NKR 57, ADHD for børn og unge, PICO 2 Melatonin vs placebo

Review information

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Date of Search:	
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What's new

Date / Event	Description

History

Date / Event	Description

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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 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 F L 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

Cortesi 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."

Cortesi 2012a

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	

Risk of bias table

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

Cotesi 2012b

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	

Risk of bias table

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

Dodge 2001

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)	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."

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

Jain 2016

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)	Low risk	Quote: "concealment mechanism, implementation, and blinding The Investigational Pharmacy at CCHMC performed the random- ization by random-number generators at www.randomization.com, ensured blinding via over-encapsulation of"
Allocation concealment (selection bias)	Low risk	Quote: "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	Quote: "blinding via over-encapsulation of both the melatonin and placebo pills to have the same appearance, and dispensed the study medications. The pharmacy and the statistician were unblinded whereas the rest of the study team was blinded to the allocation throughout data collection, entry, and cleaning." Quote: "The pharmacy and the statistician were unblinded whereas the rest of the study team was blinded to the allocation throughout data collection, entry, and cleaning."
Blinding of outcome assessment (detection bias)	Low risk	Quote: "and dispensed the study medications. The pharmacy and the statistician were unblinded whereas the rest of the study team was blinded to the allocation throughout data collection, entry, and cleaning. 2.7. Statistical methods All outcome measures and" Judgement Comment: Monitor-measured primary outcomes and secondary outcomes included parent-reported diary, patient-reported questionnaires, sleep time measures by actigraph. Likely all were blinded.
Incomplete outcome data (attrition bias)	Low risk	Quote: "Data were available for all 10 sub- jects for the primary and secondary outcomes except for the PVT and sleep diary data (n = 9) and actigraphy (n = 8) due to technical problems." Judgement Comment: 1 drop out in the placebo group due to unwillingnes to swallow capsules.
Selective reporting (reporting bias)	High risk	Quote: "The study was registered with ClinicalTrials.gov (NCT00965575)." Judgement Comment: Protocol available however, more secondary outcomes are reported than pre-specified. Improved lapse time on psychomotor vigilance task (PVT) was stated as primary outcome measure in the protocol but was repoted as secondary outcome measure.
Other bias	Low risk	Quote: "The project described was supported by the National Center for Research Resources and the National Center for Advancing Trans- lational Sciences, National Institutes of Health, through Grant 8 UL1 TR000077, and by the Clinical Research Feasibility Funds (CReFF) by the Center for Clinical and Translational Science, and Training, Cincinnati Children's Hospital Medical Center." Judgement Comment: Comprehensive reporting of conflicts of interest. Holland K, SimaKajornboon N, Byars N and Glauser T havereceived funding from the medical industry but they do not seem to have influenced the design or other parts of this pilot study.

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

Maras 2018

Methods	
Participants	
Interventions	
Outcomes	
Identification	
Notes	

Risk of bias table

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

Mohammadi 2012

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention ● *Age (mean, SD)*: (9.57, 1.65) ● *Male gender (%)*: 73,1 ● *proportion using ADHD medication (%)*: 100 Control ● *Age (mean, SD)*: (8.83, 1.80) ● *Male gender (%)*: 70,8 ● *proportion using ADHD medication (%)*: 100 Overall ● *proportion using ADHD medication (%)*: 100 **Inclusion criteria:** Children aged 7-12 years who were diagnosed with ADHD (combined form) by a child and adolescent psychologist. **Exclusion criteria:** No use of confounding drugs or supplements. Children with history of major prenatal complications such as prematurity, low birth weight (reported by parents), any past or present psychosis, comorbid tourette syndrome, celiac, phenylketonuria, autism, or other persistent developmental disorders were excluded. Furthermore, narcotics use was among our exclusion criteria.
Interventions	**Intervention Characteristics** Intervention ● *Description*: Melatonin ● *Dose*: 3 mg pr barn<30 kg; 6 mg pr barn> 30 kg ● *Duration of intervention*: 8 uger ● *follow-up time*: ingen follow-up Control ● *Description*: Starch placebo

