Review information

Authors

Sundhedsstyrrelsen[1]

[1][Empty affiliation]

Citation example: S. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Characteristics of studies

Characteristics of included studies

Appleton 2012

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	See Abdelgadir 2018 "Melatonin for the management of sleep problems in children with neurodevelopmental disorders: A systematic review and meta-analysis."

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reference: Abdelgadir et al. 2018
Allocation concealment (selection bias)	Low risk	Reference: Abdelgadir et al. 2018
Blinding of participants and personnel (performance bias)	Low risk	Reference: Abdelgadir et al. 2018
Blinding of outcome assessment (detection bias)	Low risk	Reference: Abdelgadir et al. 2018
Incomplete outcome data (attrition bias)	Unclear risk	Reference: Abdelgadir et al. 2018
Selective reporting (reporting bias)	Low risk	Reference: Abdelgadir et al. 2018
Other bias	Low risk	See Abdelgadir 2018 "Melatonin for the management of sleep problems in children with neurodevelopmental disorders: A systematic review and meta-analysis."

Ardakani 2018

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention ● *Age (mean, SD)*: 8.9, 2.1 ● *Male gender (%)*: 54.2 Control ● *Age (mean, SD)*: 8.4, 2.2 ● *Male gender (%)*: 48.6 **Included criteria:** Both boys and girls, aged 6-12years, who were diagnosed with AD, using the Hanifin and Rajka criteria, were recruited for this study. **Excluded criteria:** Children diagnosed with acquired im-munosuppressive disease or other chronic conditions and patients who were receiving any systemic corticosteroid or other immuno-suppressive drugs or taking antihistamines within the last 3months before the study were excluded. **Pretreatment:**

Interventions	**Intervention Characteristics** Intervention ● *Description*: Initially, study participants were matched according to their age, se-verity of disease, and the degree of sleep disturbance. Then, they were randomly allocated into two intervention groups to take either 6mg melatonin (2 melatonin tablets, 3mg each) (n=35) or placebo (n=35) once a day an hour before bedtime for 6weeks. All patients were instructed to receive usual treatment of AD including bath-ing habits, moisturizing cream (Eucerin), and topical corticosteroid (mometasone 0.1% or hydrocortisone 1% ointments). During the study period, all of the participants were asked to take a bath once daily with warm water for 5-10minutes and to apply an emollient immediately after bathing. Due to lack of proper evidence regard-ing the optimal dosage of melatonin for children with AD, we used the above-mentioned dose and duration of intervention based on a previously published study conducted in children with AD.12Melatonin and placebo tablets were produced in the same shape and package by Webber Naturals Pharmaceutical Company (Coquitlam, Canada) and Barij Essence Pharmaceutical Company (Kashan, Iran), respectively. Randomization assignment was conducted using computer-generated random numbers. Randomization and alloca-tion concealment for both the researchers and participants were carried out by a trained staff at the pediatric clinic. Compliance rate was determined by counting the number of tablets in the contain-ers returned back to the clinic by participants. In addition, parents received a daily reminder message on their cell phones to give sup-plements to their children regularly. ● *Dose*: 6 mg ● *Duration*: 6 weeks
Outcomes	Bivirkninger ● **Outcome type**: ContinuousOutcome
Identification	**Sponsorship source:** The present study was supported by a grant from the Vice-chancellor for Research, KAUMS, Kashan, and Iran (grant no. 96110) **Country:** Iran **Authors name:** Zatollah Asemi **Institution:** Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, Iran **Email:** asemi_r@yahoo.com
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization assignment was conducted using computer- generated random numbers."
Allocation concealment (selection bias)	Low risk	Quote: "Melatonin and placebo tablets were produced in the same shape and package by Webber Naturals Pharmaceutical Company (Coquitlam, Canada) and Barij Essence Pharmaceutical Company (Kashan, Iran), respectively. Randomization assignment was conducted using computer- generated random numbers. Randomization and alloca- tion concealment for both the researchers and participants were carried out by a trained staff at the pediatric clinic."
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Melatonin and placebo tablets were produced in the same shape and package by Webber Naturals Pharmaceutical Company (Coquitlam, Canada) and Barij Essence Pharmaceutical Company (Kashan, Iran), respectively." Judgement Comment: Double-blinded. Participants likely blinded (see quote). Tablets packed by two independent companies, personnel likely blinded.
Blinding of outcome assessment (detection bias)	Low risk	Judgement Comment: Double-blinded
Incomplete outcome data (attrition bias)	Low risk	Quote: "Overall, there were nine participants who discontinued the study, four in the melatonin intervention group and five in the placebo group, all due to personal reasons (Figure 1). However, using ITT, all 70 participants who had been recruited for the study were included in the final analysis." Quote: "The intention- to- treat (ITT) analysis was applied to all randomly allocated subjects."
Selective reporting (reporting bias)	High risk	Quote: "DS 2.1 | Participants and ethics statements This randomized, double- blinded, placebo- controlled trial was ini- tially registered in the Iranian registry of clinical trials (http://www. irct.ir: IRCT2017082733941N12). The study was" Judgement Comment: There are reported on more outcomes that are stated a priori in the study protocol, thus they do not match on the reported outcomes,

Other bias	Low risk	Quote: "The present study was supported by a grant from the Vice- chancellor for Research, KAUMS, Kashan, and Iran (grant no. 96110). C O N FL I C T O F I N T E R E S T None." Judgement Comment: The study appears to be free from other sources of bias

Barlow 2021

Methods	RCT
Participants	Børn + unge med hjernerystelse
Interventions	2 uger med melatonin 10 mg
Outcomes	Bivirkninger
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias)	Low risk	
Blinding of outcome assessment (detection bias)	Low risk	
Incomplete outcome data (attrition bias)	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Chang 2016

Methods	RCT Cross-over
Participants	Atopic dermatitis
Interventions	4 uger melatonin 3 mg
Outcomes	Bivirkninger
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed with a computer-generated sequence by special- ized personnel who had no further involvement in the rest of the trial.
Allocation concealment (selection bias)	Low risk	Allocation codes were disclosed only after the entire clinical trial was completed.The melatonin and placebo tablets were identical in appearance.
Blinding of participants and personnel (performance bias)	Low risk	The participants and their caregivers, treating phy- sicians, those assessing outcomes, and those analyzing the data were all masked to group assignment.
Blinding of outcome assessment (detection bias)	Low risk	The participants and their caregivers, treating phy- sicians, those assessing outcomes, and those analyzing the data were all masked to group assignment.
Incomplete outcome data (attrition bias)	Unclear risk	Uklart hvilken impact hhv 4 (melatonin gruppen) og 6 (placebo gruppen) har i dette cross over study, idet alle deltagere EoT har modtaget intervention og placebo. 79% gennemfører hele studiet
Selective reporting (reporting bias)	Low risk	No apparent sources of bias
Other bias	Low risk	No apparent sources of bias

Cortesi 2012a

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	See Abdelgadir 2018 "Melatonin for the management of sleep problems in children with neurodevelopmental disorders: A systematic review and meta-analysis."

