NKA 62 - Behandling med melatonin til børn og unge med søvnforstyrrelser - Gavnlige effekter

Characteristics of studies

Characteristics of included studies

Barlow 2021

Methods	**Study design:** Randomized controlled trial, single center, three arms **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Overall ● 71 participants with persistent post-concussion symptoms (PPCS), Gender: 29m/42f ● *Age*: 8-18years Melatonin (3 mg group) ● Melatonin group (n=25) Gender: 12m/13f ● *Age*: mean age: 13,7 yr Melatonin (10 mg group) ● Melatonin group (n=25) Gender: 9m/16f ● *Age*: mean age: 14,2 yr Placebo ● Control (placebo) group (n=22) Gender: 11m/11f ● *Age:* mean age: 14,2 yr **Included criteria:** The study enrolled children aged 8 to 18 years if they had PPCS and a >10-point increase in their total symptom score on the Post Concussion Symptom Inventory (PCSI) postinjury when compared with their preinjury score (assessed at enrollment) **Excluded criteria:** Children were ineligible if they had a significant medical or psychiatric history, a previous concussion within the last 3 months, persistent symptoms after a previous concussion, or a more severe TBI previously. Other exclusions included lactose intolerance, use of neuroactive drugs, and inability to complete questionnaires **Pretreatment:** None
Interventions	**Intervention Characteristics** Intervention 1 ● Melatonin group 3mg sustained-release sublingual melatonin preparations, (n=25) - Duration 4 weeks Intervention 2 ● Melatonin group 10mg sustained-release sublingual melatonin preparations, (n=25) - Duration 4 weeks Control ● Control (placebo) group (n=22)
Outcomes	*Alvorlige skadevirkninger (SAE) n,N EoT* ● **Outcome type**: DichotomousOutcome *Ikke alvorlige skadevirkninger (AE) n,N. EoT* ● **Outcome type**: DichotomousOutcome *Frafald n,N* ● **Outcome type**: DichotomousOutcome *Indsovningstid, mean SD EoT*

	● **Outcome type**: ContinuousOutcome *Total sovetid, mean SD, EoT* ● **Outcome type**: ContinuousOutcome *Antal opvågninger, mean SD, EoT* ● **Outcome type**: ContinuousOutcome Objective measurements: Actigraph (Actiwatch-2 (Philips Respironics)
Identification	**Sponsorship source:** Funded by the Canadian Institutes of Health Research (grant 293375), the Alberta Children's Hospital Research Institute, and the University of Calgary **Country:** Australien / Canada **Setting:** clinic **Comments:** None **Authors name:** Karen M. Barlow **Institution:** Child Health Research Centre, The University of Queensland **Email:** kbarlow@uq.edu.au **Address:** Karen M. Barlow, MBChB, Child Health Research Centre, The University of Queensland, Level 6, 62 Graham St, South Brisbane, QLD 4101, Australia.
Notes	*HC* on 15/03/2022 07:05 **Select** Sekundær analyse af Barlow 2020

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "participants were randomly assigned by using a random-block-size design (block sizes 3, 6, and 9) to 3 parallel treatment groups"
Allocation concealment (selection bias)	Low risk	The computergenerated randomization list was created and held by an external statistician
Blinding of participants and personnel (performance bias)	Low risk	Quote: "All investigators, outcome assessors, parents, and children were blinded to treatment groups"
Blinding of outcome assessment (detection bias)	Low risk	Quote: "All investigators, outcome assessors, parents, and children were blinded to treatment groups"
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: No apparent sources of bias - Protocol available: http://www.clinicaltrials.gov/; NCT01874847
Selective reporting (reporting bias)	Low risk	Judgement Comment: No apparent sources of bias
Other bias	Low risk	Judgement Comment: No apparent sources of bias

Braam 2008

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Overall ● *Diagnosis,* 8 participants with Angelman syndrome and idiopathic chronic insomnia, Gender: 3m/5f ● *Age*: 4-21 years Melatonin

	● *Melatonin*: n = 4 ● *Age*: n.a. Control ● Placebo: n = 4 ● *Age*: n.a. **Included criteria:** Sleep latency more than 30 minutes, or 2 or more wakes, lasting more than 15 minutes a night, at least 5 nights a week, during more than 1 year. **Excluded criteria:** Prior use of Melatonin, liver disease, renal failure, chronic pain, and age less than 2 years **Pretreatment:**
Interventions	**Intervention Characteristics** Intervention ● Melatonin (hard capsules containing 5 mg of fast release melatonin (5-methoxy-N-acetyltryptamine). Participants under age 6 years received 2.5mg melatonin - Duration 4 weeks Control: ● Placebo (hard capsules)
Outcomes	*Alvorlige skadevirkninger (SAE) n,N EoT* ● **Outcome type**: DichotomousOutcome *Ikke alvorlige skadevirkninger (AE) n,N. EoT* ● **Outcome type**: DichotomousOutcome *Indsovningstid, mean SD EoT* ● **Outcome type**: ContinuousOutcome *Total sovetid, mean SD, EoT* ● **Outcome type**: ContinuousOutcome ● **Scale**: Minutter ● **Data value**: Endpoint ● **Notes**: Omregnet til minutter fra tabel 2 *Antal opvågninger, mean SD, EoT* ● **Outcome type**: ContinuousOutcome ● **Scale**: minutter ● **Direction**: Lower is better ● **Data value**: Endpoint ● **Notes**: Varighed af opvågninger i minutter (Mean (SD)): Melatonin: 11.75 (9.87) - Placebo 60,75 (45.02)
Identification	**Sponsorship source:** Research grant from Heeren Loo Zorggroep Steunfonds **Country:** The Netherlands **Setting:** Medication at home **Comments:** **Authors name:** Wiebe Braam **Institution:** Department of Neurology, Geldersee Vallai Hospital **Email:** wiebe.braam@sheerenloo.nl **Address:** Heeren Loo Zuid-Veluwe, PO Box 75, 6710 BB Ede, The Netherlands
Notes	*HC* on 15/03/2022 06:58 **Select** Uvist om søvnhygiejne er forsøgt

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: Nothing mentioned
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: Nothing mentioned
Blinding of participants and personnel (performance bias)	High risk	Judgement Comment: Open label for participants + personnel
Blinding of outcome assessment (detection bias)	Low risk	Judgement Comment: All investigators blinded
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: No apparent sources of bias
Selective reporting (reporting bias)	Low risk	Judgement Comment: No apparent sources of bias
Other bias	Low risk	Judgement Comment: No apparent sources of bias

Chang 2016

Methods	**Study design:** Randomized controlled cross over study, single center parallel group, two arms. **Study grouping:** Crossover
Participants	**Baseline Characteristics** Overall ● 48 participants with Atopic Dermatitis and Sleep Disturbance ● *Age*: 1-18years Melatonin ● Melatonin group (n=24) Gender: 11m/13f ● *Age*: 1-18 years, mean age (SD): 7,6 (4,0) years Placebo ● Control (placebo) group (n=24) Gender: 14m/10f ● *Age*: 1-18 years, mean age (SD): 7,3 (3,5) years **Included criteria:** Those patients with sleep problems occurring more than 3 days per week during the previous 3 months were eligible. Asleep problem was defined as any difficulty withsleep initiation or maintenance that led to impaired quality oflife or interfered with daytime activities for the child or for family members. **Excluded criteria:** Exclusion criteria included documented sleep disorders, such as dyssomnias, parasomnias, and circadian rhythm sleep disorders; neuropsychiatric disorders or any other medical condition that might produce sleep problems; or use of medication for insomnia or of antidepressants within 4weeks before the baseline visit. **Pretreatment:** None
Interventions	**Intervention Characteristics** Intervention ● Melatonin 3mg fast release capsules (GeneralNutrition Corporation) at bedtime - Duration 4 weeks pr cycle after two weeks wash-out Control ● Placebo (Standard Chem & Pharm Co, Ltd) – capsules similar to the ones in intervention group
Outcomes	*Søvnkvalitet generelt, mean SD (både subjektive som objektive (Actigraph) estimater* ● **Outcome type**: ContinuousOutcome *Indsovningstid, mean SD, EoT, (sleep log, Actigraph)* ● **Outcome type**: ContinuousOutcome

	Total sovetid, mean SD, EoT, (sleep log, Actigraph) ● **Outcome type**: ContinuousOutcome ● **Notes**: Udgangspunkt er forskellen for de to grupper fra tabel 2 *Frafald, n,N EoT* ● **Outcome type**: DichotomousOutcome
Identification	**Sponsorship source:** Not stated **Country:** Taiwan **Setting:** Single tertiary care hospital in Taiwan **Comments:** **Authors name:** Yung-Sen Chang **Institution:** Department ofMedical Research, NationalTaiwan University Hospital, **Email:** gicmbor@ntu.edu.tw **Address:** 7 Chung-Shan S Rd, Taipei 100, Taiwan
Notes	*HKA* on 21/03/2022 07:30 **Select** Cross-over RCT på 48 deltagere (1-18 år), med 2 ugers wash-out periode inden cross-over. Undrer mig at kønsfordeling ændrer sig for de to grupper i et cross-over studie!

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "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	Quote: "Allocation codes were disclosed only after the entire clinical trial was completed." Quote: "The melatonin and placebo tablets were identical in appearance."
Blinding of participants and personnel (performance bias)	Low risk	Quote: "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	Quote: "The participants and their caregivers, treating phy- sicians, those assessing outcomes, and those analyzing the data were all masked to group assignment. Allocation codes"
Incomplete outcome data (attrition bias)	Unclear risk	Judgement Comment: Lidt 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	Judgement Comment: No apparent sources of bias (protocol avilable http://www.clinicaltrials.gov/; NCT01638234)
Other bias	Low risk	Judgement Comment: No apparent sources of bias

Coppola 2004

Methods	**Study design:** Randomized controlled cross-over trial, single center, parallel group, two arms **Study grouping:** Crossover
Participants	**Baseline Characteristics** Overall ● 25 participants with mental retardation with or without epilepsy. Mental delay was mild in 3 (12%) patients, moderate in 8 (32%), and severe in 14 (56%), Gender: 16m/9f ● *Age*: mean 10,5 (3,6 to 26 years), Melatonin ● Melatonin group (n=25) Gender: 16m/9f ● *Age*: mean 10,5 (3,6 to 26 years) Control ● Placebo group (n=25) Gender: 16m/9f ● *Age*: mean 10,5 (3,6 to 26 years) **Included criteria:** Patients were enrolled into the study based on the following criteria: (i) mental retardation with/without epileptic seizures; (ii) age more than 12 months, in order to avoid difficulty with calculating infant dosages; (iii)diagnosis of sleep disorder, defined according to the Diagnostic and Statistical Manual of Mental Disorders(DSM), 4th edition (IV) criteria (307,45) as the circadian rhythm sleep disorder[14]including delayed onset of sleep, multiple night awakenings, and short duration of night sleep through a baseline period of 6 months; (iv) exclusion of medical issues such as gastroesophageal reflux, pain or epileptic seizures mimicking sleep disorders; (v) persisting sleep disturbances despite maintaining appropriate sleep hygiene; (vi) informed consent by parents and/or caregivers. Patients were excluded from the trial if there were: (i) progressive neurological and/or systemic diseases;(ii) age,12 months; (iii) poor compliance from parents/caregivers with the study requirements before trial entry. **Excluded criteria:** Patients were excluded from the trial if there were:(i) progressive neurological and/or systemic diseases;(ii) age,12 months; (iii) poor compliance from parents/caregivers with the study requirements before trial entry. **Pretreatment:**
Interventions	**Intervention Characteristics** Intervention ● Melatonin 3-9 mg. Melatonin 3 mg fast release capsules, at nocturnal bedtime. Dose could be titrated up to 9 mg the following 2 weeks at increments of 3 mg/week, unless the patient was unable to tolerate it. - Duration 4 weeks pr cycle after 1 week wash-out Control ● Placebo – capsules similar to the ones in intervention group
Outcomes	*Indsovningstid, mean SD EoT (sleep log)* ● **Outcome type**: ContinuousOutcome *Total sovetid, mean SD, EoT (sleep log)* ● **Outcome type**: ContinuousOutcome *Antal opvågninger, n,N EoT (sleep log)* ● **Outcome type**: DichotomousOutcome
Identification	**Sponsorship source:** Not stated **Country:** Italy **Setting:** Domestic **Comments:** **Authors name:** Giangennaro Coppola **Institution:** Clinic of Child and Adolescent Neuropsychiatry, CIRN, Second University of Naples **Email:** n.a. **Address:** Via Pansini 5 80131, Naples, Italy

Notes	*HC* on 15/03/2022 07:05 **Select** Obs! aged from 3.6 to 26 years *HKA* on 21/03/2022 03:46 **Select** Mener godt denne kan indgå med relevante outcomes