Outcomes	*Duration of intervention*: 8 uger
	follow-up time: ingen follow-up
	Indsovningstid (Lights out) (sleep latency) (mÃ¥lt med SDSC sleep)
	● **Outcome type**: Continuous Outcome
	● **Reporting**: Fully reported
	● **Scale**: SDSC sleep
	● **Direction**: Lower is better
	● **Data value**: Endpoint
	SÃ¸vnforstyrrelser generelt
	● **Outcome type**: Continuous Outcome
	● **Reporting**: Fully reported
	● **Scale**: SDSC sleep
	● **Direction**: Lower is better
	● **Data value**: Endpoint
	Total sovetid (minutes) (mÃ¥lt med SDSC sleep)
	● **Outcome type**: ContinuousOutcome
	● **Reporting**: Fully reported
	● **Scale**: SDSC sleep
	● **Direction**: Higher is better
	● **Data value**: Endpoint
	ADHD kernesymptomer, forÃ¥lderbedÃ¸mt (opgjort som hyperactivity) (mÃ¥lt med ADHD rating scale)
	● **Outcome type**: Continuous Outcome
	● **Reporting**: Fully reported
	● **Scale**: ADHD rating scale
	● **Direction**: Lower is better
	● **Data value**: Endpoint

Identification	**Sponsorship source:** We thank the Research Deputy of Tehran University of Medical Sciences for their financial support.
	Country: Iran
	Setting: University/Hospital

| **Notes** | |

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Children were then divided into two groups in a double blind permuted block randomized allocation design based on gender blocks. One group".
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: Insufficient information on allocation concealment

Blinding of participants and personnel (perfomance bias)	Low risk	Quote: "Children were then divided into two groups in a double blind permuted block randomized allocation design based on gender blocks. One group." Judgement Comment: Beskrives på p. 88 at der er dobbelt blindet men procedurer beskrives ikke for hvordan denne blindning sikres eller opretholdes. Uklar risk og bias her.
Blinding of outcome assessment (detection bias)	Low risk	Judgement Comment: double-blinded
Incomplete outcome data (attrition bias)	High risk	Judgement Comment: 16% drop-outs (10/60) - bivirkninger blev rapporteret i 38 af 50 completers
Selective reporting (reporting bias)	Low risk	Judgement Comment: No reference to study protocol, but appears to report on all outcomes of ineterest
Other bias	Low risk	Quote: "ADHD children. Conflict of Interest. Authors declare no conflict of interest related to this work. Judgement Comment: The study appears to be free from other 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) (målt 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

Wasdell 2008

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	Low risk	See Abdelgadir 2018 "Melatonin for the management of sleep problems in children with neurodevelopmental disorders: A systematic review and meta-analysis."

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¦lgt • *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

Bias	Judgement	Support for judgement
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 consent. 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