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reference: Abdelgadir et al. 2018
Allocation concealment (selection bias)	Low risk	Reference: Abdelgadir et al. 2018
Blinding of participants and personnel (performance bias)	Low risk	Reference: Abdelgadir et al. 2018
Blinding of outcome assessment (detection bias)	Low risk	Reference: Abdelgadir et al. 2018
Incomplete outcome data (attrition bias)	Unclear risk	Reference: Abdelgadir et al. 2018
Selective reporting (reporting bias)	Low risk	Reference: Abdelgadir et al. 2018
Other bias	Low risk	See Abdelgadir 2018 "Melatonin for the management of sleep problems in children with neurodevelopmental disorders: A systematic review and meta-analysis."

Cortesi 2012b

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	See Abdelgadir 2018 "Melatonin for the management of sleep problems in children with neurodevelopmental disorders: A systematic review and meta-analysis."

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reference: Abdelgadir et al. 2018
Allocation concealment (selection bias)	Low risk	Reference: Abdelgadir et al. 2018
Blinding of participants and personnel (performance bias)	Low risk	Reference: Abdelgadir et al. 2018
Blinding of outcome assessment (detection bias)	Low risk	Reference: Abdelgadir et al. 2018
Incomplete outcome data (attrition bias)	Unclear risk	Reference: Abdelgadir et al. 2018
Selective reporting (reporting bias)	Low risk	Reference: Abdelgadir et al. 2018
Other bias	Low risk	See Abdelgadir 2018 "Melatonin for the management of sleep problems in children with neurodevelopmental disorders: A systematic review and meta-analysis."

Dodge 2001

Methods	RCT - cross-over
Participants	developmental disabilities
Interventions	4-6 weeks with melatonin 5mg
Outcomes	Bivirkninger
Identification	
Notes	Fundet i Abdelgadir 2018 "Melatonin for the management of sleep problems in children with neurodevelopmental disorders: A systematic review and meta-analysis."

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reference: Abdelgadir et al. 2018
Allocation concealment (selection bias)	Low risk	Reference: Abdelgadir et al. 2018
Blinding of participants and personnel (performance bias)	Low risk	Reference: Abdelgadir et al. 2018
Blinding of outcome assessment (detection bias)	Unclear risk	Reference: Abdelgadir et al. 2018
Incomplete outcome data (attrition bias)	Unclear risk	Reference: Abdelgadir et al. 2018
Selective reporting (reporting bias)	Low risk	Reference: Abdelgadir et al. 2018
Other bias	Low risk	See Abdelgadir 2018 "Melatonin for the management of sleep problems in children with neurodevelopmental disorders: A systematic review and meta-analysis."

Eckerberg 2012

Methods	RCT - cros-over
Participants	isiopathic sleep, sleep onset difficulties
Interventions	2 uger med melatonin 1 mg
Outcomes	Bivirkninger
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The capsules were dispensed in numbered sets of three bottles, labelled 1, 2 and 3, each containing six capsules. The sets had been randomized and were delivered together with sealed data in envelopes, separate for each set.
Allocation concealment (selection bias)	Low risk	The melatonin and PL were administered to the students as hard- gelatin capsules, which were indistinguishable from one another by appearance, taste and smell. The capsules were dispensed in numbered sets of three bottles, labelled 1, 2 and 3, each containing six capsules. The sets had been randomized and were delivered together with sealed data in envelopes, separate for each set.
Blinding of participants and personnel (performance bias)	Low risk	The randomization of the first two bottles was blind to students and study team and the code was broken only after all study procedures were terminated.
Blinding of outcome assessment (detection bias)	Low risk	The randomization of the first two bottles was blind to students and study team and the code was broken only after all study procedures were terminated.
Incomplete outcome data (attrition bias)	Low risk	No apparent sources of bias
Selective reporting (reporting bias)	Low risk	No apparent sources of bias

Other bias	Low risk	No apparent sources of bias

Garstang 2006

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	See Abdelgadir 2018 "Melatonin for the management of sleep problems in children with neurodevelopmental disorders: A systematic review and meta-analysis."

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reference: Abdelgadir et al. 2018
Allocation concealment (selection bias)	Unclear risk	Reference: Abdelgadir et al. 2018
Blinding of participants and personnel (performance bias)	Unclear risk	Reference: Abdelgadir et al. 2018
Blinding of outcome assessment (detection bias)	Unclear risk	Reference: Abdelgadir et al. 2018
Incomplete outcome data (attrition bias)	High risk	Reference: Abdelgadir et al. 2018
Selective reporting (reporting bias)	Low risk	Reference: Abdelgadir et al. 2018
Other bias	Low risk	Reference: Abdelgadir et al. 2018

Gringras 2017

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	See Abdelgadir 2018 "Melatonin for the management of sleep problems in children with neurodevelopmental disorders: A systematic review and meta-analysis."

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias)	Low risk	
Blinding of outcome assessment (detection bias)	Low risk	
Incomplete outcome data (attrition bias)	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	See Abdelgadir 2018 "Melatonin for the management of sleep problems in children with neurodevelopmental disorders: A systematic review and meta-analysis."

Hancock 2005

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	See McDaid 2019 "Outcome domains and outcome measures used in studies assessing the effectiveness of interventions to manage non-respiratory sleep disturbances in children with neurodisabilities: a systematic review".

