GRADE assessments, ADHD population

Assessors and date: IL, ML, PJ, March 2022

Outcome: ADHD symptoms

Result:
Can sleep interventions decrease ADHD symptoms among children and adolescents with ADHD?

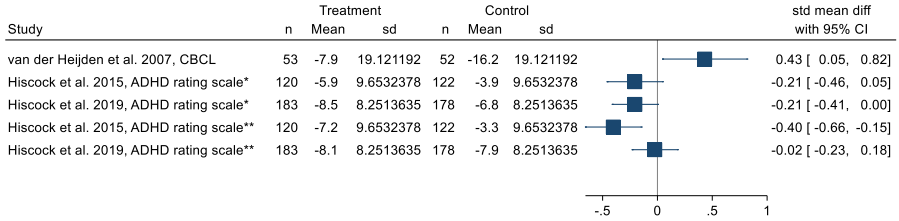
Three studies report changes in ADHD symptoms but use two different instruments to measure the outcome; CBCL (Child Behavior Checklist ref) in one (van der Heijden, 2007) and ADHD rating scale IV (ref) in two (Hiscock 2015; Hiscock 2019). All three studies include children, but one study is on the pharmaceutical melatonin compared with placebo (van der Heijden, 2007) while two studies (Hiscock 2015; Hiscock 2019) compare sleep hygiene strategies and behavioral sleep management plans with standard care. The two behavioral intervention studies report data at 3 and 6 month follow up. The forest plot reports the data in SMD.

Kommenterad [PJ1]: Achenbach TM (1991a), Manual for the Child Behavior Checklist/4-18 and 1991 Profile. Burlington: University of Vermont, Department of Psychiatry

Kommenterad [PJ2]: DuPaul GJ, Power TJ, Anastopoulos AD, Reid R. ADHD rating scale IV: checklists, norms, and clinical interpretation. Guilford Publications, 1998.

Forest plot

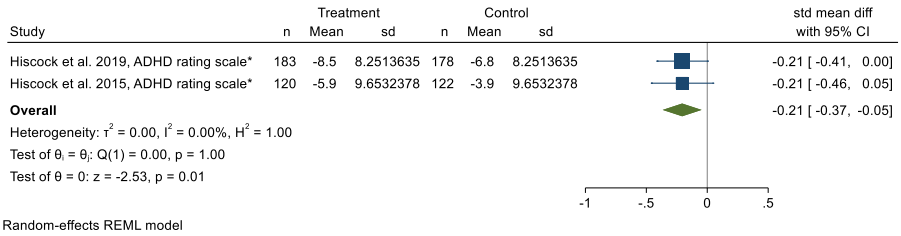
ADHD-symptoms



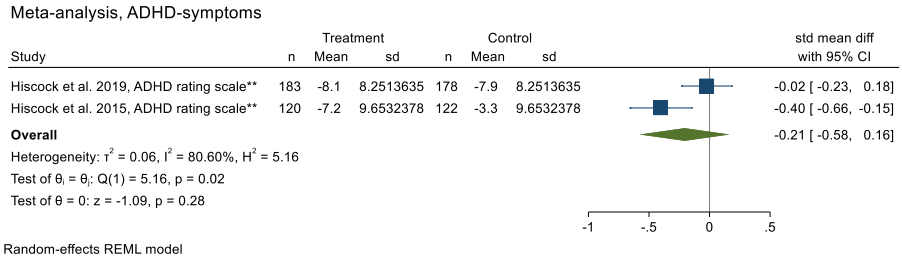
*3 months, **6 months

Meta-analysis

Meta-analysis, ADHD-symptoms



Random-effects REML model



*3 months, **6 months

Result in text:
Children receiving the pharmaceutical melatonin (van der Heijden, 2007) experience decreases in ADHD symptoms but to a lesser extent than the placebo control group children, leading to an overall increased change in symptoms after the intervention. The two behavioral interventions (Hiscock, 2015; Hiscock 2019) however report decreased ADHD symptoms, with SMDs ranging -0.02 to -0.40, of which one study reports statistically significant decreases at 6-month follow-up. The trend over follow-up periods is different among those interventions; one reports larger decreases at 6 months than at 3 months follow-up (Hiscock, 2015) while in the other (Hiscock, 2019) the decreases approached 0 at 6 months.
The meta-analyses that combine the data from the two behavioral interventions at 3 months and 6 months follow-up, respectively, report decrease in symptoms of -0.21 SMD at both follow-ups, which is generally considered a small effect size. However, at the shorter follow-up the effects are consistent in the studies and the meta-analysis result is statistically significant while at the longer follow-up one study reports a larger decrease in symptoms (Hiscock, 2015) while the other (Hiscock, 2019) reports no effect. Thus, the longer-term meta-analysis reports a high degree of heterogeneity, and the synthesized effect is statistically non-significant.