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

Abdelgadir 2018

Reason for exclusion	Wrong study design

Abramova 2019

| Reason for exclusion | Wrong study design |

Anand 2017

| Reason for exclusion | Wrong study design |

Beresford 2018

| Reason for exclusion | Wrong study design |

Beresford 2019

| Reason for exclusion | Wrong outcomes |

Boafo 2019

| Reason for exclusion | Wrong patient population |

Borrington 2017

| Reason for exclusion | Wrong study design |

Bruni 2018

| Reason for exclusion | Wrong study design |

Cortese 2017

| Reason for exclusion | Wrong study design |

Findling 2017

| Reason for exclusion | Wrong study design |

Gelfand 2017

| Reason for exclusion | Wrong indication |

Gringras 2017a

| Reason for exclusion | Wrong patient population |

Gringras 2018

Reason for exclusion	Wrong patient population

Gringras 2018a

Reason for exclusion	Wrong study design

Gubin 2017

Reason for exclusion	Adult population

Han 2018

Reason for exclusion	Wrong intervention

Harvey 2017

Reason for exclusion	Wrong intervention

Khan 2017

Reason for exclusion	Wrong study design

Khan 2017a

Reason for exclusion	Wrong study design

Lang 2018

Reason for exclusion	Wrong intervention

McDonagh 2019

Reason for exclusion	Wrong study design

Owens 2017

Reason for exclusion	Wrong study design

Schroder 2019

Reason for exclusion	Wrong outcomes

Shahnawaz 2019

Reason for exclusion	Wrong patient population

Sletten 2018

Reason for exclusion	Wrong patient population

Smits 2017

Reason for exclusion	Wrong outcomes

Smits 2017a

Reason for exclusion	Dublet

Zwart 2018

Reason for exclusion	Wrong study design

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of findings tables

Additional tables

References to studies

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[Empty]

Cotesi 2012b

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Gringras 2017

[Empty]

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[Empty]

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Jan 2000

[Empty]

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[Empty]

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[Empty]

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Studies awaiting classification

Ongoing 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
2.1 ADHD funktionsniveau, kliniker/observatør bedømt (beskrives narrativt)	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.2 Indsovningstid (Lights out) (sleep latency) (målt med SDSC sleep, actigraf, somnolog)	3	168	Mean Difference (IV, Random, 95% CI)	-16.36 [-25.84, -6.89]
2.3 Søvnforstyrrelser generelt	1	50	Mean Difference (IV, Fixed, 95% CI)	-4.20 [-17.16, 8.76]
2.4 Total sovetid (minutes) (målt med SDSC sleep, actigraf)	3	80	Mean Difference (IV, Random, 95% CI)	33.40 [8.68, 58.12]
2.5 ADHD kernesymptomer, forækdrebedømt (opgjort som hyperactivity) (målt med ADHD rating scale)	1	50	Mean Difference (IV, Fixed, 95% CI)	-0.66 [-4.25, 2.93]
2.6 ADHD kernesymptomer, forældrebedømt (opgjort som attention def) (målt med ADHD rating scale)	1	50	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-10.94, 10.58]
2.7 Livskvalitet	1	71	Mean Difference (IV, Fixed, 95% CI)	0.60 [-4.67, 5.87]
2.8 Alvorlige bivirkninger, antal personer (serious adverse events), EoT	7	447	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.64, 2.02]
2.9 Bivirkninger, antal personer (adverse events)	7	442	Risk Ratio (M-H, Random, 95% CI)	3.93 [0.09, 177.66]
2.10 Bivirkninger, antal personer (adverse events) -risk difference	7	442	Risk Difference (M-H, Fixed, 95% CI)	0.07 [0.02, 0.12]
2.11 Alvorlige bivirkninger, antal personer (serious adverse events), EoT - risk difference estimat	7	447	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.04, 0.06]

Figures

Figure 1

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Appleton 2012	+	+	+	+	?	+	+
Ardakani 2018	+	+	+	+	+	–	+
Cortesi 2012	+	+	+	+	?	+	+
Cortesi 2012a							
Cortesi 2012b							
Dodge 2001	?	+	+	?	?	+	+
Gringras 2017	+	+	+	+	+	+	?
Hancock 2005	?	+	+	+	+	+	+
Jain 2016	+	+	+	+	+	–	+
Jan 2000	?	?	+	+	?	+	+
Maras 2018							
Mohammadi 2012	+	?	+	+	–	+	+
Van der Heijden 2007	+	?	+	+	+	+	+
Wasdell 2008	+	+	+	+	+	+	+
Weiss 2006	+	?	+	+	+	+	+
Wirojanan 2009	–	+	+	+	+	+	+
Wright 2011	+	+	+	?	+	+	+

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

Figure 2 (Analysis 2.2)