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the pharmacy department of the Royal United Hospital, which was responsible for generating random numbers and using these to deter- mine whether to start with 5 or 10 mg of melatonin." Judgement Comment: Insufficient information on sequence generation
Allocation concealment (selection bias)	Low risk	Quote: "Identical capsules of 5 mg of melatonin and placebo were used (two capsules per dose), dis- pensed by the pharmacy department of the Royal United Hospital, which was responsible for generating random numbers and using these to deter- mine whether to start with 5 or 10 mg of melatonin. The dosage regimens were revealed to the investigators and parents or carers only after all of the patients had completed the trial." Judgement Comment: Identical capsules
Blinding of participants and personnel (performance bias)	Low risk	Judgement Comment: Double-blinded, so likely that the participants and personnel were blinded
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The dosage regimens were revealed to the investigators and parents or carers only after all of the patients had completed the trial. The" Judgement Comment: Outcomes were parent/carer reported, and these were likely blinded.
Incomplete outcome data (attrition bias)	Low risk	Quote: "One patient completed the study, but the diaries were lost in the mail, and we had not thought to ask to have them photocopied before they were posted to us."
Selective reporting (reporting bias)	Low risk	Quote: "The sleep diaries were used to monitor the sleep latency (ie, time taken to fall asleep), the total sleep time, and the number of awakenings each night. The seizure diaries were used to monitor the frequency and type of seizures (if any) experienced by the patients during the study period. The carers were also asked to record any illnesses the child had or any possible side effects that they suffered during the trial period." Judgement Comment: No reference to study protocol, but appears to report on all outcomes of interest
Other bias	Low risk	Quote: "Supported by a grant from the Bath Unit for Research in Paediatrics. E.H. was funded by the Tuberous Sclerosis Association and Cow and Gate. F.O. was in receipt of a Wellcome Trust research training fellowship in epidemiology." Judgement Comment: The study appears to be free from other sources of bias

Hayashi 2021

Methods	RCT
Participants	
Interventions	
Outcomes	
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Medidata Balance® (Medidata Solu-tion, Inc.; New York, NY, USA) was used to allocate the random numbers to eligible children that had been generated by an independent manager. The minimization method for randomization used a history of ramelteon treatment and the median SOL during the last 7 days of the screening phase in an attempt to avoid the skew randomization to either of the 3 study groups of children with the history or a biased median SOL, if any.
Allocation concealment (selection bias)	Unclear risk	Information on allocation concealment was not provided
Blinding of participants and personnel (performance bias)	Low risk	Patients and personnel who were involved in the present study were blinded to treatment assignments.
Blinding of outcome assessment (detection bias)	Low risk	Patients and personnel who were involved in the present study were blinded to treatment assignments.
Incomplete outcome data (attrition bias)	Low risk	Data missing did not occur during the screening and randomization phases. Information on all outcomes seem sufficient to use in further analyses although main outcome data could be more clearly presented
Selective reporting (reporting bias)	Low risk	No reference to study protocol, but appears to report on outcomes of interest
Other bias	Unclear risk	The study sponsor, Nobelpharma Co., Ltd., provided investigational drugs for this study—melatonin granules and placebo. Nobelpharma Co., Ltd. manufac-tured placebo, and an independent third party organization ensured indistinguishability between active drug—1- and 4-mg melatonin granules—and placebo. Not clearly stated that funder was not involved in any processes.

Jain 2015

Methods	RCT cross-over
Participants	Epilepsi
Interventions	4 uger med melatonin 9 mg
Outcomes	Bivirkninger
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The Investigational Pharmacy at CCHMC performed the randomization by random number generators in www.randomization.com
Allocation concealment (selection bias)	Low risk	Random number generators in www.randomization.com, <b>ensured blinding via over-encapsulation of both the melatonin and placebo pills to have the same appearance, and dispensed the study medications.
Blinding of participants and personnel (performance bias)	Low risk	Participants and the rest of the study team was blinded to the allocation throughout data collection
Blinding of outcome assessment (detection bias)	High risk	The pharmacy and the statistician were unblinded
Incomplete outcome data (attrition bias)	Low risk	No apparent sources of bias
Selective reporting (reporting bias)	Low risk	No apparent sources of bias
Other bias	Low risk	No apparent sources of bias

Jan 2000

Methods	
Participants	
Interventions	
Outcomes	

Identification	
Notes	See McSee McDaid 2019 "Outcome domains and outcome measures used in studies assessing the effectiveness of interventions to manage non-respiratory sleep disturbances in children with neurodisabilities: a systematic review".

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: Insufficient information on sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "Then the 16 subjects were randomly prescribed CR or FR melatonin in a bubble pack, each for 11 days, following which the drugs were crossed over." Judgement Comment: Insufficient information on allocation concealment
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Both investigators and caregivers were blinded as to the order of the medications."
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Both investigators and caregivers were blinded as to the order of the medications."
Incomplete outcome data (attrition bias)	Unclear risk	Judgement Comment: No information on missing data
Selective reporting (reporting bias)	Low risk	Judgement Comment: No reference to study protocol, but appears to report on all outcomes of interest
Other bias	Low risk	Quote: "NEURIM Pharmaceuticals, Tel Aviv, Israel" Judgement Comment: Last author from the pharma industry. Conflicts of interest not reported nor how the study was funded. The study appears otherwise to be free from other sources of bias

McArthur 1998

Methods	RCT cross-over
Participants	Rett Syndrome
Interventions	4 uger med melatonin 2,5-7,5 mg
Outcomes	Bivirkninger
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Low risk	Identical looking capsules
Blinding of participants and personnel (performance bias)	Unclear risk	Nothing mentioned
Blinding of outcome assessment (detection bias)	Unclear risk	Nothing mentioned
Incomplete outcome data (attrition bias)	Low risk	No drop outs
Selective reporting (reporting bias)	Low risk	No apparent sources of bias
Other bias	Low risk	No apparent sources of bias

Smits 2001

Methods	RCT
Participants	Idiopathic Chronic Sleep onset insomnia (komorbiditet primært ADHD)
Interventions	4 uger med melatonin 5 mg
Outcomes	Bivirkninger
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on randomization method
Allocation concealment (selection bias)	Low risk	Melatonin and placebo provided in identical packages. Code was broken when all data was recorded
Blinding of participants and personnel (performance bias)	Unclear risk	Nothing mentioned
Blinding of outcome assessment (detection bias)	Low risk	All investigators were blinded
Incomplete outcome data (attrition bias)	Low risk	No apparent sources of bias
Selective reporting (reporting bias)	Low risk	No apparent sources of bias
Other bias	Low risk	No apparent sources of bias