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Each patient enrolled into the study was randomized to oral synthetic fast-release melatonin or placebo, and then entered phase 1 (melatonin or placebo) that lasted 4 weeks." Judgement Comment: Nothing mentioned regarding method
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: Nothing mentioned
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: Participants blinded - no info on personel
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: Nothing mentioned
Incomplete outcome data (attrition bias)	Unclear risk	Quote: "Seven patients (28%) were lost to the study because of the following reasons: change of mind about participation in two; intercurrent illness in other two; family lost to follow- up due to poor results in three patients while assuming first phase placebo." Judgement Comment: No mentioned on how many dropped out pr group
Selective reporting (reporting bias)	Low risk	Judgement Comment: No apparent sources of bias
Other bias	Low risk	Judgement Comment: No apparent sources of bias

deCastro Silva 2010

Methods	**Study design:** Randomized controlled trial, single center, two arms **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Overall ● 19 participants with cystic fibrosis, Gender: 11m/8f ● *Age*: n.a. Melatonin ● Melatonin group (n=9), Gender: 6m/3f ● *Age (SD)*: mean 16.6 (8.3) years Control ● Placebo group (n=10), Gender: 5m/5f ● *Age (SD)*: mean 12.1 (6.0) years **Included criteria:** Inclusion criteria were having a diagnosis of CF confirmed by sweat test and genetic analysis, the presence of clinical lung disease, the absence of, use of antidepressant or hypnotic medications, clinical stability or the absence of infection or hospitaliza-tion in the last 30 days and signed informed

	consent from patient or parent. **Excluded criteria:** Exclusion criteria were a history of infective exacerbation within the previous 4 wk, hospitalization, co-morbidities, including diabetes mellitus, use of hypnotic-sedative drugs or unwillingness to participate in the study **Pretreatment:** None
Interventions	**Intervention Characteristics** Intervention ● Melatonin 3 mg fast release capsules taken 2 hr before bedtime - Duration 3 weeks Control ● Placebo capsules, which looked identical to the melatonin capsules
Outcomes	*Søvnkvalitet generelt, mean SD,* subjective (Pittsburg sleep quality index) and objective (PSQI) measurements ● **Outcome type**: ContinuousOutcome *Indsovningstid, mean SD, EoT, Actigraph* ● **Outcome type**: ContinuousOutcome *Total sovetid, mean SD, EoT, Actigraph* ● **Outcome type**: ContinuousOutcome *Antal opvågninger, n,N EoT* ● **Outcome type**: DichotomousOutcome *Antal opvågninger (WASO), mean SD, EoT, Actigraph* ● **Outcome type**: ContinuousOutcome
Identification	**Sponsorship source:** Not stated **Country:** Brazil **Setting:** Domestic **Comments:** **Authors name:** Claudia de Castro-silva **Institution:** Department of Medicine, Universidade Federaldo Ceara´. **Email:** veralice@superig.com.br **Address:** Rua Prof. Costa Mendes 1608 - 4Andar, Fortaleza, Ceara´, Brazil
Notes	*HC* on 15/03/2022 06:10 **Select** Obs! alder 7-28 år, uvist om søvnhygiejniske tiltag har været forsøgt *HKA* on 19/03/2022 05:53 **Select** Det er rigtigt at deciderede søvnhygiejniske tiltag ikke nævnes (hvilket iøvrigt oplyses i meget få studier), men der måles på søvnkvalitet og andre søvnparametre inden randomiseringen. Jeg inkluderer i første omgang

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were then randomized into the melatonin or placebo group." Judgement Comment: No information on method provided
Allocation concealment (selection bias)	Low risk	Quote: "Melatonin and placebo were supplied in identical 3-mg capsules"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "a previously described method [26]. Patients and investigators were unaware of treatment allocation at all times. Clinical and laboratory investigations The"
Blinding of outcome assessment (detection bias)	Low risk	Judgement Comment: Patients and investigators were unaware of treatment allocation at all times. Clinical and laboratory investigations The
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: No apparent sources of bias
Selective reporting (reporting bias)	Low risk	Judgement Comment: No apparent sources of bias
Other bias	Low risk	Judgement Comment: No apparent sources of bias

Dodge 2001

Methods	**Study design:** Randomized controlled trial, single center, parallel group **Study grouping:** Crossover
Participants	**Baseline Characteristics** Overall ● 20 participants with Developmental Disabilities, Gender: n.a. ● *Age*: mean 7,4 years (1-15 years) Melatonin ● 20 participants with Developmental Disabilities, Gender: n.a ● *Age*: mean 7,4 yr (1-15 years) . Placebo ● 20 participants with Developmental Disabilities ● *Age*: mean 7,4 yr (1-15 years) Gender: n.a. **Included criteria:** Moderate to severe developmental disability as defined by spastic quadriparesis, mental retardation or global developmental delay with an IQ less than or equal to 50, or autism. **Excluded criteria:** n.a. **Pretreatment:**
Interventions	**Intervention Characteristics** Intervention ● Melatonin 5 mg fast release capsules - Duration 2 weeks pr cycle (1 week baseline measurement and 1 week wash-out) Control ● Placebo capsules, which looked identical to the melatonin capsules
Outcomes	*Indsovningstid, mean SD EoT, Sleep log* ● **Outcome type**: ContinuousOutcome *Total sovetid, mean SD, EoT, Sleep log* ● **Outcome type**: ContinuousOutcome *Antal opvågninger, n,N, EoT*

	● **Outcome type**: DichotomousOutcome *Antal opvågninger, mean SD, EoT, Sleep log* ● **Outcome type**: ContinuousOutcome
Identification	**Sponsorship source:** United Cerebral Palsy Association of Greater Indiana **Country:** USA **Setting:** Clinic **Comments:** **Authors name:** Nancy N Dodge **Institution:** University of Texas, Southwestern Medical Center at Dallas **Email:** ndodge@tsrh.org **Address:** Welborn Street, Dallas, TX 75219
Notes	*HC* on 15/03/2022 06:16 **Select** Obs! alder 1-12 år *HKA* on 19/03/2022 06:17 **Select** Marginalt udenfor vores population, som er 2-24 år!

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Judgement Comment: Randomization performed by pharmacy personal
Allocation concealment (selection bias)	Low risk	Judgement Comment: Identical filler and capsules
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: Personal not blindedParticipants blinded
Blinding of outcome assessment (detection bias)	Low risk	Judgement Comment: Families blinded. Based on sleep logs
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: No apparent source of bias
Selective reporting (reporting bias)	Low risk	Judgement Comment: No apparent sources of bias
Other bias	Low risk	Judgement Comment: No apparent sources of bias

Eckerberg 2012

Methods	**Study design:** Randomized, double blind, placebo-controlled crossover trial **Study grouping:** Crossover
Participants	**Baseline Characteristics** Overall ● 21 participants with sleep-onset difficulties, Gender: 10m/11f ● *Age*: 14-19 years Melatonin ● 21 participants with sleep-onset difficulties, Gender: 10m/11f ● *Age*: 14-19 years

	Placebo ● 21 participants with sleep-onset difficulties, Gender: 10m/11f ● *Age*: 14 - 19 years **Included criteria:** Criteria for participation selection included a motivation to be helped, being unable to go to sleep before 01:00 h at least two out of five nights every school week,and a substantial sense of morning fatigue. **Excluded criteria:** Exclusion criteria were prior use of melatonin and use of light therapy **Pretreatment:** none - it's a cross over study
Interventions	**Intervention Characteristics** Intervention ● Melatonin (hard capsules containing 1 mg of fast release melatonin (5-methoxy-N-acetyltryptamine) - Duration 5 weeks Control ● Placebo
Outcomes	*Total sovetid, mean SE, EoT* (Actigraph (Actiwatch™, Cambridge Neurotechnology, Cambridge, UK)) ● **Outcome type**: ContinuousOutcome *Døsighed i dagtimer, mean SD, EoT (*Karolinska Sleepiness Scale) ● **Outcome type**: ContinuousOutcome
Identification	**Sponsorship source:** NATURAL PHARMA International NPI AB, StockholmSweden, was the sponsor of the study, and provided the melatonin and PL capsules. **Country:** Sweden **Setting:** Domestic **Comments:** **Authors name:** Berndt Eckerberg **Institution:** Stress Research Institute, Stockholm University **Email:** arne.lowden@stress.su.se **Address:** Stress Research Institute, Stockholm University,106 91 Stockholm, Sweden
Notes	*HC* on 15/03/2022 06:20 **Select** "Diagnose" baseret på et spørgeskema omkring søvn sendt rundt til svenske skolebørn *HKA* on 19/03/2022 06:15 **Select** Og det fremgår ikke at der er afprøvet non-farmakologiske tiltag inden melatonin *HKA* on 04/04/2022 07:15 **Included** Det ser ud som om der rapporteres både indsovningstid og total sovetid, men opgjort i ugedage og weekend.Se tabel 1. Skal lige diskuteres hvilke der skal rapporteres. HUSK det er SE

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The cap- sules 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	Quote: "The melato- nin and PL were administered to the students as hard- gelatin capsules, which were indistinguishable from one another by appearance, taste and smell. The cap- sules 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. In"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "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	Quote: "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. The"
Incomplete outcome data (attrition bias)	Low risk	Quote: No protocol identified
Selective reporting (reporting bias)	Low risk	Judgement Comment: No apparent sources of bias
Other bias	Low risk	Judgement Comment: No apparent sources of bias

Gupta 2004

Methods	**Study design:** Randomized controlled trial, single center, two arms **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Overall ● 30 participants with Epilepsy, Gender: 18m/12f ● *Age*: 3-12 years Melatonin group ● 16 participants, Gender: 8m/8f ● *Age*: mean(SD): 7,4 (3,2) years Placebo group ● 14 participants, Gender: 10m/4f ● *Age*: mean (SD): 6,6 (3,9) years **Included criteria:** Age 3 - 12 years. Only those patients were included who were on valproate monotherapy, had a confirmed diagnosis of epilepsy limited to partial or generalized seizures as classified according to the Inter-national Classification of Epileptic Seizures, and were seizure-free at least for the last 6 months **Excluded criteria:** All children with a history of psychiatric or other progressive neuro-logical disorder or a chronic hematological, cardiac, hepatic, renal, or thyroid disorder were excluded **Pretreatment:** None
Interventions	**Intervention Characteristics** Intervention ● Valproat + Melatonin 6 mg fast release capsules for children <30kgMelatonin 9 mg fast release capsules for children >30kg - Duration 4 weeks Control ● Placebo + Valporat

Outcomes	*Funktionsniveau, mean SD,* QOLCE (attention /concentration) ● **Outcome type**: ContinuousOutcome *Frafald n,N* ● **Outcome type**: DichotomousOutcome *Døsighed i dagtimer, mean SD, EoT, Daytime drowsiness score* ● **Outcome type**: ContinuousOutcome *Livskvalitet hos barnet, mean SD, EoT, QOLCE* ● **Outcome type**: ContinuousOutcome
Identification	**Sponsorship source:** Not stated **Country:** India **Setting:** Domestic **Comments:** **Authors name:** Madhur Gupta **Institution:** Department of Pharmacology, Lady Hardinge Medical College, Shaheed Bhagat Singh Marg, New Delhi **Email:** madhurgupta@hotmail.com **Address:** Shaheed Bhagat Singh Marg, New Delhi 110001, India.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A randomization code list was prepared by a statistician who was not connected to the study. The permutation of code numbers was computer generated for the treatment groups."
Allocation concealment (selection bias)	Low risk	Quote: "The placebo tablets, identical in shape, size, color, and packaging, were"
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: Not mentioned who is blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: Not mentioned who is blinded
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: No apparent sources of bias
Selective reporting (reporting bias)	Low risk	Judgement Comment: No apparent sources of bias
Other bias	Low risk	Judgement Comment: No apparent sources of bias

Gupta 2005

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Overall ● 30 participants with Epilepsy, Gender: 18m/12f ● *Age*: 3-12 years

	Melatonin group ● 16 participants, Gender: 8m/8f ● *Age*: mean(SD): 7,4 (3,2) years Placebo group ● 14 participants, Gender: 10m/4f ● *Age*: mean (SD): 6,6 (3,9) years **Included criteria:** Age 3 - 12 years. Only those patients were included who were on valproate monotherapy, had a confirmed diagnosis of epilepsy limited to partial or generalized seizures as classified according to the Inter-national Classification of Epileptic Seizures, and were seizure-free at least for the last 6 months **Excluded criteria:** All children with a history of psychiatric or other progressive neuro-logical disorder or a chronic hematological, cardiac, hepatic, renal, or thyroid disorder were excluded **Pretreatment:** None
Interventions	**Intervention Characteristics** Intervention ● Valproat + Melatonin 6 mg fast release capsules for children <30kgMelatonin 9 mg fast release capsules for children >30kg - Duration 4 weeks Control ● Placebo + Valporat
Outcomes	*Indsovningstid, mean SD EoT - Actigraph* ● **Outcome type**: ContinuousOutcome *Total sovetid, mean SD, EoT - Lickert scale* ● **Outcome type**: ContinuousOutcome *Antal opvågninger (WASO), mean SD, EoT - Actigraph* ● **Outcome type**: ContinuousOutcome
Identification	**Sponsorship source:** Not stated **Country:** India **Setting:** Domestic **Comments:** **Authors name:** Madhur Gupta **Institution:** Department of Pharmacology, Lady Hardinge Medical College, Shaheed Bhagat Singh Marg, New Delhi **Email:** madhurgupta@hotmail.com **Address:** Shaheed Bhagat Singh Marg, New Delhi 110001, India.
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization code list was prepared by a statistician, who was not connected to the study. The permutation of code numbers was computer generated for the treatment groups."
Allocation concealment (selection bias)	Low risk	Quote: "Ltd, Mumbai, India) were used. The placebo tablets, identical in shape, size, color, and packag- ing, were specially prepared for the study by Aristo Pharmaceuticals Ltd. They contained dicalcium phosphate in place"
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: Not mentioned who is blinded

Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: Not mentioned who is blinded
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: No apparent sources of bias
Selective reporting (reporting bias)	Low risk	Judgement Comment: No apparent sources of bias
Other bias	Low risk	Judgement Comment: No apparent sources of bias

Jain 2015

Methods	**Study design:** Randomized controlled trial, single center, two arms **Study grouping:** Crossover
Participants	**Baseline Characteristics** Overall ● 11 participants with Epilepsy, Gender: n.a. ● *Age*: 6-11 years Melatonin group ● 10 participants ● *Age*: 6-11 years Placebo group ● 10 participants ● *Age*: 6-11 years **Included criteria:** Six to eleven years old pre-pubertal (Tanner stage I) children with epilepsy, with normal development based on school placement (in appropriate grade based on age) and developmental history or IQ>70, were screened with sleep behavior questionnaire (SBQ).2 A combined score of 30, or more on sleep fragmentation, parasomnia and daytime drowsiness subscales was required for enrollment. We enrolled pre-pubertal children to avoid patients with potential delayed sleep phase syndrome where melatonin may have a phase advancing effec **Excluded criteria:** Subjects were excluded if they had a history of loud snoring, diagnosis of obstructive sleep apnea [obstructive apnea hypopnea index >2/hour] or periodic limb movement (PLM) disorder [PLM Index >5/ hour] on polysomnography. We also excluded patients with Vagus nerve stimulator, history of a major psychiatric disease, pervasive development disorder, severe neuro-developmental disabilities, immune disorders or lympho-proliferative disorders. Concurrent use of hypnotics, stimulants, systemic corticosteroids or other immuno-suppressants, or history of using SR melatonin was also exclusionary **Pretreatment:** None - it's a cross over study
Interventions	**Intervention Characteristics** Intervention ● Melatonin 9mg sustained release capsules - Duration 4 weeks pr cycle (1 week washout) Control ● Placebo - capsules, which looked identical to the melatonin capsules
Outcomes	*Søvnkvalitet generelt, mean SD* - subjective measurements (Sleep Behavior Questionnaire (SBQ)) ● **Outcome type**: ContinuousOutcome *Frafald n,N* ● **Outcome type**: DichotomousOutcome *Indsovningstid, mean SD, EoT - Sleep log* ● **Outcome type**: ContinuousOutcome *Total sovetid, mean SD, EoT - Lickert scale* ● **Outcome type**: ContinuousOutcome

	Antal opvågninger (WASO), n,N, EoT - Actigraph ● **Outcome type**: DichotomousOutcome
Identification	**Sponsorship source:** Sejal V Jain is funded by CTSA and CReFF,Katherine Holland is funded by NIH grants R01 NS062756, R01 NS062806, and R01 NS065020.Narong Simakajornboon is funded by NIH U01DK072493,Dean Beebe is funded by NIH grants R01 HL092149, R01 NR012734, and UL1 RR026314, American Diabetes Association grant ADA 7-13-CE-32 and Lupus Foundation of America grant 013-02.Anna Byars is funded by NIH grants 1R01-NS082320-01, 1P20-NS080199-01, and 1R01-NS065840 and contract HHSN275200900018C and TS Alliance/Simonds Foundation/NovartisTracy Glauser is funded by NIH grants 2U01-NS045911, U10-NS077311, R01-NS053998, R01-NS062756, R01-NS043209, R01-LM011124, and R01-NS065840. **Country:** USA **Setting:** Domestic **Comments:** **Authors name:** Sejal V Jain **Institution:** Division of Neurology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH **Email:** Sejal.Jain@cchmc.org **Address:** Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, MLC 2015, Cincinnati, OH 45229,
Notes	*HKA* on 18/03/2022 22:50 **Select** Lille cross-over studie (11 deltagere, hvoraf 1 drop-out)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The Investigational Pharmacy at CCHMC performed the randomization by random number generators in www.randomization.com,"
Allocation concealment (selection bias)	Low risk	Quote: "random number generators in www.randomization.com, ensured 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"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "and dispensed the study medications. The pharmacy and the statistician were unblinded while the rest of the study team was blinded to the allocation throughout data collection, entry and cleaning. 2.8 Statistical methods All outcome"
Blinding of outcome assessment (detection bias)	High risk	Quote: "and dispensed the study medications. The pharmacy and the statistician were unblinded while the rest of the study team was blinded to the allocation throughout data collection, entry and cleaning. 2.8 Statistical methods All outcome measures and"
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: No apparent sources of bias - Protocol available: http://www.clinicaltrials.gov/;NCT00965575
Selective reporting (reporting bias)	Low risk	Judgement Comment: No apparent sources of bias
Other bias	Low risk	Judgement Comment: No apparent sources of bias

McArthur 1998

Methods	**Study design:** Randomized controlled trial, single center, parallel group **Study grouping:** Crossover
Participants	**Baseline Characteristics** Overall ● 9 participants with Rett syndrome, Gender: 9 females ● *Age*: mean(SD): 10.1(1.5) years

	Melatonin group ● 9 participants with Rett syndrome ● *Age*: mean(SD): 10.1(1.5) years Placebo group ● 9 participants with Rett syndrome ● *Age*: mean(SD): 10.1(1.5) years **Included criteria:** 9 females with Rett syndrome **Excluded criteria:** Not stated **Pretreatment:** None - it's a crossover study
Interventions	**Intervention Characteristics** Intervention ● Melatonin 2.5-7.5mg fast release capsules, based upon individual body weight (Regis Chemical Company (Morton Grove, Il, USA) - Duration 2 weeks pr cycle (1 week wash-out) Control ● Placebo - capsules, which looked identical to the melatonin capsules
Outcomes	*Indsovningstid, mean SD, EoT - Actigraph* ● **Outcome type**: ContinuousOutcome *Total sovetid, mean SD, EoT - Actigraph* ● **Outcome type**: ContinuousOutcome *Sleep efficiency, mean SD, EoT* ● **Outcome type**: ContinuousOutcome *Antal opvågninger, n,N, EoT* ● **Outcome type**: DichotomousOutcome
Identification	**Sponsorship source:** Not stated **Country:** USA **Setting:** clinic **Comments:** **Authors name:** Angela McArthur **Institution:** Oregon Health Sciences University **Email:** Not stated **Address:** 3181 SW Sam Jackson Park Rd, Portland, OR97201-3098
Notes	*HKA* on 19/03/2022 03:13 **Select** Kun 9 deltagere, alle piger

Risk of bias table

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

Myers 2018

Methods	**Study design:** Randomized controlled trial, single center, parallel group **Study grouping:** Crossover
Participants	**Baseline Characteristics** Overall ● 13 participants with Dravet syndrome and sleep disturbance, Gender: 4m/9f ● *Age*: mean(range): 12.2 (4.9 - 38) years Melatonin group ● 13 participants with Dravet syndrome and sleep disturbance, Gender: 4m/9f ● *Age*: mean(range): 12.2 (4.9 - 38) years Placebo group ● 13 participants with Dravet syndrome and sleep disturbance, Gender: 4m/9f ● *Age*: mean(range): 12.2 (4.9 - 38) years **Included criteria:** Patients were selected if they, or their family, reported disturbed sleep of any kind **Excluded criteria:** Patients were excluded if they had taken melatonin in the past 4 weeks, had a diagnosis of obstructive sleep apnea, had known hypersensitivity to melatonin, had a musculoskeletal abnormality that prevented them from being able to wear the actigraphy wristband, or were pregnant **Pretreatment:** None - it's a cross-over study
Interventions	**Intervention Characteristics** Intervention ● Melatonin 6 mg fast release capsules - Duration 2 weeks pr cycle - 1 week wash-out Control ● Placebo capsules, which looked identical to the melatonin capsules
Outcomes	*Søvnkvalitet generelt, mean SD,* - subjective measurements (Sleep disturbances Scale in children (SDSC)) ● **Outcome type**: ContinuousOutcome *Antal opvågninger, n,N, EoT* ● **Outcome type**: DichotomousOutcome *Total sovetid, mean SD, EoT - Actigraph* ● **Outcome type**: ContinuousOutcome *Livskvalitet hos barnet, mean SD, EoT - (QOLCE-55)*

	• **Outcome type**: ContinuousOutcome
Identification	**Sponsorship source:** National Health and Medical Research Council (NHMRC) Program Grants (628952, 1091593) **Country:** Australia **Setting:** Clinic **Comments:** **Authors name:** Kenneth Myers **Institution:** Montreal Children's Hospital **Email:** kenneth.myers@mcgill.ca **Address:** 1001 Décarie Blvd, Montreal, PQ, H4A 3J1, Canada
Notes	*HC* on 15/03/2022 07:24 **Select** aged 2 to 50 years *HKA* on 21/03/2022 04:15 **Select** Der er kun én deltager over 24 år? Den kunne godt være relevant og er fra 2018. Cross over RCT, men med blot 13 deltagere med Dravets syndrome (epilepsi)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Randomization was performed by a pharmacist at the Austin Health Clinical Trials Pharmacy. After"
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: Nothing mentioned
Blinding of participants and personnel (performance bias)	Low risk	Judgement Comment: Seems that participants and investigators were blinded during entire study
Blinding of outcome assessment (detection bias)	High risk	Quote: "After all patients had com- pleted the study, initial unblinding was partial, so that in- vestigators learned whether individual patients had received "Treatment A" first or second but did not know if "Treatment A" was melatonin or placebo. This allowed statistical analysis to be performed while investigators were still blinded to treat- ment received. After"
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: No apparent sources of bias
Selective reporting (reporting bias)	Low risk	Quote: "Clinical Trials Notification Scheme (protocol number 2241)" Protocol available: http://www.clinicaltrials.gov/;NCT00965575
Other bias	Low risk	Judgement Comment: No apparent sources of bias

Saxvig 2014

Methods	**Study design:** Randomized controlled trial, single center, four arms **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Overall: • n = 40, participants with delayed sleep phase disorder (DSPD) Gender: 12m/28f, • *Age*, (mean (SD)): 20.7 (3.1) years

	Melatonin group: ● 10 participants, Gender: 5m/5f, ● *Age*, (mean (SD)): 21.2 (2.7) years Control (placebo) group: ● 10 participants, Gender: 3m/7f, ● *Age*, (mean (SD)): 20.8 (3.4) years Furthermore, two intervention arms: Bright light (n=10), and combination of Bright light, and melatonin (n=10) – not relevant for this review. **Included criteria:** (1) living in Bergen, Norway, (2) age 16–25 years, (3) good general health as specified by the exclusion criteria and (4) DSPD diagnosis **Excluded criteria:** Sleep disorders other than DSPD based on subjective reports and polysomnography (apnea-hypopnea index 45 and periodic limb movement index 415), moderate to severe psychopathology or treatment for psychopathology within the last four weeks (based on SCID-I interview (First et al., 1995)), somatic disorders or conditions assumed to affect sleep (i.e. migraine, B12 deficiency), all serious somatic disorders (i.e. rheumatoid arthritis and diabetes), medications assumed to affect sleep (i.e. sedative anti-histamines, antidepressants and hypnotics), substance abuse or night work, IQ570 (Raven's matrices (Raven, 2000; Raven et al., 2000)), breast feeding and pregnancy. **Pretreatment:** The participants kept a sleep diary and wore an actigraph for seven days prior to intervention (baseline assessment)
Interventions	**Intervention Characteristics** Intervention ● Melatonin (hard capsules containing 3 mg of fast release melatonin (5-methoxy-N-acetyltryptamine) - Duration 2 weeks Control ● Placebo, dim light lamp and placebo (hard capsules containing 3 mg of rice flour)
Outcomes	*Søvnkvalitet generelt, mean SD, EoT* ● **Outcome type**: ContinuousOutcome Subjective measurement: Pittsburg sleep quality index (PSQI) Objective measurement: Actigraph (Actiwatch™ recorder AW7, Cambridge Neurotechnology, Cambridge, UK) *Indsovningstid, mean SD, EoT* ● **Outcome type**: ContinuousOutcome (Actigraph) *Total sovetid, mean SD, EoT* ● **Outcome type**: ContinuousOutcome (Actigraph) *Antal opvågninger, n,N EoT* ● **Outcome type**: DichotomousOutcome (Actigraph)
Identification	**Sponsorship source:** Meltzer Foundation for grant funding used for the execution of the study **Country:** Norway **Setting:** Domestic **Comments:** **Authors name:** Ingvild West Saxvig **Institution:** Department of Public Health and Primary Care, University of Bergen, Postboks 7804, 5020 Bergen, Norway. Tel: +47 55586064. Fax: +47 55586130. E-mail: ingvild.saxvig@isf.uib.no **Email:** ingvild.saxvig@isf.uib.no **Address:** Postboks 7804, 5020 Bergen, Norway. Tel: +47 55586064. Fax: +47 55586130. E-mail: ingvild.saxvig@isf.uib.no