Study or Subgroup	Melatonin			Placebo				Mean Difference	Risk of Bias
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	A B C D E F G
Mohammadi 2012 (1)	17.96	26.5	26	26.37	26.5	24	35.0%	-8.41 [-23.11, 6.29]	+ + + ? + + +
Van der Heijden 2007	-21.3	32.96	41	3.04	31.74	39	37.2%	-24.34 [-38.52, -10.16]	+ + + ? + + +
Weiss 2006	46.4	26.4	19	62.1	26.6	19	27.7%	-15.70 [-32.55, 1.15]	+ + + ? + + +
Total (95% CI)			**86**			**82**	**100.0%**	**-16.36 [-25.84, -6.89]**	

Heterogeneity: Tau² = 10.40; Chi² = 2.35, df = 2 (P = 0.31); I² = 15%
Test for overall effect: Z = 3.39 (P = 0.0007)

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

Footnotes
(1) SD er ikke oplyst i dette studie, men extrapoleret fra SD værdier fra Van der Heijden 2007

Forest plot of comparison: 2 Melatonin vs. placebo, outcome: 2.2 Indsovningstid (Lights out) (sleep latency) (målt med SDSC sleep, actigraf, somnolog).

Figure 3 (Analysis 2.3)

Study or Subgroup	Melatonin			Placebo				Mean Difference	Risk of Bias
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	A B C D E F G
Mohammadi 2012	41.3	23.3512	26	45.5	23.3512	24	100.0%	-4.20 [-17.16, 8.76]	+ ? + + + + +
Total (95% CI)			**26**			**24**	**100.0%**	**-4.20 [-17.16, 8.76]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.64 (P = 0.53)

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: 2.3 Søvnforstyrrelser generelt.

Figure 4 (Analysis 2.4)

Study or Subgroup	Melatonin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
Mohammadi 2012 (1)	0	0	0	0	0	0		Not estimable		
Van der Heijden 2007	19.82	61.9	41	-13.58	50.6	39	100.0%	33.40 [8.68, 58.12]		
Weiss 2006	0	0	0	0	0	0		Not estimable		
Total (95% CI)			41			39	100.0%	33.40 [8.68, 58.12]		

Heterogeneity: Not applicable
Test for overall effect: Z = 2.65 (P = 0.008)

Footnotes
(1) SD er ikke oplyst i dette studie, men extrapoleret fra SD værdier fra Van der Heijden 2007
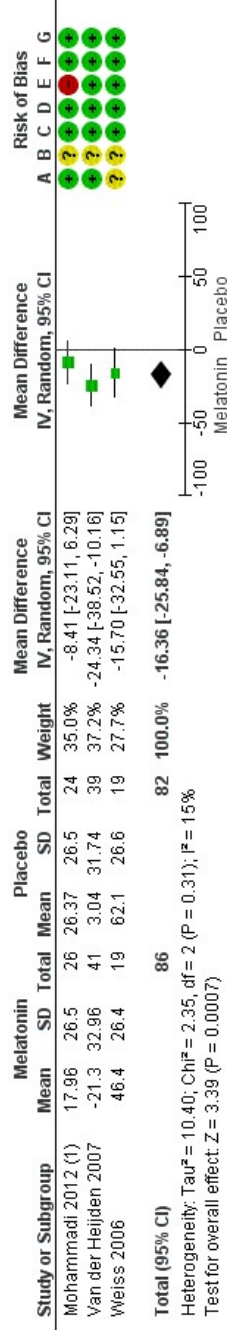
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 2 Melatonin vs. placebo, outcome: 2.4 Total sovetid (minutes) (målt med SDSC sleep, actigraf).