Smits 2003

Methods	RCT
Participants	Idiopathic Chronic Sleep onset insomnia (komorbiditet primært ADHD)
Interventions	4 uger med melatonin 5 mg
Outcomes	Bivirkninger
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not mentioned
Allocation concealment (selection bias)	Low risk	All investigators were unaware of treatment allocation. Code broken when all data were recorded
Blinding of participants and personnel (performance bias)	Low risk	As above
Blinding of outcome assessment (detection bias)	Low risk	All investigators were unaware of treatment allocation. Code broken when all data were recorded
Incomplete outcome data (attrition bias)	Low risk	No drop outs
Selective reporting (reporting bias)	Low risk	No apparent sources of bias
Other bias	Low risk	No apparent sources of bias

Van der Heijden 2007

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention ● *Age (mean, SD)*: 9.1, 2.3 ● *Male gender (%)*: 66 ● *proportion using ADHD medication (%)*: 0 Control ● *Age (mean, SD)*: 9.3, 1.8 ● *Male gender (%)*: 82.7 ● *proportion using ADHD medication (%)*: 0 **Inclusion criteria:** Inclusion criteria were 6 to 12 years old, diagnosis of ADHD and SOI, and written informed consent obtained from parents. **Exclusion criteria:** Exclusion criteria were total IQ <80, pervasive developmental disorder, chronic pain, known disturbed hepatic or renal function, epilepsy, earlier use of melatonin, and use of stimulants, neuroleptics, benzodiazepines, clonidine, antidepressants, hypnotics, or " -blockers" within 4 weeks before

	enrollment.
Interventions	**Intervention Characteristics** Intervention ● *Description*: Melatonin ● *Dose*: 3 mg pr barn <40 kg (n=44); 6 mg pr barn >40 kg (n=9) ● *Duration of intervention*: 4 uger Control ● *Description*: Placebo ● *Duration of intervention*: 4 uger
Outcomes	*Indsovningstid (Lights out) (mÃ¥lt med actigraph)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Actigraph ● **Direction**: Lower is better ● **Data value**: Endpoint *Total sovetid (minutes) (mÃ¥lt med Actigraph)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Actigraph ● **Direction**: Higher is better ● **Data value**: Endpoint *Livskvalitet* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: TNO-AZL ● **Direction**: Higher is better ● **Data value**: Endpoint
Identification	**Sponsorship source:** This study was supported by the Maarten Kapelle Foundation and Foundation De Drie Lichten. The authors thank Pharma Nord for making available the trial medication. **Country:** Holland **Authors name:** Kristiaan B. Van der Heijden **Institution:** Epilepsy Center Kempenhaeghe, Heeze; Van der Heijden is also with the Maastricht Institute of Brain and Behavior, Maastricht.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed by a hospital pharmacist not connected to the study in blocks of four to keep the number of patients in each treatment group closely balanced at all times. The following stratification criteria were used: (1) presence of psychiatric comorbidity (disruptive behavior disorder [n = 59]; anxiety disorder [n = 16]; depressive disorder [n = 1]), (2) age category (6-9 years [n = 66]; 10-12 years [n = 39]), and (3) body weight (<40 kg [n = 88]; = 40 kg [n = 17]). Investigators and participants were unaware of treatment allocation. The code was broken after all of the children completed treatment and data were recorded (October 2005)."
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: Insufficient information on allocation concealment
Blinding of participants and personnel (performance bias)	Low risk	Quote: "A 4-week randomized, double-blind, placebo-controlled study, immediately following a 1-week baseline period, was conducted between November 2001 and June 2005."
Blinding of outcome assessment (detection bias)	Low risk	Judgement Comment: Double-blinded og ActigrafmÃ¥ling er ikke i risiko for at vÃ¦re under indflydelse af dette
Incomplete outcome data (attrition bias)	Low risk	Quote: "Analyses were conducted using SPSS, 12.0.1 (SPSS, Inc., Chicago, IL) on an intention-to-treat basis (significance p = .05, two-sided)." Judgement Comment: af 107 patienter er der to drop-outs (1 i hver gruppe)
Selective reporting (reporting bias)	Low risk	Quote: "The protocol was approved by the institutional review board at each center, as a multicenter trial by the Central Committee on Research Involving Human Subjects, and registered in the International Standard Randomized Controlled Trial Number Register (ISRCTN- 47283236). The trial was performed according to the 1997 European Guidelines for

		Good Clinical Research Practice in children and followed the 1983 revised provisions of the 1975 Declaration of Helsinki." Judgement Comment: Study protocol and reported outcomes match
Other bias	Low risk	Judgement Comment: The study appears to be free from other sources of bias

van Geijlswijk 2010

Methods	RCT (Meldos study)
Participants	70 children with Chronic Sleep Onset Insomnia
Interventions	1 uge med hhv 0,05, 0.10, 0.15 mg melatonin pr kg legemsvægt (3 IV arme - 1 kon)
Outcomes	Bivirkninger
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	For this trial, a specialized internet software application (Medsys/De Nieuwe Coster/2004) was developed for randomization of participants, for calculation of the assigned dose (based on body weight), and for collection of sleep log data.
Allocation concealment (selection bias)	Low risk	The capsules were packed in unit dose strips, labeled with “Melatonine×mg” masked with an X to keep participants blind to the treatment allocation and subject number.
Blinding of participants and personnel (performance bias)	Low risk	All participants, care providers, and investigators involved in the study were unaware of the treatment allocation.
Blinding of outcome assessment (detection bias)	Unclear risk	All participants, care providers, and investigators involved in the study were unaware of the treatment allocation.
Incomplete outcome data (attrition bias)	Unclear risk	Afhængig af outcome er der en samlet dropout rate på 5-10 deltagere
Selective reporting (reporting bias)	Low risk	No apparent sources of bias
Other bias	Low risk	No apparent sources of bias

Wasdell 2008

Methods	RCT cross-over
Participants	Neurodevelopmental disabilities
Interventions	10 dage med melatonin 5 mg
Outcomes	Bivirkninger
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A blocked randomization method was employed in which every four patients had equal probability of receiving either of the two treatment sequences.Patients were randomly assigned by the hospital pharmacy to receive either melatonin or placebo first.
Allocation concealment (selection bias)	Low risk	placebo was prepared by the hospital pharmacy in identical capsules as melatonin
Blinding of participants and personnel (performance bias)	Low risk	Patients, caregivers, study investigator, and clinical staff were blind to the medication randomization.
Blinding of outcome assessment (detection bias)	Low risk	Patients, caregivers, study investigator, and clinical staff were blind to the medication randomization.
Incomplete outcome data (attrition bias)	Low risk	One patient (1%) withdrew and was hence excluded from the analysis.