Notes	*HC* on 15/03/2022 06:50 **Select** Obs! age 16–25 years, uvist omkring søvnhygiejne *HKA* on 19/03/2022 06:01 **Select** population OK, forsøget med melatonin varer kun 2 uger og rigtigt at der ikke er oplyst om forudgående initiativer. Revurder.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Two randomization lists were produced (four groups Â two-week intervention, two groups Â three-month follow-up), using the Internet–based program Research Randomizer (www.randomizer.org/form.htm)."
Allocation concealment (selection bias)	Low risk	Quote: "Melatonin and placebo capsules were packed in iden- tical containers,"
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "The two-week intervention was double blinded." Judgement Comment: Unclear who was blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: Unclear who was blinded
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: No apparent sources of bias Dropouts from dim light melatonin intervention group (n=1) and placebo group (n=1). Some missing data. ITT analysis. Likely no influence on outcome.
Selective reporting (reporting bias)	Unclear risk	Quote: "(ClinicalTrials.gov NCT00834886)." Judgement Comment: Protocolled 2nd primary outcome:Subjective sleepiness; Karolinska sleepiness scale (KSS). The KSS is a scale in which the subjects rate their concurrent sleepiness level. The scale is verbally anchored with steps ranging from 1 ("very alert") to 9 ("very sleepy, fighting sleep, effort to stay awake").This self-reported outcome is not reported.No statement regarding deviations from protocol. BSI and PSQI and DLMO not pre-specified either.
Other bias	Low risk	Judgement Comment: No apparent sources of bias

Smits 2001

Methods	**Study design:** Randomized controlled trial, single center parallel group, two arms **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Overall: ● 40 participants with idiopathic chronic sleep-onset insomnia. Gender: n.a., ● *Age*: 6-12 years Intervention: ● Melatonin group: n=20. Gender: n.a., ● *Age*: 6-12 years Control: ● Placebo group: (n=20) Gender: n.a., ● *Age*: 6-12 years **Included criteria:** Children suffering from sleep onset insomnia more than 4 nights a week during past 12 months, aged 6-12.

	Excluded criteria: n.a. **Pretreatment:** n.a.
Interventions	**Intervention Characteristics** Intervention ● Melatonin 5 mg fast release capsules. Administration time: 18:00 CET - Duration 4 weeks ● Placebo
Outcomes	*Frafald n,N* ● **Outcome type**: DichotomousOutcome *Indsovningstid, mean SD EoT* - Actigraph (Gähwiler Electronics, Hombrechtikon, Switzerland)) ● **Outcome type**: ContinuousOutcome *Total sovetid, mean SD, EoT* - Actigraph ● **Outcome type**: ContinuousOutcome
Identification	**Sponsorship source:** Jan Dekker en dr Ludgardine Bouwman Foundation and Dutch Society for sleep-wake Research **Country:** The Netherlands **Setting:** Domestic **Comments:** **Authors name:** Marcel Smits **Institution:** Hospital De Gelderse Vallai, sleep Centre **Email:** Smits.M@inter.nl.net **Address:** Stationsweg 86, 6711 PV Ede, The Netherlands
Notes	*HKA* on 21/03/2022 06:01 **Select** 40 deltagere placebo contr RCT - alder 6-12 år og relevante outcomes

Risk of bias table

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

Smits 2003

Methods	**Study design:** Randomized controlled trial, single center parallel group, two arms **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Overall: ● 40 participants with idiopathic chronic sleep-onset insomnia. Gender: n.a., ● *Age*: 6-12 years Intervention: ● Melatonin group: n=20. Gender: n.a., ● *Age*: 6-12 years Control: ● Placebo group: (n=20) Gender: n.a., ● *Age*: 6-12 years **Included criteria:** Children suffering from sleep onset insomnia more than 4 nights a week during past 12 months, aged 6-12. **Excluded criteria:** n.a. **Pretreatment:** n.a.
Interventions	**Intervention Characteristics** Intervention ● Melatonin 5mg fast release capsules. Administration time: 18:00 CET - Duration 4 weeks Control ● Placebo
Outcomes	*Funktionsniveau, mean SD, EoT* - FS-II tool ● **Outcome type**: ContinuousOutcome *Frafald n,N* ● **Outcome type**: DichotomousOutcome *Indsovningstid, mean SD EoT* - Actigraph (Gähwiler Electronics, Hombrechtikon, Switzerland)) ● **Outcome type**: ContinuousOutcome *Total sovetid, mean SD, EoT* - Actigraph ● **Outcome type**: ContinuousOutcome
Identification	**Sponsorship source:** Jan Dekker en dr. Lugardine Bouwman Foundation **Country:** The Netherlands **Setting:** Domestic **Comments:** **Authors name:** Marcel Smits **Institution:** Hospital Gelderse Vallei, Sleep centre **Email:** smitsm@zgv.nl **Address:** Willy Brandtlaan 10, Box 9025, 6710HN Ede, The Netherlands
Notes	*HKA* on 21/03/2022 07:26 **Select** Population OK og med brugbare data

Risk of bias table

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

TaghaviArdakani 2018

Methods	**Study design:** RCT, single center, parallel group, two arms. **Study grouping:** Parallel
Participants	**Baseline Characteristics** Overall: ● 70 participants with Atopic Dermatitis and Sleep Disturbance. Gender: 34m/36f ● Age: 6-12 years Intervention: ● Melatonin group: n=35. Gender: 16m/19f ● Age, Mean (SD): 8.9 (2.1) years Control: ● Placebo group: (n=35) Gender: 18m/17f ● Age, Mean (SD): 8.4 (2.2) years **Included criteria:** not stated **Excluded criteria:** not stated **Pretreatment:** not stated
Interventions	**Intervention Characteristics** Intervention ● Melatonin 6mg fast release capsules (2x3mg) one hour before bedtime - Duration 6 weeks Control ● Placebo capsules, which looked identical to the melatonin capsules
Outcomes	*Søvnkvalitet generelt, mean SD - Subjective measurements (Childrens sleep habits questionnaire)* ● **Outcome type**: ContinuousOutcome *Frafald n,N* ● **Outcome type**: DichotomousOutcome *Indsovningstid, mean SD, EoT - Actigraph* ● **Outcome type**: ContinuousOutcome *Total sovetid, mean SD, EoT - Actigraph*

	● **Outcome type**: ContinuousOutcome *Døsighed i dagtimer, mean SD, EoT - Daytime drowsiness score* ● **Outcome type**: ContinuousOutcome
Identification	**Sponsorship source:** Kashan University of Medical Sciences, Grant/Award Number: 96110 **Country:** Iran **Setting:** Domestic **Comments:** **Authors name:** Abbas Taghavi Ardakani **Institution:** Infectious Diseases Research Center, Kashan University of Medical Sciences, Kashan, Iran **Email:** asemi_r@yahoo.com **Address:** n.a.
Notes	*HKA* on 21/03/2022 07:33 **Select** Brugbare data for en population (70 deltagere), alder 6-12 år, med atopisk dermatitis.

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: "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: "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"
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Randomization and allocation concealment for both the researchers and participants were carried out by a trained staff at the pediatric clinic. Compliance rate"
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: No apparent sources of bias
Selective reporting (reporting bias)	Low risk	Quote: "IRCT2017082733941N12). The" Judgement Comment: No apparent sources of bias
Other bias	Low risk	Judgement Comment: No apparent sources of bias

vanderHeijden 2005

Methods	**Study design:** Randomised controlled trial, single center, parallel group **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Overall: ● 110 participants with idiopathic chronic sleep onset insomnia (SOI) Gender: n.a., ● *Age*: 6-12 years Melatonin group: ● 55 participants

	● *Age*: 6-9 and 10-13 years Control (placebo) group: ● 55 participants ● *Age*: 6-9 and 10-13 years **Included criteria:** As for studies by Smits et al. 2001 and 2003 **Excluded criteria:** Exclusion criteria were sleep maintenance insomnia (one awakening >30 min or two or more awakenings of >5 min summing up to at least 40 min, occurring on one or more nights a week, for a period of at least 4 weeks preceding the start of the trial); disturbed sleep architecture measured by ambulatory polysomnography; mental handicap; severe learning disabilities; any prior use of melatonin; liver diseases; renal failure; use of hypnotics, antidepressants, and neuroleptics; chronic pain; and severe neurologic or psychiatric disorders. **Pretreatment:**
Interventions	**Intervention Characteristics** Intervention ● Melatonin 5 mg fast release capsules (Duchefa Farma BV, Harlem, the Netherlands) - Duration 4 weeks Control ● Placebo capsules, which looked identical to the melatonin capsules
Outcomes	Individual patient data of two previously published randomised, placebo-controlled, double blind, clinical trials, using similar methodology (Smits et al., 2001, 2003), were combined. Aim of this study is whether melatonin efficacy can be predicted from the time at which administration occurs within the circadian rhythm.
Identification	**Sponsorship source:** Supported by the Dr. Ludgardine Bouwman Foundation **Country:** the Netherlands **Setting:** Domestic **Comments:** **Authors name:** Kristiaan B. van der Heijden **Institution:** Department of Child and Adolescent Psychiatry, University of Amsterdam, **Email:** k.b.vanderheijden@amc.uva.nl **Address:** Meibergdreef 9, PO Box 12474, Amsterdam
Notes	*HKA* on 18/03/2022 22:37 **Select** Predictive - ikke umiddelbart relevant, trods comparator er placebo

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: Method not mentioned
Allocation concealment (selection bias)	Low risk	Judgement Comment: No apparent sources of bias
Blinding of participants and personnel (performance bias)	Low risk	Judgement Comment: All investigators were unaware of treatment allocation. Code broken when all data were recorded
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)	Unclear risk	No protocol identified
Selective reporting (reporting bias)	Low risk	Judgement Comment: No apparent sources of bias
Other bias	Low risk	Judgement Comment: No other sources of bias detected

vanGeijlswijk 2010

Methods	**Study design:** Randomized controlled trial, single center, four arms **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Overall: ● 72 participants with chronic sleep onset insomnia, Gender: 30m/42f ● *Age*: 6-12 years Melatonin group: ● 53 participants receiving either 0.05 or 0.1 or 0.15 mg/kg (supplied by Pharma Nord, Denmark) in the appropriate calculated dosage and microcrystalline cellulose. Administered between 17:30 and 19:30, Gender: 24m/29f, ● *Age*: 6-12 years Control (placebo) group: ● 17 participants, Gender: 6m/11f, ● *Age*: 6-12 years **Included criteria:** Children were eligible if they were 6–12 years old, suffering from sleep onset insomnia more than four nights a week for more than 1 year, and insufficiently responded to sleep hygiene improving measures based on parental reports. Sleep onset insomnia was defined as sleep onset later than 8:30 p.m. in children aged 6 years and for older children 15 min later per year until age 12 (10:00 p.m.).Furthermore, the latency between lights-off time and sleep onset (sleep onset latency) had to be more than 30 min on average. Their sleep onset had not been advanced sufficiently with the usual sleep hygiene improving measures. Further inclusion criteria were normal sleep architecture as indicated by a normal hypnogram, performed within 2 months prior to participation, and written informed consent obtained from parents **Excluded criteria:** Exclusion criteria were chronic sleep onset insomnia due to psychiatric or pedagogic problems, known intellectual disability, pervasive develop-mental disorder, chronic pain, known disturbed hepatic or renal function, epilepsy, prior use of melatonin, and use of stimulants, neuroleptics, benzodiazepines, clonidine, anti depressants, hypnotics, or beta-blockers within 4 weeks before enrollment. **Pretreatment:** None
Interventions	**Intervention Characteristics** Intervention 1 ● Melatonin 0.05mg/kg - Duration 2 weeks Intervention 2 ● Melatonin 0.1mg/kg - Duration 2 weeks Intervention 3 ● Melatonin 0.15mg/kg - Duration 2 weeks Control ● Placebo
Outcomes	*Indsovningstid, mean SD EoT* ● **Outcome type**: ContinuousOutcome (Actigraph) *Total sovetid, mean SD, EoT* ● **Outcome type**: ContinuousOutcome (Actigraph) *Antal opvågninger, n,N EoT* ● **Outcome type**: DichotomousOutcome (Actigraph)

Identification	**Sponsorship source:** Not stated **Country:** The Netherlands **Setting:** Domestic **Comments:** **Authors name:** Ingeborg M. van Geijlswijk **Institution:** Department of Pharmacy, Faculty of Veterinary Medicine, Utrecht Universit **Email:** i.m.vangeijlswijk@uu.nl **Address:** Yalelaan 106, 3584 CM Utrecht, The Netherlands
Notes	*HKA* on 18/03/2022 22:46 **Select** Dosis afhængige gavnlige effekter på børn 6-12 år, der har haft søvnproblemer i mere end et år *HKA* on 05/04/2022 00:37 **Included** De opgiver indsovningstid som Mean diff sammenlignet med placebo gruppen, men det er lidt svært at tolke værdierne for SOL (sleep onset latency), da værdier for alle tre anvendte melatonin-doser er positive, dvs længere tid end placebo-gruppen, hvilket ikke kan være tilfældet.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "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	Quote: "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	Quote: "All participants, care providers, and investigators involved in the study were unaware of the treatment allocation."
Blinding of outcome assessment (detection bias)	Low risk	Quote: "treatment allocation and subject number. All participants, care providers, and investigators involved in the study were unaware of the treatment allocation. Data analysis The time measurements bed-, sleep"
Incomplete outcome data (attrition bias)	Unclear risk	Judgement Comment: Afhængig af outcome er der en samlet dropout rate på 5-10 deltagere
Selective reporting (reporting bias)	Low risk	Judgement Comment: No apparent sources of bias. Randomized Controlled Trial Number Register (ISRCTN20033346).
Other bias	Low risk	Judgement Comment: No apparent sources of bias

