogeneity is identified during the analysis of the review results.[57] We will disclose any new subgroup analyses not reported in this protocol in the 'Differences between protocol and review' section of the systematic review.

Sensitivity analysis

To assess the potential impact of the missing data, we will perform the two following sensitivity analyses on the primary outcomes:

'Best-worst-case' scenario: we will assume that all participants lost to follow-up in the experimental group had beneficial outcomes (no serious adverse events/improved quality of sleep defined as the group mean plus two SDs).[57] We will accordingly assume that all participants lost to follow-up in the control group had poor outcomes (serious adverse events/deteriorated quality of sleep defined as the group mean plus two SDs).[57]

'Worst-best-case' scenario: we will assume that all participants lost to follow-up in the experimental group had poor outcomes (serious adverse events/deteriorated quality of sleep defined as the group mean plus two SDs).[57] We will accordingly assume that all participants lost to follow-up in the control group had beneficial outcomes (no serious adverse events/improved quality of sleep defined as the group mean plus two SDs).[57]

We will present the results of both scenarios in our review.

We will assess the potential impact of missing SDs for quality of sleep as follows: when SDs are missing, and it is not possible to calculate them, we will impute SDs from trials with similar populations and low risk of bias. If we find no such trials, we will impute SDs from trials with a similar population. As the final option, we will impute SDs from all trials. We will present results of this scenario in our review.

Summary of findings and assessment of the certainty of the evidence

Review authors in pairs will use GRADE to assess the certainty of the body of evidence associated with each of the primary and secondary outcomes at end of treatment in our review. We will construct ‘Summary of findings' tables using the GRADEpro GDT.[71] The GRADE approach appraises the certainty of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. We will assess the GRADE levels of evidence as either high, moderate, low, or very low certainty on the following quality measures: risk of bias (the overall risk of bias will be used for each outcome), directness of the evidence, heterogeneity of the data, precision of effect estimates (assessed by Trial Sequential Analysis), and risk of publication bias.[71] We will downgrade the evidence by one or two levels due to serious or very serious issues. We will downgrade imprecision in GRADE by two levels if the accrued number of participants is below 50% of the DARIS, and one level if between 50 and 100% of DARIS. We will not downgrade if the cumulative Z-curve crosses the monitoring boundaries for benefit, harm, or futility, or DARIS is reached. Two review authors will assess the certainty of evidence independently and decide on downgrading. If no agreement can be reached, a third review author (JCJ) will resolve the discussion. We will justify all decisions to downgrade the certainty of evidence using footnotes, and we will make comments to aid the reader's understanding of the review where necessary. The 'Summary of findings' table will also report the anticipated absolute effects, relative effects, number of participants, type of participants, and setting.

Differences between the protocol and the review

We will conduct the review according to this published protocol and report any deviations from it in the “differences between the protocol and the review” section of the systematic review.

Patient and public involvement

None.

Ethics and dissemination

Ethical approval was not required for this protocol and systematic review. The results of the systematic review will be published in a peer-reviewed journal to help inform future research and clinical practice.

Acknowledgements

We thank Sarah Louise Klingenberg (Information Specialist, The Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital - Rigshospitalet, Denmark) for the help with developing the search strategy.

Contributors

CKJ, RH, SJ, PF, MH, JM, CG, and JCJ contributed to the conceptualisation and design of the study. CKJ and JCJ wrote the original draft. All authors commented and approved the final manuscript. JCJ is the guarantor of the review.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

None declared.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Section
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Title
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Abstract
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title page
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Contributors
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Differences between the protocol and the review
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Funding
Sponsor	5b	Provide name for the review funder and/or sponsor	Funding
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Why it is important to do this review
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Why it is important to do this review
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Criteria for considering studies for this review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Search methods for identification of studies
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that	Supplementary material 2

		it could be repeated	
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Data collection and analysis
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Selection of studies
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Data extraction and management
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Data extraction and management
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Types of outcomes measures
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Assessment of risk of bias in included studies
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Data synthesis
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Dealing with missing data, Assessment of heterogeneity
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Subgroup analysis and investigation of heterogeneity, Sensitivity analysis
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Unit of analysis issues
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Assessment of reporting biases
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Summary of findings and assessment of the certainty of the evidence