Selective reporting (reporting bias)	Low risk	No apparent sources of bias
Other bias	High risk	Study sponsoring in favour of melatonin?

Weiss 2006

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** ● Overall *Age (mean)*: 10.29 ● *Male gender (%)*: 90.9 **Inclusion criteria:** This two-phase treatment study began with sleep hygieneintervention. Only children who continued to have initial insomnia of 960 minutes were eligible to enter the double-blind, randomized, crossover trial of melatonin versus placebo. Inclusion criteria for participation in the study required that the child be taking stimulant medication with no change in dose for at least 2 months and be willing to maintain the current dose for the duration of the protocol. Parents had to demonstrate competence at completing the somnolog and children had to be willing and able to wear an actigraph wrist monitor and assent to the demands of the sleep hygiene program of a fixed bedtime and awakening time. **Exclusion criteria:** Exclusion criteria included children who were in stressful life circumstances that could account for new onset sleep difficulties or children who could or would not comply with sleep hygiene recommendations because they were sharing a bed or had some other environmental factor that would account for their sleep deficits. This included children who had comorbid medical or psychiatric illness that could be associated with insomnia or required treatment with a medication other than a stimulant at dosages known to cause insomnia or sedation. Children living in multiple households were excluded unless all of the caregivers could reliably participate in the program. The resulting sample was nonetheless comorbid for difficulties with oppositional disorder, enuresis, learning problems, and some degree of anxiety or depressive symptoms. We did not accept children with known diagnoses of other major sleep disorders but neither were these children evaluated in a sleep laboratory to rule out these conditions with a polysomnogram.
Interventions	**Intervention Characteristics** Intervention ● *Description*: Melatonin ● *Dose:* 5 mg uanset vÃ¦gt ● *Duration*: 10 days Placebo ● *Description*: Placebo ● *Duration*: 10 days
Outcomes	*Indsovningstid (Lights out) (sleep latency) (mÃ¥lt med somnolog), (mean, SD)* ● **Outcome type**: Continuous Outcome ● **Reporting**: Fully reported ● **Scale**: Somnolog ● **Direction**: Lower is better ● **Data value**: Endpoint
Identification	**Sponsorship source:** This study was sponsored as an investigator-initiated trial by Circa Dia BV. (melatonin-producent). **Country:** Canada **Authors name:** Margaret Weiss **Institution:** UBC **Email:** weiss@cw.bc.ca
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Subjects were randomly assigned by the pharmacy in blocks of four to receive either melatonin and then placebo or the reverse. All of the patients and study" Judgement Comment: Insufficient information on sequence generation
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: Insufficient information on allocation concealment Insufficient information on allocation concealment
Blinding of participants and personnel (performance bias)	Low risk	Judgement Comment: double-blinded

Blinding of outcome assessment (detection bias)	Low risk	Judgement Comment: double-blinded
Incomplete outcome data (attrition bias)	Low risk	Quote: "Parents of 33 patients seen in the ADHD clinic at British Columbia Children's Hospital consented to their child's participation and all of the children provided written accept. Five parents/patients later with- drew consent or were unable to continue participating in the study. Five patients were sleep hygiene responders and did not continue into randomization. Of the 23 patients eligible for randomization, 1 with- drew consent. Three patients were discontinued because of protocol violations during the randomized treatment phases, which left 19 cases that were able to be evaluated. There were no major differences in outcomes if these patients were or were not included; thus, the results presented include the data for the patients who completed as per protocol (N = 19)."
Selective reporting (reporting bias)	Low risk	Judgement Comment: No reference to study protocol, but the study appears to report on all outcomes of interest.
Other bias	Low risk	Quote: "Disclosure: Dr. Weiss is a consultant, an advisory board and speaker's bureau member, and holds research contracts/grants with Eli Lilly, Shire, and Janssen Ortho; she is a consultant to and an advisory board and a speaker's bureau member of Novartis; she holds a research contract with and is a consultant to Purdue; she is a consultant to and an advisory board member of Johnson & Johnson; and holds a research contract/grant with Circa Dia. The other authors have no financial relationships to disclose." Judgement Comment: The study appears to be free from other sources of bias

Wilhelmsen-Langeland 2013

Methods	RCT
Participants	Delayed sleep phase disorder (DSPD)
Interventions	2 uger med melatonin 3 mg
Outcomes	
Identification	
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomization lists were created (4 groups for the 2-week intervention and 2 groups for the 3-month follow-up) using the Internet-based program Research Randomizer
Allocation concealment (selection bias)	Low risk	Participants were further informed that the capsules contained either melato- nin or maize starch. The melatonin and placebo capsules were packed in identical containers differ- entiated by a number code (1 and 2).
Blinding of participants and personnel (performance bias)	Unclear risk	The 2-week treatment study was double blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear who was blinded
Incomplete outcome data (attrition bias)	Low risk	No apparent sources of bias
Selective reporting (reporting bias)	Low risk	No apparent sources of bias
Other bias	Low risk	No apparent sources of bias

Wirojanan 2009

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	See Abdelgadir 2018 "Melatonin for the management of sleep problems in children with neurodevelopmental disorders: A systematic review and meta-analysis."

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias)	Low risk	
Blinding of outcome assessment (detection bias)	Low risk	
Incomplete outcome data (attrition bias)	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	See Abdelgadir 2018 "Melatonin for the management of sleep problems in children with neurodevelopmental disorders: A systematic review and meta-analysis."

Wright 2011

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	See Abdelgadir 2018 "Melatonin for the management of sleep problems in children with neurodevelopmental disorders: A systematic review and meta-analysis."