VanGeijlswijk 2011

Methods	**Study design:** Follow up from the RCT study Van Geijlswijk, 2010 **Study grouping:** Single arm
Participants	**Baseline Characteristics** Overall: ● n = 59, participants with chronic sleep onset insomnia ● Subgroup a. Age: <13 years ● Subgroup b. Age: >13 years **Included criteria:** Not stated

	Excluded criteria: Not stated **Pretreatment:**
Interventions	**Intervention Characteristics** Intervention 1 ● Long term use of melatonin, mean daily dose 2,69 mg (min 0,3 mg, max 10 mg) - Duration 6 months
Outcomes	*Sleep quality, mean SD - CSQH* ● **Outcome type**: ContinuousOutcome *Effects of prolonged use of melatonin, EoT* ● **Outcome type**: Narrative presentation of effect on Puberty development: Tanner score (Tanner Stages standard deviation scores could be determined for 16 boys and 30 girls) *Dropouts, n,N EoT* ● **Outcome type**: DichotomousOutcome
Identification	**Sponsorship source:** Not stated **Country:** The Netherlands **Setting:** Domestic **Comments:** **Authors name:** Ingeborg M. van Geijlswijk **Institution:** Department of Pharmacy, Faculty of Veterinary Medicine, Utrecht Universit **Email:** i.m.vangeijlswijk@uu.nl **Address:** Yalelaan 106, 3584 CM Utrecht, The Netherlands
Notes	*HC* on 15/03/2022 18:39 **Select** FU studie af van Geijlswijk et al. 2010, med langtidsbivirkninger

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "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	Quote: "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	Quote: "All participants, care providers, and investigators involved in the study were unaware of the treatment allocation."
Blinding of outcome assessment (detection bias)	Low risk	Quote: "treatment allocation and subject number. All participants, care providers, and investigators involved in the study were unaware of the treatment allocation. Data analysis The time measurements bed-, sleep"
Incomplete outcome data (attrition bias)	Unclear risk	Judgement Comment: Afhængig af outcome er der en samlet dropout rate på 5-10 deltagere
Selective reporting (reporting bias)	Low risk	Judgement Comment: No apparent sources of bias. Randomized Controlled Trial Number Register (ISRCTN20033346).
Other bias	Low risk	Judgement comment: No apparent sources of bias

vanMaanen 2017

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Overall: ● 54 participants with idiopathic chronic sleep onset insomnia (SOI) Gender: (33m/21f). ● *Age*: 10 years (mean) Intervention: ● Melatonin group: 26 participants, Gender: 17m/9f ● *Age*, mean (SD): 10.01 (1.47) years Control (placebo) group: ● 28 participants, Gender: 16m/12f ● *Age*, mean (SD): 10.04 (1.63) years **Included criteria:** (1) age between 7 and 12 years old; (2) chronic sleep onset problems, as indicated by (a) complaints of inability to fall asleep at the desired clock time (sleep onset later than 20:45 h in children aged 7 years and for older children 15 minutes later per year) and a latency between lights-off time and sleep onset (sleep onset latency) of more than 30 minutes, and (b) the symptoms were present for at least four nights a week, for at least 1 month during a regular school period; (c) the sleep problems resulted in problems with daytime functioning. **Excluded criteria:** (1) a diagnosis of a childhood psychiatric disorder other than ADHD or autism spectrum disorder; (2) chronic pain; (3) known disturbed hepatic or renal function; (4) Roter or Dubin-Johnson syndrome; (5) epilepsy; (6) use of neuroleptics, benzodiazepines, clonidine, antidepressants, hypnotics, or β-blockers within 4 weeks before enrolment; (7) intellectual disability. Furthermore, other psychiatric disorders than ADHD or autism, for example, bipolar disorders, because these are often associated with a broader range of sleep problems. **Pretreatment:**
Interventions	**Intervention Characteristics** Intervention 1 ● Melatonin 3 mg fast release (Pharma Nord), administrated at 19:00 h - Duration 3-4 weeks Control ● Placebo (identical looking tablets as intervention)
Outcomes	*Søvnkvalitet generelt, mean SD, EoT- Sleep efficacy (%) / AW4 actiwatches (Cambridge Neurotechnology Ltd, Cambridge,UK) - Actigraph* ● **Outcome type**: ContinuousOutcome *Indsovningstid, mean SD, EoT* ● **Outcome type**: ContinuousOutcome - Actigraph *Total sovetid, mean SD, EoT* ● **Outcome type**: ContinuousOutcome - Actigraph *Antal opvågninger, n,N EoT* ● **Outcome type**: DichotomousOutcome - Actigraph
Identification	**Sponsorship source:** Pharma Nord sponsored the melatonin and placebo tablets for the study **Country:** The Netherlands **Setting:** Domestic **Comments:** **Authors name:** Annette van Maanen **Institution:** Research Institute of Child Development and Education, University of Amsterdam. **Email:** A.vanMaanen@uva.nl

	Address: PO Box 15776, 1001 NG Amsterdam, The Netherlands
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization took place using a preset list specifying whether a participant should receive medication (melatonin or placebo) or light on a 2:1 ratio." Quote: "Children who were randomized to medication received either melatonin or placebo, dependent on a coding deter- mined by the manufacturer, blind for the researcher and treatment provider (neurologist). Only"
Allocation concealment (selection bias)	Low risk	Quote: "Children who were randomized to medication received either melatonin or placebo, dependent on a coding deter- mined by the manufacturer, blind for the researcher and treatment provider (neurologist). Only at post-treatment,"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Pharma Nord) at 19:00 h. Children in the melatonin condition received melatonin for 3 to 4 weeks. In the placebo condition, children received placebo tablets, which looked iden- tical to the melatonin tablets. Sleep diary reports indicated that" Quote: "Children who were randomized to medication received either melatonin or placebo, dependent on a coding deter- mined by the manufacturer, blind for the researcher and treatment provider (neurologist). Only at post-treatment, when they returned to the center, the code was broken by the neurologist."
Blinding of outcome assessment (detection bias)	Low risk	Quote: "blind for the researcher and treatment provider (neurologist). Only at post-treatment, when" Judgement Comment: Only objective measures (actigraph)
Incomplete outcome data (attrition bias)	Unclear risk	Quote: "Data were analyzed on an intention to treat basis." Judgement Comment: NI about missing data
Selective reporting (reporting bias)	Low risk	Quote: "Nederlands Trial Register (NTR): NTR4045" Judgement Comment: https://www.trialregister.nl/trial/3884 This study seems free from selective outcome reporting No apparent sources of bias
Other bias	Low risk	Judgement Comment: No apparent sources of bias

Wasdell 2008

Methods	**Study design:** Randomized controlled trial, parallel **Study grouping:** Cross-over
Participants	**Baseline Characteristics** Overall: ● 50 participants with Neurodevelopmental disabilities, Gender: 31m/19f, ● *Age*: mean 7,38 years (range 2,05-17,81 years) Melatonin group: ● 50 participants with Neurodevelopmental disabilities, Gender: 31m/19f, ● *Age*: mean 7,38 years (range 2,05-17,81 years) Control (placebo) group: ● 50 participants with Neurodevelopmental disabilities, Gender: 31m/19f, ● *Age*: mean 7,38 years (range 2,05-17,81 years) **Included criteria:** Participants were eligible to participate if they were between the ages of 2 and 18 yr, had multiple NDD and chronic DSPS or ISM (longer than 1.5 yr) **Excluded criteria:** Children were not eligible when their sleep difficulties were mild and not associated with daytime symptoms of insomnia (such as excessive drowsiness, inability to stay awake, lethargy, increased irritability and decreased functioning) and had progressive degenerative neurologic disorders, or life-threatening illnesses

	Pretreatment: None, it's a crossover trial
Interventions	**Intervention Characteristics** Intervention ● Melatonin 5 mg (1 mg fast release; 4 mg sustained release) capsules (provided by Circa Dia BV, The Netherlands). Administered 20-30 minutes before bedtime - Duration 10 days Control ● Placebo capsules, which looked identical to intervention group
Outcomes	*Søvnkvalitet generelt, mean SD - Objective measurements - Actigraph* ● **Outcome type**: ContinuousOutcome *Funktionsniveau, mean SD - CGI (Parents global assessment scale)* ● **Outcome type**: ContinuousOutcome *Frafald n,N* ● **Outcome type**: DichotomousOutcome *Indsovningstid, mean SD EoT - Actigraph* ● **Outcome type**: ContinuousOutcome *Total sovetid, mean SD, EoT - Actigraph* ● **Outcome type**: ContinuousOutcome *Antal opvågninger, n,N, EoT* ● **Outcome type**: DichotomousOutcome
Identification	**Sponsorship source:** This study was sponsored as an investigator-initiated trial by Circa Dia BV **Country:** Canada **Setting:** Clinic **Comments:** **Authors name:** Michael B. Wasdell **Institution:** Diagnostic Neurophysiology, BC Childrens Hospital **Email:** jjan@cw.bc.ca **Address:** 4500 Oak Street, Vancouver, BC, Canada V6H 3N1
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A blocked randomization method was employed in which every four patients had equal probability of receiving either of the two treatment sequences." Quote: "Patients were randomly assigned by the hospital pharmacy to receive either melatonin or placebo first."
Allocation concealment (selection bias)	Low risk	Quote: "placebo was prepared by the hospital pharmacy in identical capsules"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Patients, caregivers, study inves- tigator, and clinical staff were blind to the medication randomization." Quote: "Patients, caregivers, study inves- tigator, and clinical staff were blind to the medication randomization."
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Patients, caregivers, study inves- tigator, and clinical staff were blind to the medication randomization. Unblinding of"

Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: One patient (1%) withdrew and was hence excluded from the analysis.
Selective reporting (reporting bias)	Low risk	Judgement Comment: No apparent sources of bias
Other bias	High risk	Quote: "The authors wish to thank Ruth Milner, Derryck Smith, the Department of Psychiatry, Diane Fast, Hilary Espezel, and Circa Dia BV for their support." Quote: "This study was sponsored as an investigator-initiated trial by Circa Dia BV. Dr. Jan holds a research contract/grant with Circa Dia BV. Professor Rietveld is the Scientific Director of Circa Dia BV. Dr. Weiss is a consultant, an advisory board and speakerÕs 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 speakerÕs 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 BV." Judgement Comment: Circa Dia BV (medical provider) initiated the trial and authors hold positions within the company. No descriptions of the sponsor's role (s).

Wilhelmsen Langeland 2013

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Overall ● 20 participants with Delayed Sleep Phase Disorder (DSPD), Gender: 8m/12f ● *Age*: range 16-25 years Intervention ● Melatonin group (n=10) Gender: 5m/5f ● *Age*, mean (SD): 21.2 (2.7) years Control ● Control (placebo) group (n=10) Gender: 3m/7f ● *Age*, mean (SD): 20.8 (3.4) years **Included criteria:** Inclusion criteria were 1) living in Bergen, Norway; 2) aged 16 to 25 years; 3) good general health as speci-fied by the exclusion criteria (see below); and 4) ful-filling the diagnostic criteria for DSPD. The participants were diagnosed according to the criteria found in the International Classification of Sleep Disorders, 2nd version (ICSD-2) (American Academy of Sleep Medicine, 2005), operationalized for this study as the following: 1) problems falling asleep in the evening, 2) falling asleep after 0200 h at least 3 days a week, 3) ability to sleep until early afternoon, 4) problems waking up in time for school/work, 5) early wake-up times associated with extreme day-time sleepiness, 6) good subjective sleep quality and duration when given the opportunity to sleep at self-chosen times, and 7) verbally self-reporting the afore-mentioned sleep problems as chronic (>6 months).The DSPD diagnosis was confirmed as required by the ICSD-2 criteria by sleep diary data covering a 1-week period and showing a delayed sleep pattern **Excluded criteria:** Exclusion criteria were sleep disorders other than DSPD, moderate to severe psychopathology (see later for procedure), conditions assumed to affect sleep (i.e., migraine, B12 deficiency), all serious somatic disorders (i.e., rheumatoid arthritis, diabe-tes), medications or treatments assumed to affect sleep (i.e., sedative antihistamines, antidepressants, hypnotics), substance abuse, night work, intelligence quotient <70, breast feeding, and pregnancy. **Pretreatment:** None
Interventions	**Intervention Characteristics** Intervention 1 ● *Type*: Melatonin, hard capsules containing 3 mg of fast release melatonin (5-methoxy-N-acetyltryptamine) - Duration 2 weeks Control ● *Type*: Placebo, dim light lamp and placebo (hard capsules containing 3 mg of maydis amylum (maize starch))