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Search strategies for
Melatonin for neurodevelopmental disorders and non-respiratory sleep disorders
Preliminary searches prepared 3 June 2022

Cochrane Central Register of Controlled Trials (latest issue) in the Cochrane Library

#1 MeSH descriptor: [Neurodevelopmental Disorders] explode all trees
#2 MeSH descriptor: [Central Nervous System Diseases] explode all trees
#3 MeSH descriptor: [Intellectual Disability] explode all trees
#4 (((neurodevelopment* or neurotic* or development* or mental* or central nervous system or cns or intellectual* or ((disruptive or child) and behavio*) or Communicati* or speech* or language or Learning or Motor* or psychomotor or Reactive Attachment* or Stereotypic Movement*) and (disease* or disorder* or disabilit* or syndrom* or dysfunc* or impair* or deficienc* or retardation*)) or neurodisabilit* or neuro-disabilit* or idiocy or dyslexia or dyscalculia or autis* or kaunner* or ASD or Asperger* or attention deficit* or ADHD* or ADDH or hyperactivity* or impulsiv* cerebral pals* or spastic displeg* or epilep* or mutism* or tic* or Tourette* or ((happy or child*) and puppet*) or fragile x or Frax* or angelman* or prader-willi* or rett* or smith-magenis or williams or Cri-du-Chat or De Lange or down* or Coffin-Lowry or Lesch-Nyhan or Menkes Kinky Hair or Rubinstein-Taybi or WAGR or schizophreni* or Adrenoleukodystrophy or Mucopolysaccharidosis)
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Melatonin] explode all trees
#7 (melatonin* or Circadin* or Slenyto* or (Methoxy near Acetyl near tryptamin*))
#8 #6 or #7
#9 #5 and #8
#10 MeSH descriptor: [Adolescent] explode all trees
#11 MeSH descriptor: [Child] explode all trees
#12 MeSH descriptor: [Infant] explode all trees
#13 MeSH descriptor: [Pediatrics] explode all trees
#14 (baby or babies or infan* or child* or toddler* or pre-school* or preschool* or adolescen* or teen* or schoolchild* or schoolage* or pediatric* or paediatric*)
#15 #10 or #11 or #12 or #13 or #14
#16 #9 and #15

MEDLINE Ovid (1946 to the date of the search)

1. exp Neurodevelopmental Disorders/
2. exp Central Nervous System Diseases/
3. exp Intellectual Disability/
4. (((neurodevelopment* or neurotic* or development* or mental* or central nervous system or cns or intellectual* or ((disruptive or child) and behavio*) or Communicati* or speech* or language or Learning or Motor* or psychomotor or Reactive Attachment* or Stereotypic Movement*) and (disease* or disorder* or disabilit* or syndrom* or dysfunc* or impair* or deficienc* or retardation*)) or neurodisabilit* or neuro-disabilit* or idiocy or dyslexia or dyscalculia or autis* or kanner* or ASD or Asperger* or attention deficit* or ADHD* or ADDH or hyperactivity* or impulsiv* cerebral pals* or spastic displeg* or epilep* or mutism* or tic* or Tourette* or ((happy or child*) and puppet*) or fragile x or Frax* or angelman* or prader-willi* or rett* or smith-magenis or williams or Cri-du-Chat or De Lange or down* or Coffin-Lowry or Lesch-Nyhan or Menkes Kinky Hair or Rubinstein-Taybi or WAGR or schizophreni* or Adrenoleukodystrophy or Mucopolysaccharidosis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
5. 1 or 2 or 3 or 4
6. exp Melatonin/
7. (melatonin* or Circadin* or Slenyto* or 5-Methoxy-N-Acetyltryptamin* or N-Acetyl-5-Methoxytryptamin*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
8. 6 or 7
9. 5 and 8
10. exp adolescent/ or exp child/ or exp infant/
11. exp Pediatrics/
12. (baby or babies or infan* or child* or toddler* or pre-school* or preschool* or adolescen* or teen* or schoolchild* or schoolage* or pediatric* or paediatric*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