Kommenterad [PJ3]: Lipsey M.W., Wilson D.B. The Efficacy of Psychological, Educational, and Behavioral Treatment. Confirmation from Meta-Analysis. Am. Psychol. 1993;48:1181–1209. doi: 10.1037/0003-066X.48.12.1181.

Conclusion: Behavioral sleep interventions, but not pharmaceuticals with melatonin, decrease ADHD symptoms slightly among children with ADHD.

Outcome	ADHD behavioral symptoms is a composite measure formed from multiple questions in standardized instruments.		
Design	**Alternatives**	**GRADE value**	**Comments**
Study design	(⊕⊕⊕⊕)	⊕⊕⊕⊕	3 RCTs, n = 710 Meta-analysis, n = 605
Kriterier	**Alternatives**	**Mark possible deductions**	**Comments**
Risk of bias	No concerns (no deduction)		Considerable proportion of missing data in all three studies, but evenly distributed among groups.
	Some concerns (possible deduction)	x	
	Serious concerns (-1)		
	Very serious concerns (-2)		
Inconsistency	No concerns (no deduction)		Consistency in results for the two behavioral interventions, but not with the pharmaceutical intervention.
	Some concerns (possible deduction)	x	
	Serious concerns (-1)		
	Very serious concerns (-2)		
Indirectness	No concerns (no deduction)		Two types of interventions in the three studies.
	Some concerns (possible deduction)		

	Serious concerns (-1)	-1	
	Very serious concerns (-2)		
Imprecision	No concerns (no deduction)		Statistically insignificant effect and broad confidence interval in the meta-analysis on 6 months follow-up.
	Some concerns (possible deduction)		
	Serious concerns (-1)	-1	
	Very serious concerns (-2)		
Other considerations (e.g. publication bias)	No concerns (no deduction)	x	
	Some concerns (possible deduction)		
	Serious concerns (-1)		
Does the number of Some concerns imply downrating?	No (no deduction)		
	Yes (-1)	-1	
Other comments			
Summary			**Comments**
Certainty of evidence	High (⊕⊕⊕⊕)		-3 in downratings. The certainty of the evidence is very low.
	Moderate (⊕⊕⊕◯)		
	Low (⊕⊕◯◯)		
	Very low (⊕◯◯◯)	Very low (⊕◯◯◯)	

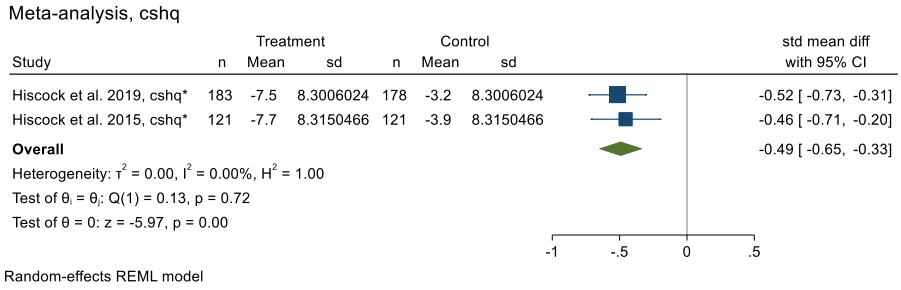
Statement: Behavioral sleep interventions, but not pharmaceuticals with melatonin, decrease ADHD symptoms slightly among children with ADHD, but the evidence is very uncertain.

Outcome: Sleep disturbances (total score CSHQ)

Result:
Two studies report sleep disturbances in the form of the total score from the instrument CSHQ (Children's Sleep Habits Questionnaire, ref); both compare sleep hygiene strategies and behavioral sleep management plans with standard care (Hiscock, 2015; Hiscock, 2019) for children. The data is reported in SMD at 3 month follow-up.

Kommenterad [PJ4]: Owens J, Spirito A, McGuinn M. The Children's Sleep Habits Questionnaire (CSHQ): psychometric properties of a survey instrument for school aged children. Sleep 2000;23:1043-51.

Meta-analysis



*3 months

Result in text:
Both studies (Hiscock, 2015; Hiscock, 2019) report statistically significant decreases in CSHQ scores for the behavioral interventions compared with standard care, of 0.45 and 0.51 SMD. The meta-analysis that combines the data from the studies shows a statistically significant medium effect size of 0.49 SMD (ref) in sleep disturbances.