Outcomes	*Funktionsniveau, mean SD* ● **Outcome type**: ContinuousOutcome - Conners continous performance test *Frafald n,N* ● **Outcome type**: DichotomousOutcome *Døsighed i dagtimer, mean SD, EoT - Karolinska Sleepiness Scale, Epworth Sleepiness Scale, Fatigue Questionnaire* ● **Outcome type**: ContinuousOutcome
Identification	**Sponsorship source:** Meltzer Foundation for grant funding used for the execution of this study **Country:** Norway **Setting:** Domestic **Comments:** **Authors name:** Ane Wilhelmsen-Langeland **Institution:** Department of Global Health and Primary Care, University of Bergen, Bergen, Norway, †Norwegian Competence Center for Sleep Disorders, Haukeland University Hospital, Bergen, Norway, ‡Department of Psychosocial Science, University of Bergen, Bergen, Norway, **Email:** wilhelmsen-langeland@ipr.no **Address:** University of Bergen, Postboks 7804, 5020 Bergen, Norway
Notes	*HC* on 15/03/2022 06:25 **Select** Obs! aged 16 to 25 years. Uvist om søvnhygiejne tiltag er blevet afprøvet *HKA* on 04/04/2022 23:25 **Included** Vi kigger kun på den første periode

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "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	Quote: "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). In"
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "The 2-week treatment study was double blinded." Judgement Comment: Unclear who was blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: Unclear who was blinded
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: No apparent sources of bias
Selective reporting (reporting bias)	Low risk	Judgement Comment: No apparent sources of bias
Other bias	Low risk	Judgement Comment: No apparent sources of bias

Footnotes

Characteristics of excluded studies

Abramova 2020

Reason for exclusion	No new studies

Alamili 2014

Reason for exclusion	Wrong study design

Andersen 2016

Reason for exclusion	No new studies

Appleton 2011

Reason for exclusion	Abstract

Appleton 2012

Reason for exclusion	No new studies

Appleton 2013

Reason for exclusion	No new studies

Arendt 2008

Reason for exclusion	Wrong study design

Armour 2004

Reason for exclusion	No new studies

Auger 2015

Reason for exclusion	No new studies

Bakken 2016

Reason for exclusion	Abstract

Barlow 2014

Reason for exclusion	Abstract

Barlow 2020

Reason for exclusion	Wrong patient population

Beresford 2018

Reason for exclusion	No new studies

Beresford 2019

Reason for exclusion	Abstract

Besag 2019

Reason for exclusion	Wrong study design

Bjorvatn 2013

Reason for exclusion	Abstract

Bjorvatn 2014

Reason for exclusion	Abstract

Blackmer 2016

Reason for exclusion	No new studies

Borrington 2017

Reason for exclusion	Wrong study design

Braam 2008a

Reason for exclusion	Wrong patient population

Braam 2009

Reason for exclusion	No new studies

Braam 2010

Reason for exclusion	Wrong patient population

Buscemi 2005

Reason for exclusion	No new studies

Buscemi 2006

Reason for exclusion	Wrong study design

Buscemi 2006a

Reason for exclusion	No new studies

Calhoun 2013

Reason for exclusion	Wrong study design

Camfield 1996

Reason for exclusion	Abstract

Campos 2004

Reason for exclusion	Wrong patient population

Carr 2007

Reason for exclusion	Wrong study design

Cavallo 2004

Reason for exclusion	Wrong comparator

Cavallo 2004a

Reason for exclusion	Wrong comparator

ChecaRos 2018

Reason for exclusion	Wrong outcomes

Chhangani 2011

Reason for exclusion	No new studies

Dagan 1998

Reason for exclusion	Wrong patient population

Dahlitz 1991

Reason for exclusion	Wrong patient population

deZambotti 2018

Reason for exclusion	No new studies

Ebrahimi Monfared 2017

Reason for exclusion	Wrong patient population

Economou 2018

Reason for exclusion	No new studies

Espezel 1996

Reason for exclusion	Wrong study design

Farina 2018

Reason for exclusion	Abstract

Feder 2021

Reason for exclusion	Wrong study design

Ferracioli Oda 2013

Reason for exclusion	No new studies

Fischer 2003

Reason for exclusion	Wrong patient population

Galland 2012

Reason for exclusion	No new studies

Gelfand 2017

Reason for exclusion	Wrong intervention

Gelfand 2020

Reason for exclusion	Wrong comparator

Glaze 2004

Reason for exclusion	Wrong study design

GoldbergStern 2010

Reason for exclusion	Abstract

Goldberg Stern 2012

Reason for exclusion	Wrong patient population

Gradisar 2013

Reason for exclusion	Wrong study design

GriggDamberger 2013

Reason for exclusion	Wrong study design

Gringras 2008

Reason for exclusion	Wrong study design

Gringras 2018

Reason for exclusion	Abstract

Gupta 2004a

Reason for exclusion	Wrong outcomes

Gupta 2004b

Reason for exclusion	Wrong outcomes

Hancock 2005

Reason for exclusion	Wrong study design

Hanish 2021

Reason for exclusion	Abstract

Hardeland 2009

Reason for exclusion	Wrong study design

Hatonen 1999

Reason for exclusion	Wrong study design

Heussler 2016

Reason for exclusion	Wrong patient population

Hoban 2010

Reason for exclusion	Wrong study design

Hollway 2011

Reason for exclusion	Wrong study design

Holmes 2002

Reason for exclusion	Wrong patient population

Hsu 2021

Reason for exclusion	Wrong patient population

Hughes 1997

Reason for exclusion	Wrong patient population

Hussain 2011

Reason for exclusion	Wrong patient population

Iyer 2020

Reason for exclusion	Wrong outcomes

Jain 2014

Reason for exclusion	Abstract

Jain 2015a

Reason for exclusion	Wrong study design

Jan 1994

Reason for exclusion	Wrong study design

Jan 2000

Reason for exclusion	Wrong study design

Jan 2004

Reason for exclusion	Wrong study design

Jan 2007

Reason for exclusion	Wrong study design

Jenni 2005

Reason for exclusion	Wrong study design

Jun 2019

Reason for exclusion	Wrong patient population

Kampmann 2021

Reason for exclusion	Wrong patient population

Kemp 2004

Reason for exclusion	Wrong patient population

Khan 2011

Reason for exclusion	Abstract

Khan 2011a

Reason for exclusion	No new studies

Khan 2011b

Reason for exclusion	No new studies

Khan 2017

Reason for exclusion	Wrong study design

Khan 2017a

Reason for exclusion	Wrong study design

Kledzik 2011

Reason for exclusion	Wrong study design

Liampas 2020

Reason for exclusion	No new studies

Liampas 2021

Reason for exclusion	No new studies

Lim 2022

Reason for exclusion	Wrong study design

Lowden 2012

Reason for exclusion	Abstract

Lubas 2022

Reason for exclusion	Wrong patient population

Mantle 2020

Reason for exclusion	No new studies

Mayer 2011

Reason for exclusion	Abstract

McDonagh 2019

Reason for exclusion	No new studies

McGrane 2015

Reason for exclusion	No new studies

Mellor 2022

Reason for exclusion	Wrong indication

Merks 2010

Reason for exclusion	Abstract

Merks 2012

Reason for exclusion	Wrong patient population

Miano 2008

Reason for exclusion	Wrong study design

Mulchahey 2004

Reason for exclusion	Wrong patient population

Muller 2006

Reason for exclusion	Wrong patient population

Nagtegaal 1998

Reason for exclusion	Wrong study design

Natale 2019

Reason for exclusion	Wrong patient population

NATALE 2019

Reason for exclusion	Wrong patient population

Nave 1995

Reason for exclusion	Wrong indication

Niederhofer 2003

Reason for exclusion	Wrong outcomes

OCallaghan 1999

Reason for exclusion	Wrong study design

Ogundele 2021

Reason for exclusion	Abstract

Oldani 1994

Reason for exclusion	Wrong patient population

Ostadmohammadi 2020

Reason for exclusion	Wrong patient population

Owens 2009

Reason for exclusion	No new studies

Owens 2011

Reason for exclusion	No new studies

Owens 2011a

Reason for exclusion	No new studies

Owens 2017

Reason for exclusion	Abstract

Owens 2021

Reason for exclusion	Abstract

Paavonen 2003

Reason for exclusion	Wrong patient population

Parker 2019

Reason for exclusion	No new studies

Patel 2018

Reason for exclusion	Wrong study design

Pelayo 2012

Reason for exclusion	No new studies

Pelc 2008

Reason for exclusion	No new studies

Peled 2001

Reason for exclusion	Wrong study design

Phillips 2004

Reason for exclusion	No new studies

Porteous 2021

Reason for exclusion	Wrong study design

Putilov 2005

Reason for exclusion	Wrong patient population

QueraSalva 2021

Reason for exclusion	No new studies

Reading 2006

Reason for exclusion	Abstract

Reading 2013

Reason for exclusion	Wrong study design

Reed 2002

Reason for exclusion	No new studies

Rimmele 2009

Reason for exclusion	Wrong patient population

Sajith 2007

Reason for exclusion	No new studies

Schwichtenberg 2015

Reason for exclusion	Wrong study design

Shamseer 2009

Reason for exclusion	No new studies

Shatkin 2015

Reason for exclusion	Wrong study design

Sletten 2001

Reason for exclusion	Wrong patient population

Sletten 2018

Reason for exclusion	Wrong patient population

Smits 2017

Reason for exclusion	Abstract

Smits 2017a

Reason for exclusion	Abstract

Tzischinsky 1994

Reason for exclusion	Wrong patient population

Uberos 2011

Reason for exclusion	Wrong study design

vanGeijlswijk 2010a

Reason for exclusion	No new studies

vanGolde 2011

Reason for exclusion	No new studies

Volpe 2017

Reason for exclusion	Wrong patient population

Wade 2011

Reason for exclusion	Wrong patient population

Wassmer 2006

Reason for exclusion	No new studies

Wei 2020

Reason for exclusion	Already included

Wetterberg 1999

Reason for exclusion	No new studies

Willey 2002

Reason for exclusion	Abstract

Wirojanan 2009

Reason for exclusion	Wrong study design

Wyatt 2006

Reason for exclusion	Wrong patient population

Wynn 2010

Reason for exclusion	No new studies

Zarezadeh 2020

Reason for exclusion	No new studies

Zhdanova 1997

Reason for exclusion	Wrong study design

Zisapel 2015

Reason for exclusion	No new studies

Zisapel 2017

Reason for exclusion	Abstract

Zwart 2018

Reason for exclusion	Wrong study design

Zybach 2016

Reason for exclusion	Wrong patient population

Footnotes

References to studies

Included studies

Barlow 2021

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Gupta, Madhur; Aneja, Satinder; Kohli, Kamlesh. Add-on melatonin improves quality of life in epileptic children on valproate monotherapy: a randomized, double-blind, placebo-controlled trial.. Epilepsy & Behavior 2004;5 (3):316-321. [DOI:]

Gupta 2005

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Jain 2015

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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:]