Figure 5 (Analysis 2.5)

Study or Subgroup	Melatonin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F G
Mohammadi 2012 (1)	10.96	6.4648	26	11.62	6.4648	24	100.0%	-0.66 [-4.25, 2.93]		
Total (95% CI)			26			24	100.0%	-0.66 [-4.25, 2.93]		

Heterogeneity: Not applicable
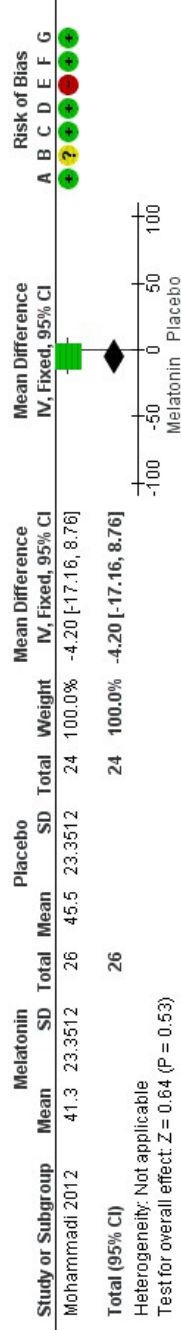Test for overall effect: Z = 0.36 (P = 0.72)

Footnotes
(1) SD er ikke oplyst i dette studie, men extrapoleret fra SD værdier fra Van der Heijden 2007

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance...
(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: 2.5 ADHD kernesymptomer, forældrebedømt (opgjort som hyperactivity) (målt med ADHD rating scale).

Figure 7 (Analysis 2.6)

Study or Subgroup	Melatonin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F G
Mohammadi 2012 (1)	11.11	19.3945	26	11.29	19.3945	24	100.0%	-0.18 [-10.94, 10.58]	+ ? + + + + +
Total (95% CI)			26			24	**100.0%**	**-0.18 [-10.94, 10.58]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.97)

Footnotes
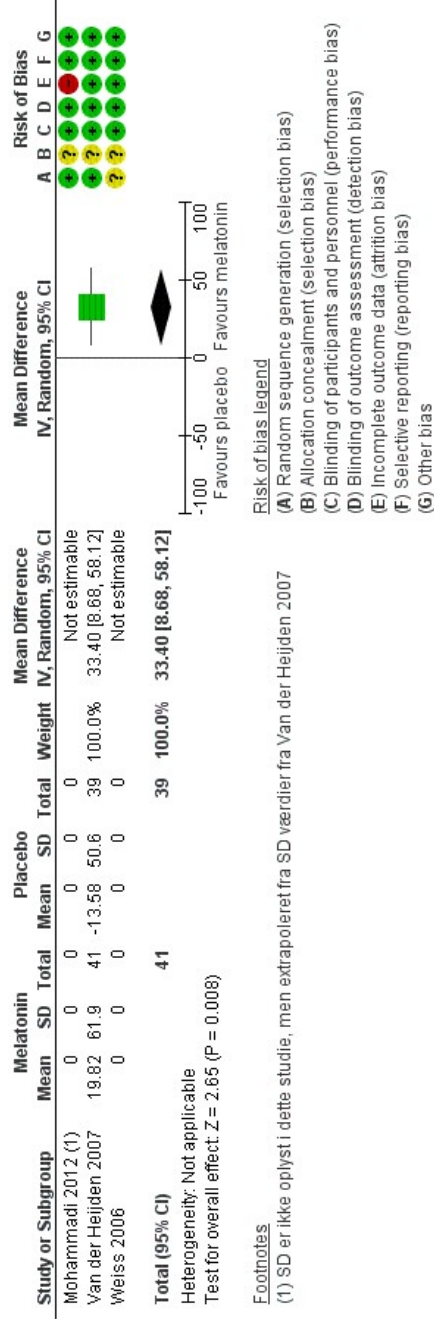(1) SD er ikke oplyst i dette studie, men extrapoleret fra SD vårdier fra Van der Heijden 2007