Kommenterad [PJ5]: Lipsey M.W., Wilson D.B. The Efficacy of Psychological, Educational, and Behavioral Treatment. Confirmation from Meta-Analysis. Am. Psychol. 1993;48:1181–1209. doi: 10.1037/0003-066X.48.12.1181.

Conclusion: Behavioral sleep interventions decrease sleep disturbances among children with ADHD.

Outcome	Sleep difficulties as measured as the total score of the instrument CSHQ is a composite measure formed from multiple questions in the standardized instrument.		
Design	**Alternatives**	**GRADE value**	**Comments**
Study design	(⊕⊕⊕⊕)	⊕⊕⊕⊕	2 RCTs, n = 605 Meta-analysis, n = 605
Kriterier	**Alternatives**	**Mark possible deductions**	**Comments**
Risk of bias	No concerns (no deduction)		Considerable proportion of missing data in both studies, but evenly distributed among groups. Some lack of adherence to intervention.
	Some concerns (possible deduction)	x	
	Serious concerns (-1)		
	Very serious concerns (-2)		
Inconsistency	No concerns (no deduction)	x	No difference in effect sizes between studies and statistically significant result of meta-analysis.
	Some concerns (possible deduction)		
	Serious concerns (-1)		
	Very serious concerns (-2)		
Indirectness	No concerns (no deduction)	x	
	Some concerns (possible deduction)		
	Serious concerns (-1)		
	Very serious concerns (-2)		

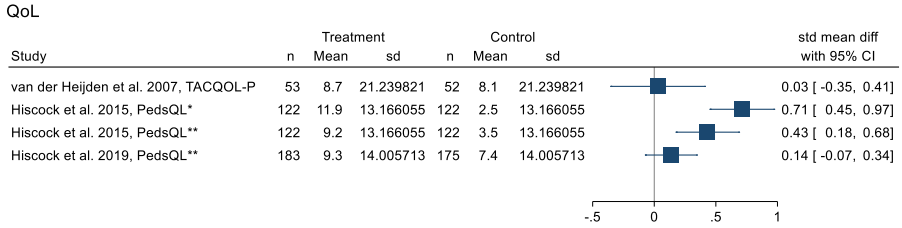
Imprecision	No concerns (no deduction)	x	
	Some concerns (possible deduction)		
	Serious concerns (-1)		
	Very serious concerns (-2)		
Other considerations (e.g. publication bias)	No concerns (no deduction)		Only two studies, performed by the same research group.
	Some concerns (possible deduction)	x	
	Serious concerns (-1)		
Does the number of Some concerns imply downrating?	No (no deduction)		
	Yes (-1)	-1	
Other comments			
Summary			**Comments**
Certainty of evidence	High (⊕⊕⊕⊕)		-1 in downratings.
	Moderate (⊕⊕⊕◯)	⊕⊕⊕◯	
	Low (⊕⊕◯◯)		
	Very low (⊕◯◯◯)		

Statement: Behavioral sleep interventions probably decrease sleep disturbances among children with ADHD.

Outcome: Quality of life, QoL

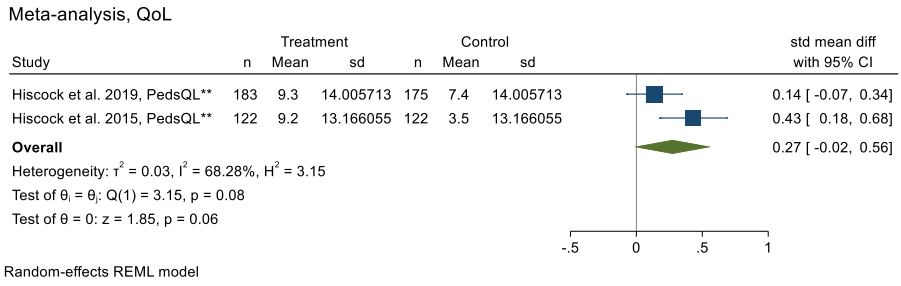
Result: Can sleep interventions increase quality of life (QoL) among children and adolescents with ADHD?
Three studies report changes in quality of life (QoL), where two studies (Hiscock, 2015; Hiscock, 2019) use the instrument PedsQL (ref) and one (van der Heijden, 2007) use the instrument TAQQOL-P (ref). One study investigates the pharmaceutical melatonin (ref van der Heijden) compared with placebo while two studies (Hiscock 2015; Hiscock 2019) compare sleep hygiene strategies and behavioral sleep management plans with standard care. All three studies include children. One study reports two follow-up periods, 3 and 6 months (Hiscock, 2015). The data in the forest plots are reported in SMD.