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Data and analyses

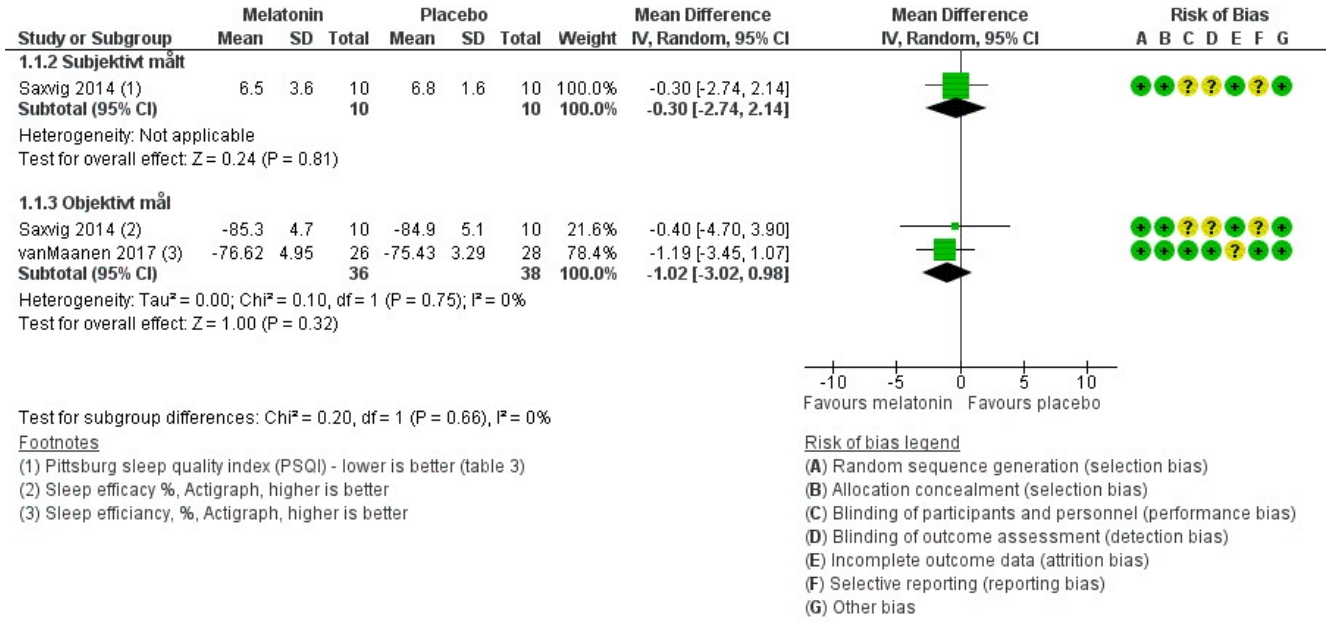
1 Melatonin vs placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Søvnkvalitet generelt - idiopatisk	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1.2 Subjektivt målt	1	20	Mean Difference (IV, Random, 95% CI)	-0.30 [-2.74, 2.14]
1.1.3 Objektivt mål	2	74	Mean Difference (IV, Random, 95% CI)	-1.02 [-3.02, 0.98]
1.2 Søvnkvalitet generelt - øvrige	6	330	Std. Mean Difference (IV, Random, 95% CI)	0.03 [-0.22, 0.29]
1.2.1 Subjektivt målt	5	173	Std. Mean Difference (IV, Random, 95% CI)	0.04 [-0.41, 0.50]
1.2.2 Objektivt målt	3	157	Std. Mean Difference (IV, Random, 95% CI)	0.04 [-0.28, 0.35]
1.3 Funktionsniveau	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.3.1 Idiopatic	2	71	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.75, 0.18]
1.3.2 Øvrige	2	130	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.71, 0.15]
1.4 Total sovetid	15		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.4.1 Idiopatisk	5	204	Mean Difference (IV, Random, 95% CI)	32.08 [18.35, 45.81]
1.4.2 Øvrige	10	401	Mean Difference (IV, Random, 95% CI)	18.97 [0.37, 37.57]
1.5 Indsovningstid	13		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.5.1 Idiopatic	4	162	Mean Difference (IV, Random, 95% CI)	-15.25 [-26.49, -4.01]
1.5.2 Øvrige	9	357	Mean Difference (IV, Random, 95% CI)	-14.88 [-23.42, -6.34]
1.6 Opvågning - idiopatisk	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.7 Opvågning - øvrige	8	301	Mean Difference (IV, Random, 95% CI)	-0.29 [-1.16, 0.59]
1.7.1 Gennemsnitlige antal opvågninger	4	198	Mean Difference (IV, Random, 95% CI)	-0.24 [-0.87, 0.39]
1.7.2 Vågentid efter start af søvnperiode(WASO)	4	103	Mean Difference (IV, Random, 95% CI)	-13.12 [-38.05, 11.81]
1.8 Døsighed/træthed i dagtimer	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.8.1 Idiopatic	2	62	Mean Difference (IV, Random, 95% CI)	-0.57 [-0.66, -0.48]
1.8.2 Øvrige	2	100	Mean Difference (IV, Random, 95% CI)	-0.10 [-1.27, 1.07]
1.9 Livskvalitet hos barnet, EoT	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.9.1 Idiopatic	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
1.9.2 Øvrige	2	56	Mean Difference (IV, Random, 95% CI)	1.32 [0.41, 2.24]

1.10 Frafald	9		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.10.1 Idiopatic	4	235	Risk Ratio (IV, Random, 95% CI)	2.89 [0.71, 11.65]
1.10.2 Øvrige	5	322	Risk Ratio (IV, Random, 95% CI)	0.58 [0.27, 1.23]
1.11 Total sovetid Baseline	14	662	Mean Difference (IV, Random, 95% CI)	-3.99 [-10.85, 2.86]
1.11.1 Idiopatisk	5	270	Mean Difference (IV, Random, 95% CI)	-4.08 [-12.09, 3.94]
1.11.2 Øvrige	9	392	Mean Difference (IV, Random, 95% CI)	-3.77 [-16.99, 9.45]
1.12 Indsovningstid baseline	13	548	Mean Difference (IV, Random, 95% CI)	1.04 [-2.85, 4.93]
1.12.1 Idiopatisk	4	162	Mean Difference (IV, Random, 95% CI)	1.47 [-5.74, 8.68]
1.12.2 Øvrige	9	386	Mean Difference (IV, Random, 95% CI)	0.86 [-3.76, 5.49]
1.13 Opvågninger Baseline	10	396	Mean Difference (IV, Random, 95% CI)	0.01 [-0.45, 0.47]
1.13.1 Idiopatisk	2	74	Mean Difference (IV, Random, 95% CI)	7.78 [-0.18, 15.73]
1.13.2 Øvrige antal opvågninger	4	198	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.48, 0.44]
1.13.3 Øvrige WASO	4	124	Mean Difference (IV, Random, 95% CI)	2.13 [-10.76, 15.02]

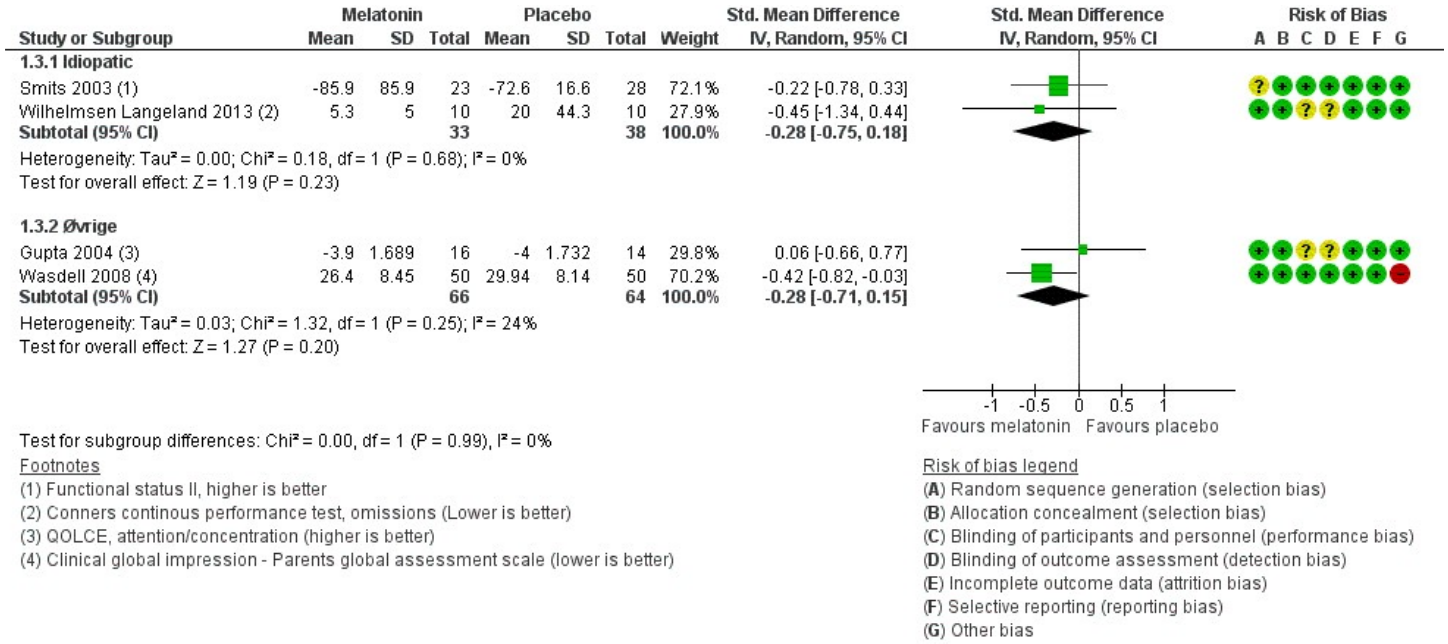
Figures

Figure 1 (Analysis 1.1)



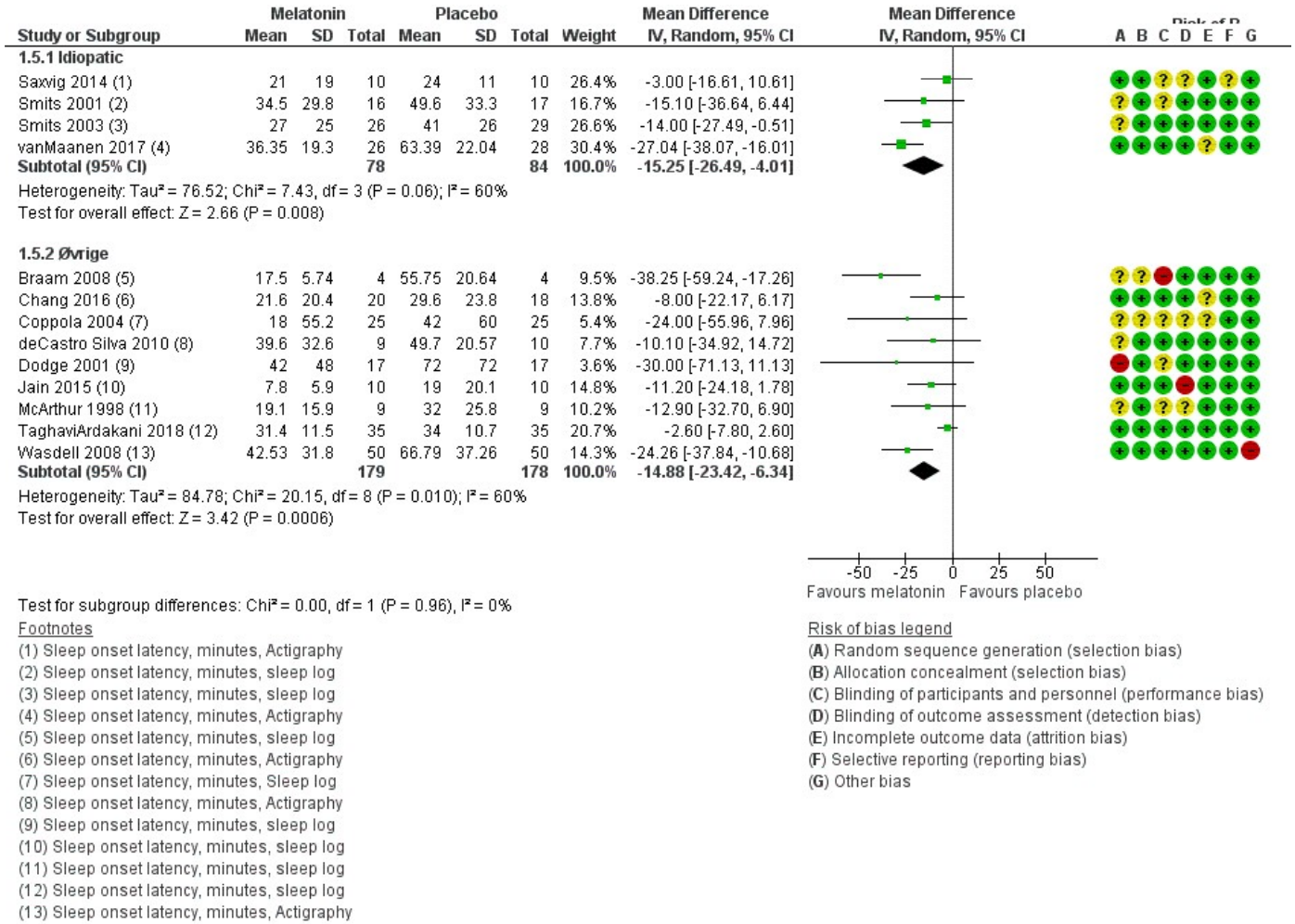
Søvnkvalitet generelt. Målt efter endt behandling (behandlingslængde 10 dage til 6 uger)

Figure 2 (Analysis 1.3)