13. 10 or 11 or 12
14. 9 and 13
15. (randomized controlled trial or controlled clinical trial or retracted publication or retraction of publication).pt. or clinical trials as topic.sh. or trial.ti.
16. (random* or blind* or placebo*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
17. 14 and (15 or 16)

Embase Ovid (1974 to the date of the search)

1. exp mental disease/
2. exp central nervous system disease/
3. exp intellectual impairment/
4. (((neurodevelopment* or neurotic* or development* or mental* or central nervous system or cns or intellectual* or ((disruptive or child) and behavio*) or Communicati* or speech* or language or Learning or Motor* or psychomotor or Reactive Attachment* or Stereotypic Movement*) and (disease* or disorder* or disabilit* or syndrom* or dysfunc* or impair* or deficienc* or retardation*)) or neurodisabilit* or neuro-disabilit* or idiocy or dyslexia or dyscalculia or autis* or kanner* or ASD or Asperger* or attention deficit* or ADHD* or ADDH or hyperactivity* or impulsiv* cerebral pals* or spastic displeg* or epilep* or mutism* or tic* or Tourette* or ((happy or child*) and puppet*) or fragile x or Frax* or angelman* or prader-willi* or rett* or smith-magenis or williams or Cri-du-Chat or De Lange or down* or Coffin-Lowry or Lesch-Nyhan or Menkes Kinky Hair or Rubinstein-Taybi or WAGR or schizophreni* or Adrenoleukodystrophy or Mucopolysaccharidosis).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
5. 1 or 2 or 3 or 4
6. exp melatonin/
7. (melatonin* or Circadin* or Slenyto* or 5-Methoxy-N-Acetyltryptamin* or N-Acetyl-5-Methoxytryptamin*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
8. 6 or 7
9. 5 and 8
10. exp adolescent/ or exp child/
11. exp pediatrics/
12. (baby or babies or infan* or child* or toddler* or pre-school* or preschool* or adolescen* or teen* or schoolchild* or schoolage* or pediatric* or paediatric*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
13. 10 or 11 or 12
14. 9 and 13
15. Randomized controlled trial/ or Controlled clinical trial/ or retracted article/ or (erratum or tombstone).pt. or trial.ti. or yes.ne.
16. (random* or blind* or placebo*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
17. 14 and (15 or 16)

LILACS (Bireme; 1982 to the date of the search)

(((neurodevelopment$ or neurotic$ or development$ or mental$ or central nervous system or cns or intellectual$ or ((disruptive or child) and behavio$) or Communicati$ or speech$ or language or Learning or Motor$ or psychomotor or Reactive Attachment$ or Stereotypic Movement$) and (disease$ or disorder$ or disabilit$ or syndrom$ or dysfunc$ or impair$ or deficienc$ or retardation$)) or neurodisabilit$ or neuro-disabilit$ or idiocy or dyslexia or dyscalculia or autis$ or kanner$ or ASD or Asperger$ or attention deficit$ or ADHD$ or ADDH or hyperactivity$ or impulsiv$ cerebral pals$ or spastic displeg$ or epilep$ or mutism$ or tic$ or Tourette$ or ((happy or child$) and puppet$) or fragile x or Frax$ or angelman$ or prader-willi$ or rett$ or smith-magenis or williams or Cri-du-Chat or De Lange or down$ or Coffin-Lowry or Lesch-Nyhan or Menkes Kinky Hair or Rubinstein-Taybi or WAGR or schizophreni$ or Adrenoleukodystrophy or Mucopolysaccharidosis) [Words] and (melatonin$ or Circadin$ or Slenyto$ or 5-Methoxy-N-Acetyltryptamin$ or N-Acetyl-5-Methoxytryptamin$) [Words] and (baby or babies or infan$ or child$ or toddler$ or pre-school$ or preschool$ or adolescen$ or teen$ or schoolchild$ or schoolage$ or pediatric$ or paediatric$) [Words]