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reference: Abdelgadir et al. 2018
Allocation concealment (selection bias)	Low risk	Reference: Abdelgadir et al. 2018
Blinding of participants and personnel (performance bias)	Low risk	Reference: Abdelgadir et al. 2018
Blinding of outcome assessment (detection bias)	Unclear risk	Reference: Abdelgadir et al. 2018
Incomplete outcome data (attrition bias)	Low risk	Reference: Abdelgadir et al. 2018
Selective reporting (reporting bias)	Low risk	Reference: Abdelgadir et al. 2018
Other bias	Low risk	See Abdelgadir 2018 "Melatonin for the management of sleep problems in children with neurodevelopmental disorders: A systematic review and meta-analysis."

Footnotes

Characteristics of excluded studies

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

References to studies

Included studies

Appleton 2012

[Empty]

Ardakani 2018

Taghavi Ardakani, Abbas; Farrehi, Maryam; Sharif, Mohammad Reza; Ostadmohammadi, Vahidreza; Mirhosseini, Naghmeh; Kheirkhah, Davood; Moosavi, Seyed Gholam Abbas; Behnejad, Milad; Reiter, Russel J.; Asemi, Zatollah. The effects of melatonin administration on disease severity and sleep quality in children with atopic dermatitis: A randomized, double-blinded, placebo-controlled trial.. Pediatric Allergy & Immunology 2018;29(8):834-840. [DOI:]

Barlow 2021

[Empty]

Chang 2016

[Empty]

Cortesi 2012a

[Empty]

Cortesi 2012b

[Empty]

Dodge 2001

[Empty]

Eckerberg 2012

[Empty]

Garstang 2006

[Empty]

Gringras 2017

[Empty]

Hancock 2005

[Empty]

Hayashi 2021

[Empty]

Jain 2015

[Empty]

Jan 2000

[Empty]

McArthur 1998

[Empty]

Smits 2001

[Empty]

Smits 2003

[Empty]

Van der Heijden 2007

Van der Heijden, K. B.; Smits, M. G.; Van Someren, E. J.; Ridderinkhof, K. R.; Gunning, W. B.. Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia. Journal of the American Academy of Child and Adolescent Psychiatry 2007;46(2):233-241. [DOI: 10.1097/01.chi.0000246055.76167.0d [doi]]

van Geijlswijk 2010

[Empty]

Wasdell 2008

[Empty]

Weiss 2006

Weiss, M. D.; Wasdell, M. B.; Bomben, M. M.; Rea, K. J.; Freeman, R. D.. Sleep hygiene and melatonin treatment for children and adolescents with ADHD and initial insomnia. Journal of the American Academy of Child and Adolescent Psychiatry 2006;45(5):512-519. [DOI: 10.1097/01 chi.0000205706.78818.ef [doi]]

Wilhelmsen-Langeland 2013

[Empty]

Wirojanan 2009

[Empty]

Wright 2011

[Empty]

Excluded studies

Other references

Additional references

Other published versions of this review

Data and analyses

2 Melatonin vs. placebo

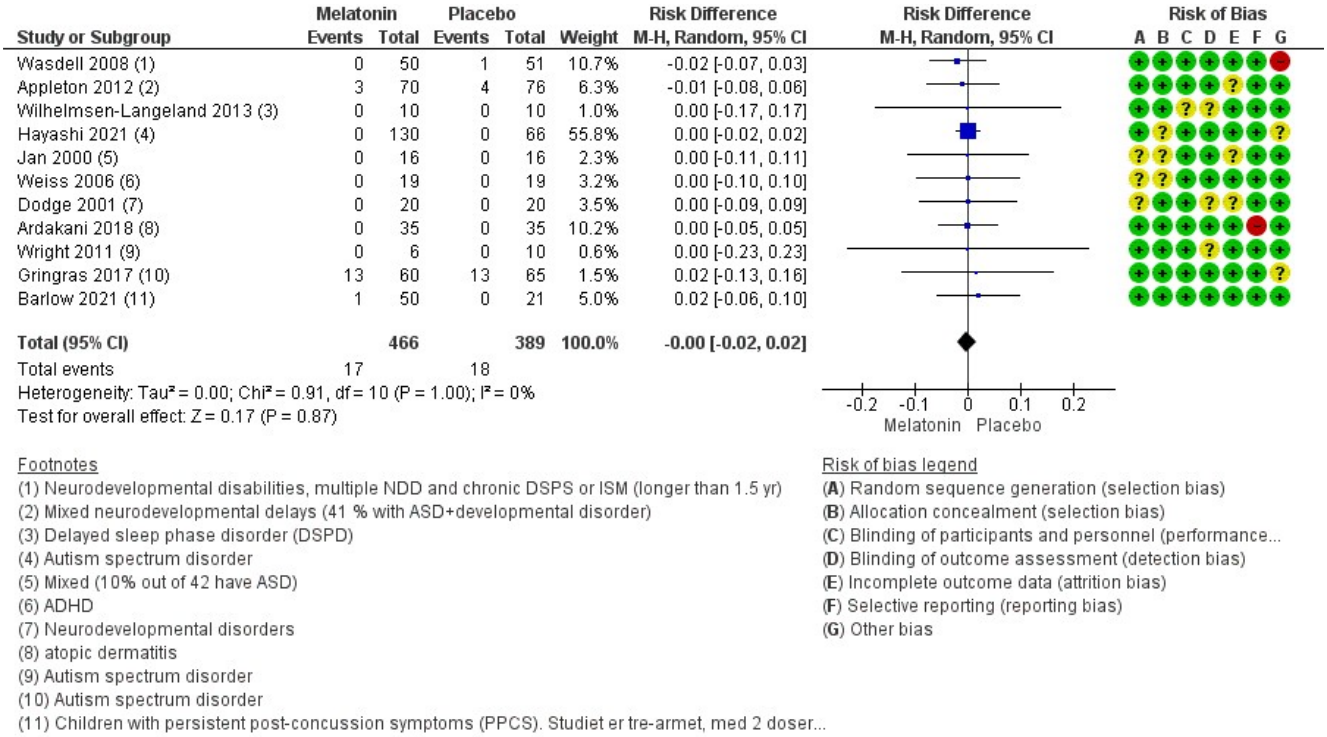
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.6 Alvorlige bivirkninger, antal personer (serious adverse events), EoT - risk difference	11	855	Risk Difference (M-H, Random, 95% CI)	-0.00 [-0.02, 0.02]
2.7 Alvorlige bivirkninger, antal personer (serious adverse events), EoT	11	855	Risk Ratio (IV, Random, 95% CI)	1.00 [0.55, 1.81]
2.8 Bivirkninger, antal personer (adverse events) - risk difference	17	1017	Risk Difference (M-H, Random, 95% CI)	0.05 [0.01, 0.09]
2.9 Bivirkninger, antal personer (adverse events)	17	1041	Risk Ratio (M-H, Random, 95% CI)	1.56 [1.01, 2.43]