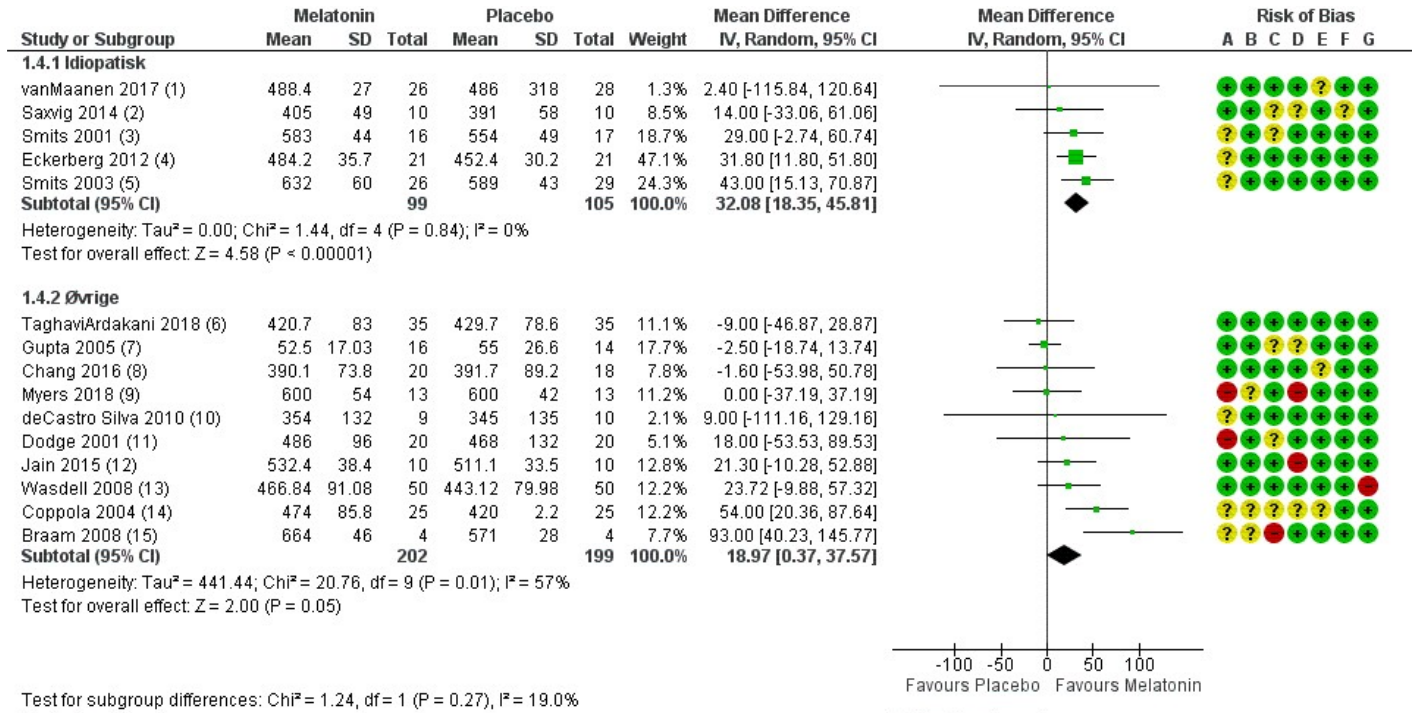
Funktionsniveau. Målt efter endt behandling (behandlingslængde 10 dage til 4 uger)

Figure 3 (Analysis 1.5)



Indsovningstid. Målt efter endt behandling (behandlingslængde 10 dage til 6 uger)

Figure 4 (Analysis 1.4)



Test for subgroup differences: Chi² = 1.24, df = 1 (P = 0.27), I² = 19.0%

Footnotes

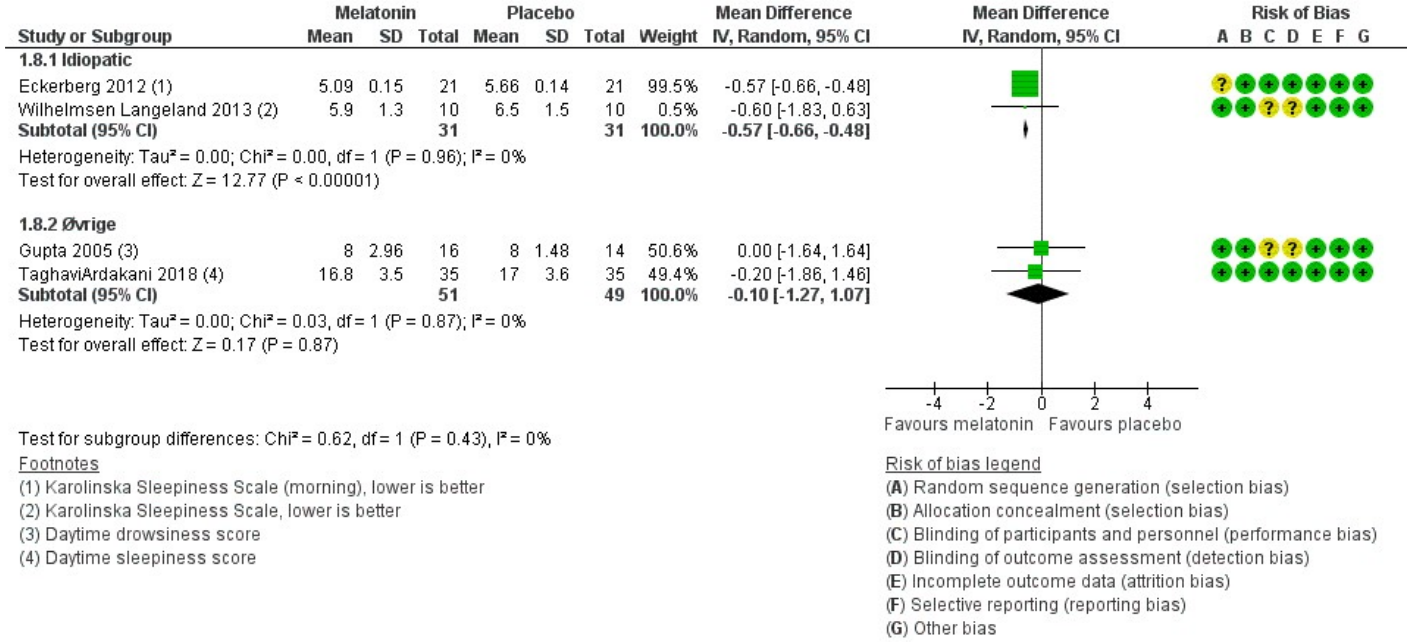
(1) Total sleep time, min/night, Actigraphy
(2) Total sleep time, min/night, Actigraphy
(3) Total sleep time, min/night, sleep log
(4) Total sleep time, min/night, sleep log
(5) Total sleep time, min/night, sleep log
(6) Total sleep time, min/night, sleep log
(7) Total sleep time, Lickert scale, Change værdi fra baseline
(8) Total sleep time, min/night, sleep log
(9) Total sleep time, min/night, Actigraphy
(10) Total sleep time, min/nights, Actigraphy
(11) Total sleep time, min/night, Sleep log
(12) Total sleep time, min/night, sleep log
(13) Total sleep time, min/night, Actigraphy
(14) Total sleep time, min/night, sleep log
(15) Total sleep time, min/night, sleep log

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

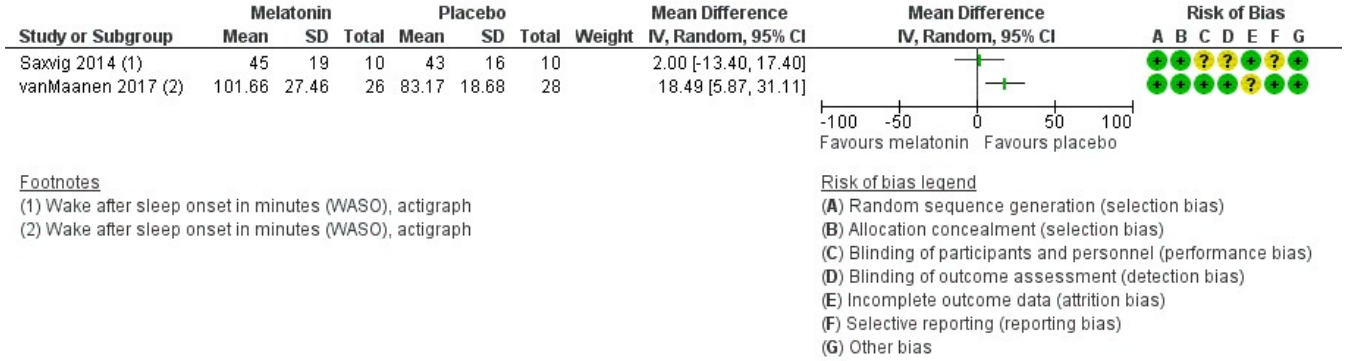
Total sovetid. Målt efter endt behandling (behandlingslængde 10 dage til 6 uger)

Figure 5 (Analysis 1.8)



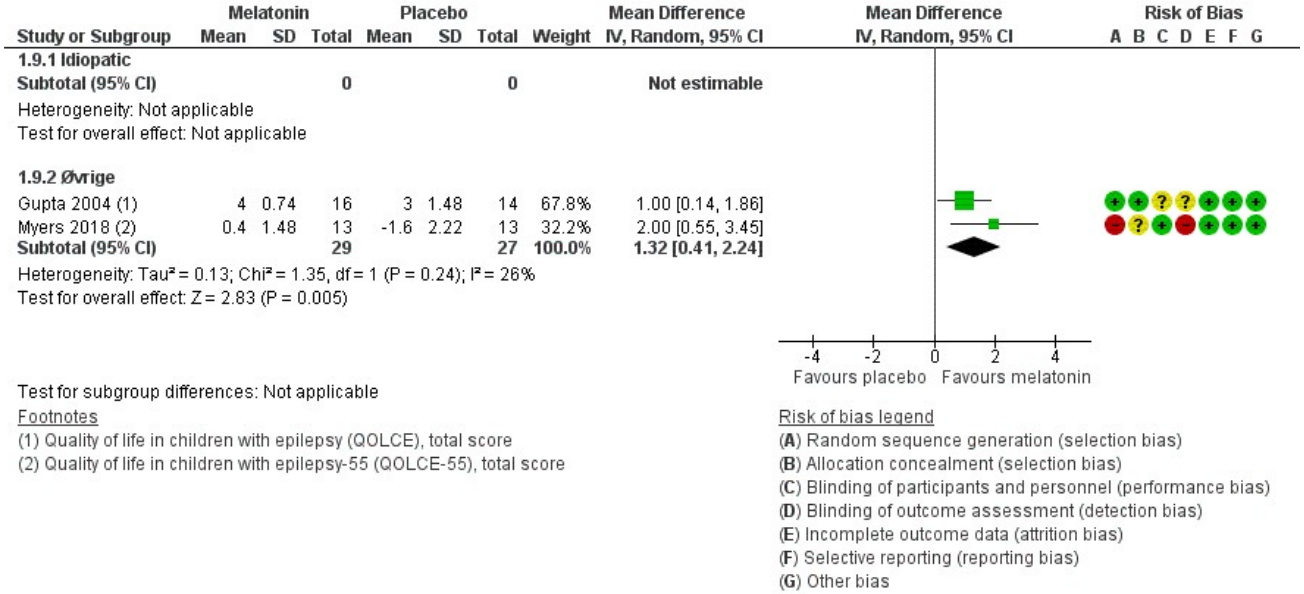
Døsighed/træthed i dagtimer. Målt efter endt behandling (behandlingslængde 2 til 6 uger)

Figure 6 (Analysis 1.6)



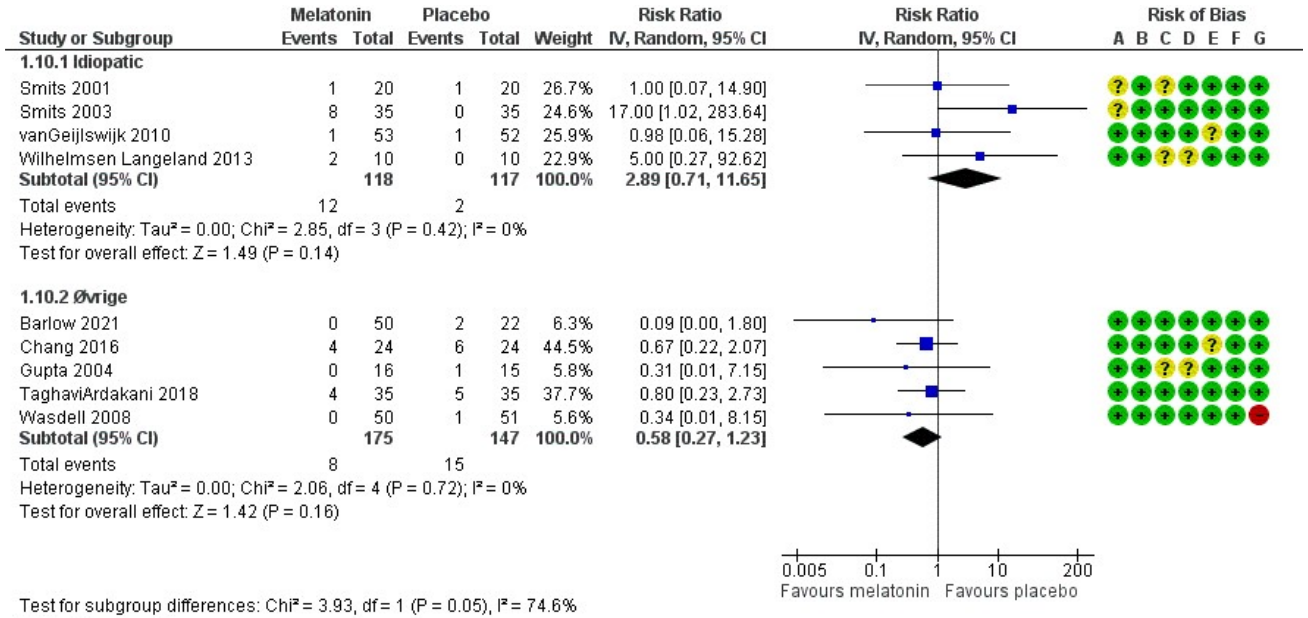
Antal opvågninger. Målt efter endt behandling (behandlingslængde 10 dage til 4 uger)

Figure 7 (Analysis 1.9)



Livskvalitet hos barnet. Målt efter endt behandling (behandlingslængde 2 til 4 uger)

Figure 8 (Analysis 1.10)



Test for subgroup differences: Chi² = 3.93, df = 1 (P = 0.05), I² = 74.6%

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

Frafald, alle årsager