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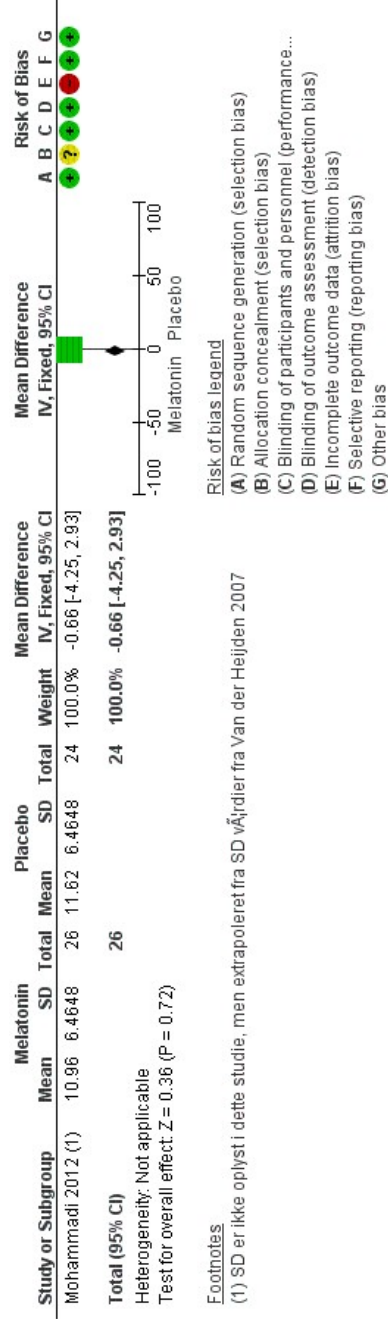(F) Selective reporting (reporting bias)
(G) Other bias

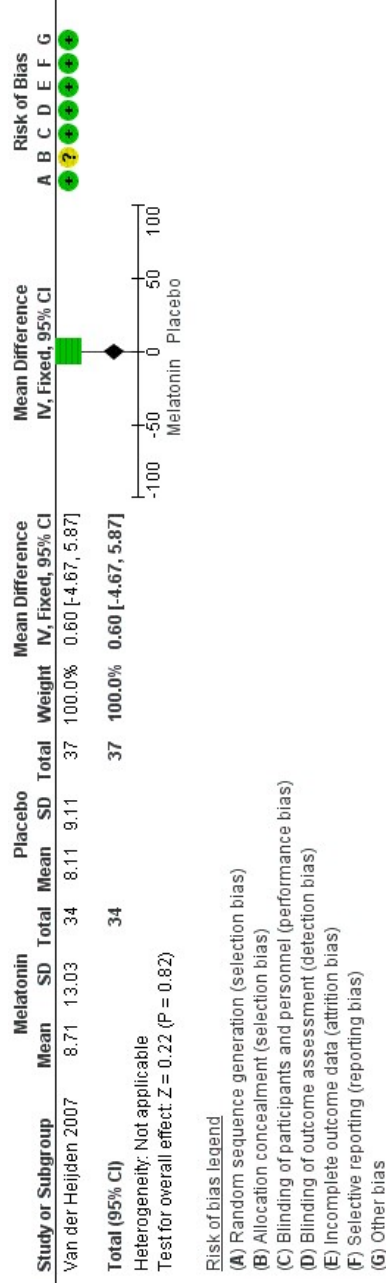Forest plot of comparison: 2 Melatonin vs. placebo, outcome: 2.6 ADHD kernesymptomer, forældrebedømt (opgjort som attention def) (målt med ADHD rating scale).

Figure 8 (Analysis 2.7)

Study or Subgroup	Melatonin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F G
Van der Heijden 2007	8.71	13.03	34	8.11	9.11	37	100.0%	0.60 [-4.67, 5.87]	+ ? + + + + +
Total (95% CI)			34			37	**100.0%**	**0.60 [-4.67, 5.87]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.22 (P = 0.82)

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: 2.7 Livskvalitet.

Sources of support

Internal sources

- No sources of support provided

External sources

- No sources of support provided

Feedback

Appendices