Figures

Figure 1

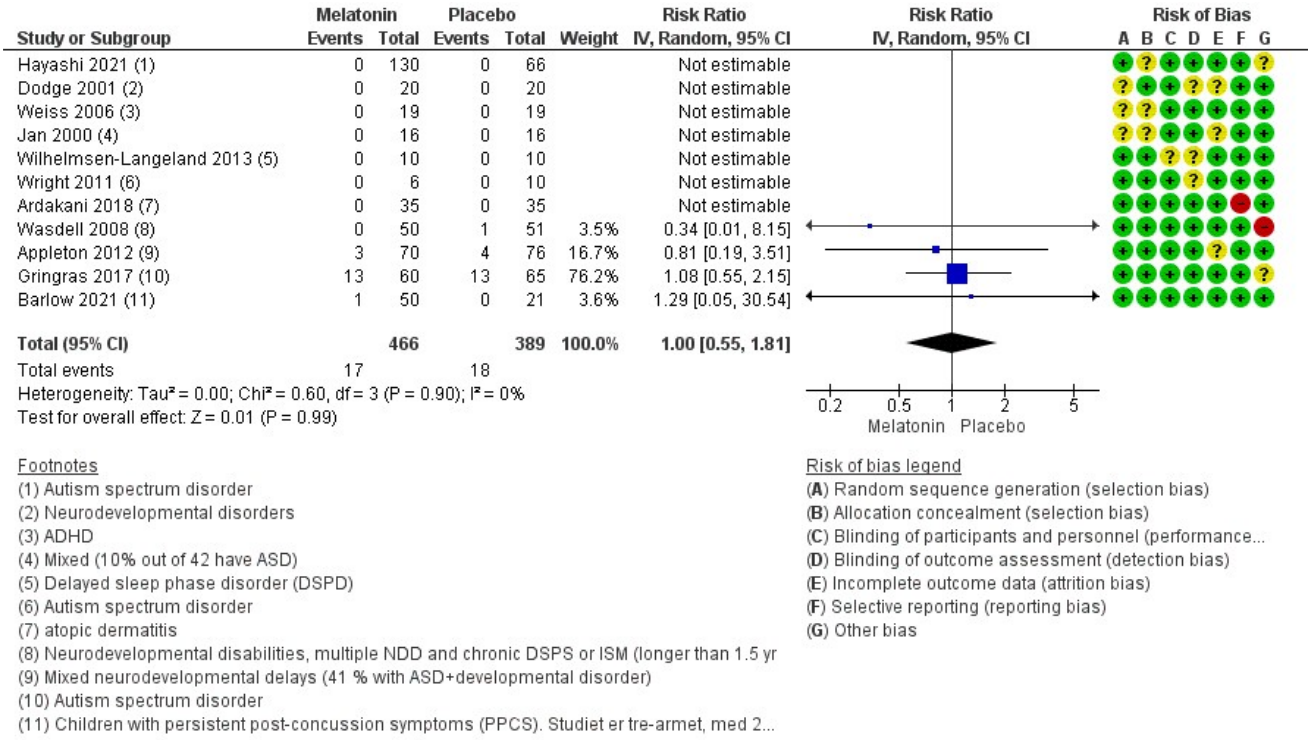
Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 2 (Analysis 2.6)



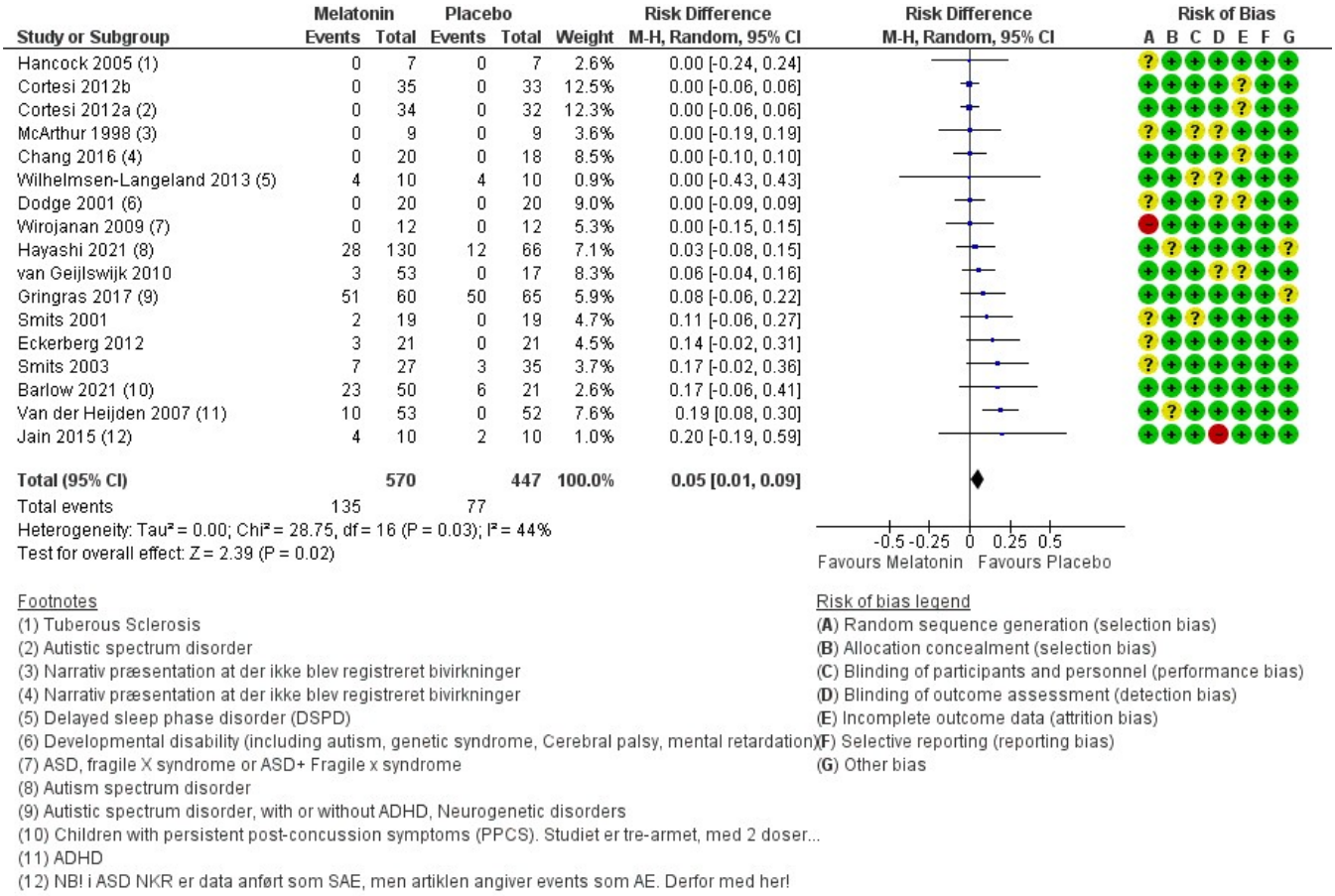
Forest plot of comparison: 2 Melatonin vs. placebo, outcome: 2.6 Alvorlige bivirkninger, antal personer (serious adverse events), EoT - risk difference.