PsycINFO (EBSCO Host; date will be given at review stage)

S11 S9 AND S10

S10 TX (random* or blind* or placebo* or trial*)
S9 S5 AND S8
S8 S6 OR S7
S7 TX (melatonin* or Circadin* or Slenyto* or 5-Methoxy-N-Acetyltryptamin* or N-Acetyl-5-Methoxytryptamin*)
S6 MA Melatonin
S5 S1 OR S2 OR S3 OR S4
S4 TX (((neurodevelopment* or neurotic* or development* or mental* or central nervous system or cns or intellectual* or ((disruptive or child) and behavio*) or Communicati* or speech* or language or Learning or Motor* or psychomotor or Reactive Attachment* or Stereotypic Movement*) and (disease* or disorder* or disabilit* or syndrom* or dysfunc* or impair* or deficienc* or retardation*)) or neurodisabilit* or neuro-disabilit* or idiocy or dyslexia or dyscalculia or autis* or kanner* or ASD or Asperger* or attention deficit* or ADHD* or ADDH or hyperactivity* or impulsiv* cerebral pals* or spastic displeg* or epilep* or mutism* or tic* or Tourette* or ((happy or child*) and puppet*) or fragile x or Frax* or angelman* or prader-willi* or rett* or smith-magenis or williams or Cri-du-Chat or De Lange or down* or Coffin-Lowry or Lesch-Nyhan or Menkes Kinky Hair or Rubinstein-Taybi or WAGR or schizophreni* or Adrenoleukodystrophy or Mucopolysaccharidosis)
S3 MA Intellectual Disability
S2 MA Central Nervous System Diseases
S1 MA Neurodevelopmental Disorders

Science Citation Index Expanded (1900 to the date of the search) and Conference Proceedings Citation Index – Science (1990 to the date of the search) (Web of Science)
#5 #4 AND #3 AND #2 AND #1
#4 TI=(random* or blind* or placebo* or trial*) OR TS=(random* or blind* or placebo*)
#3 TS=(baby or babies or infan* or child* or toddler* or pre-school* or preschool* or adolescen* or teen* or schoolchild* or schoolage* or pediatric* or paediatric*)
#2 TS=(melatonin* or Circadin* or Slenyto* or 5-Methoxy-N-Acetyltryptamin* or N-Acetyl-5-Methoxytryptamin*)
#1 TS=(((neurodevelopment* or neurotic* or development* or mental* or central nervous system or cns or intellectual* or ((disruptive or child) and behavio*) or Communicati* or speech* or language or Learning or Motor* or psychomotor or Reactive Attachment* or Stereotypic Movement*) and (disease* or disorder* or disabilit* or syndrom* or dysfunc* or impair* or deficienc* or retardation*)) or neurodisabilit* or neuro-disabilit* or idiocy or dyslexia or dyscalculia or autis* or kanner* or ASD or Asperger* or attention deficit* or ADHD* or ADDH or hyperactivity* or impulsiv* cerebral pals* or spastic displeg* or epilep* or mutism* or tic* or Tourette* or ((happy or child*) and puppet*) or fragile x or Frax* or angelman* or prader-willi* or rett* or smith-magenis or williams or Cri-du-Chat or De Lange or down* or Coffin-Lowry or Lesch-Nyhan or Menkes Kinky Hair or Rubinstein-Taybi or WAGR or schizophreni* or Adrenoleukodystrophy or Mucopolysaccharidosis)