Figure 3 (Analysis 2.7)



Forest plot of comparison: 2 Melatonin vs. placebo, outcome: 2.7 Alvorlige bivirkninger, antal personer (serious adverse events), EoT.

Figure 4 (Analysis 2.8)

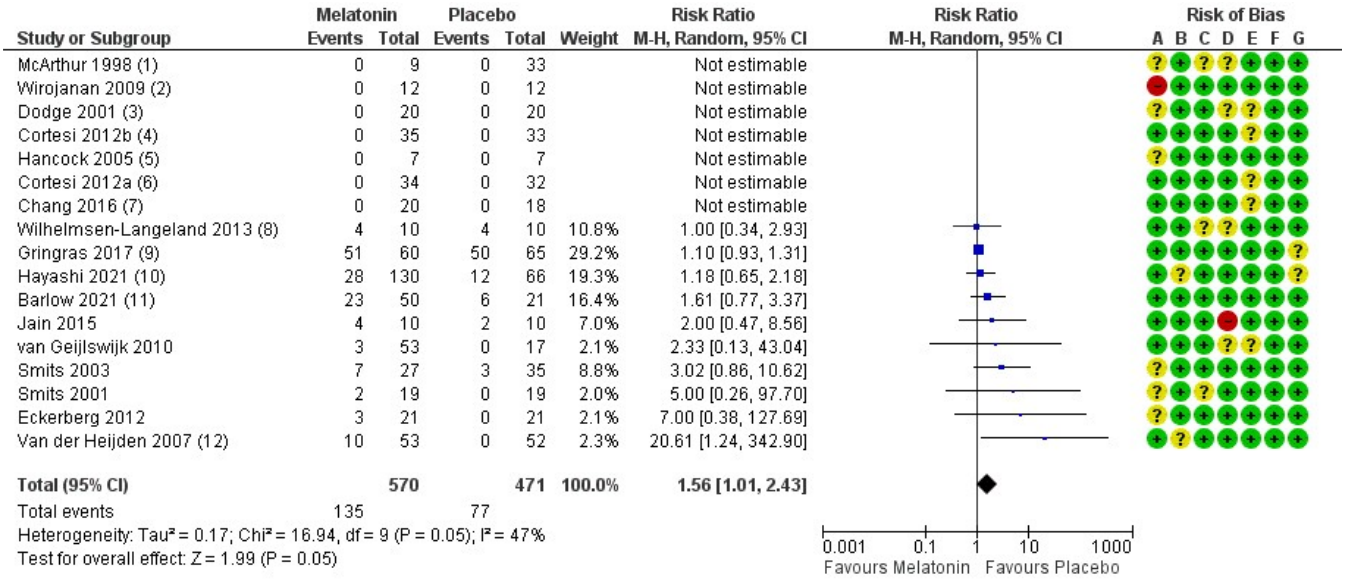


Footnotes
(1) Tuberous Sclerosis
(2) Autistic spectrum disorder
(3) Narrativ præsentation at der ikke blev registreret bivirkninger
(4) Narrativ præsentation at der ikke blev registreret bivirkninger
(5) Delayed sleep phase disorder (DSPD)
(6) Developmental disability (including autism, genetic syndrome, Cerebral palsy, mental retardation)
(7) ASD, fragile X syndrome or ASD+ Fragile x syndrome
(8) Autism spectrum disorder
(9) Autistic spectrum disorder, with or without ADHD, Neurogenetic disorders
(10) Children with persistent post-concussion symptoms (PPCS). Studiet er tre-armet, med 2 doser...
(11) ADHD
(12) NB! i ASD NKR er data anført som SAE, men artiklen angiver events som AE. Derfor med her!

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 2 Melatonin vs. placebo, outcome: 2.8 Bivirkninger, antal personer (adverse events) - risk difference.

Figure 5 (Analysis 2.9)



Footnotes
(1) Narrativ præsentation at der ikke blev registreret bivirkninger
(2) ASD, fragile X syndrome or ASD+ Fragile x syndrome
(3) Developmental disability (including autism, genetic syndrome, Cerebral palsy, mental retardation)
(4) Autisme spectrum disorder (melatonin+ CBT vs CBT alene)
(5) Tuberous Sclerosis
(6) Autistic spectrum disorder (melatonin vs placebo)
(7) Narrativ præsentation at der ikke blev registreret bivirkninger
(8) Delayed sleep phase disorder (DSPD)
(9) Autistic spectrum disorder, with or without ADHD, Neurogenetic disorders
(10) Autism spectrum disorder
(11) Children with persistent post-concussion symptoms (PPCS). Studiet er tre-armet, med 2 doser...
(12) ADHD

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 2 Melatonin vs. placebo, outcome: 2.9 Bivirkninger, antal personer (adverse events).