Forest plot



*3 months, **6 months

Meta-analysis



**6 months

Result in text:
The study on the pharmaceutical melatonin (van der Heijden, 2007) reports no increase in quality of life (QoL) in the intervention group compared with the control group. One of the behavioral intervention studies (Hiscock, 2015) report a statistically significant increase in QoL of 0.71 SMD in the intervention group compared with the control group, that is attenuated, to 0.43 SMD, at the longer follow-up period but still statistically significant. The other behavioral intervention (Hiscock, 2019) reports a more modest increase of 0.14 SMD. In the meta-analysis, the two behavioral interventions are combined into a statistically non-significant change of 0.27 SMD at 6 months follow-up, which is a small effect size (ref).

Conclusion: Sleep interventions increase quality of life (QoL) slightly among children with ADHD.

Kommenterad [PJ6]: Varni, J. W., Burwinkle, T. M., & Seid, M. (2005). The PedsQLTM as a pediatric patient-reported outcome: Reliability and validity of the PedsQLTM Measurement Model in 25,000 children. Expert Review of Pharmacoeconomics and Outcomes Research, 5, 705–719.

Kommenterad [PJ7]: Vogels T, Verrips GHW, Koopman HM, Theunissen NCM, Fekkes M, Kamphuis RP (2000), TACQOL Manual; Parent Form and Child Form. Leiden, The Netherlands: Leiden Child Center for Child Health and Paediatrics LUMC-TNO. Available 2022-03-02 at https://repository.tno.nl/islandora/object/uuid%3A92b8af0e-05f6-43af-b974-fc7d4ab440aa.

Kommenterad [PJ8]: Lipsey M.W., Wilson D.B. The Efficacy of Psychological, Educational, and Behavioral Treatment. Confirmation from Meta-Analysis. Am. Psychol. 1993;48:1181–1209. doi: 10.1037/0003-066X.48.12.1181.

Outcome	Quality of life is measured via standardized instruments with several questions that are combined to form a composite measure.		
Design	**Alternatives**	**GRADE value**	**Comments**
Study design	(⊕⊕⊕⊕)	⊕⊕⊕⊕	3 RCTs, n = 569 Meta-analysis, n = 464
Kriterier	**Alternatives**	**Mark possible deductions**	**Comments**
Risk of bias	No concerns (no deduction)		Considerable proportion of missing data in all three studies, but evenly distributed over groups.
	Some concerns (possible deduction)	x	
	Serious concerns (-1)		
	Very serious concerns (-2)		
Inconsistency	No concerns (no deduction)	x	
	Some concerns (possible deduction)		
	Serious concerns (-1)		
	Very serious concerns (-2)		
Indirectness	No concerns (no deduction)		Different types of interventions; pharmacological and non-pharmacological.
	Some concerns (possible deduction)		
	Serious concerns (-1)	-1	
	Very serious concerns (-2)		
Imprecision	No concerns (no deduction)		Somewhat different results reported from the two studies, leading to non-statistically significant results in meta-analysis.
	Some concerns (possible deduction)	x	
	Serious concerns (-1)		
	Very serious concerns (-2)		
Other considerations (e.g. publication bias)	No concerns (no deduction)	x	
	Some concerns (possible deduction)		
	Serious concerns (-1)		
Does the number of Some concerns imply downrating?	No (no deduction)		
	Yes (-1)	-1	
Other comments			
Summary			**Comments**
Certainty of evidence	High (⊕⊕⊕⊕)		-2 in downratings. The certainty of the evidence is low.
	Moderate (⊕⊕⊕◯)		
	Low (⊕⊕◯◯)	Low (⊕⊕◯◯)	
	Very low (⊕◯◯◯)		

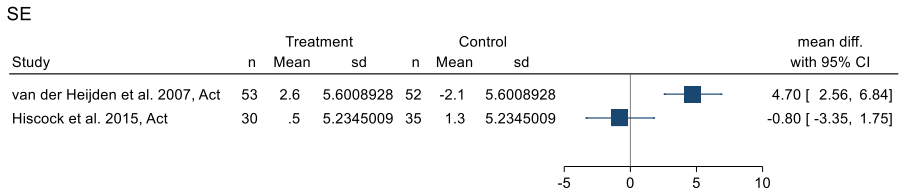
Statement: Sleep interventions may increase quality of life (QoL) slightly among children with ADHD.

Outcome: Sleep efficiency, SE

Result: Can sleep interventions increase sleep efficiency (SE) among children and adolescents with ADHD?

Two studies report changes in sleep efficiency (SE) after treatment, one with the pharmaceutical melatonin compared with placebo (van der Heijden, 2007) and the other on sleep hygiene practices and standardized behavioral strategies compared with standard care (Hiscock, 2015). Both studies involve children and measure the outcome with actigraph.

Forest plot



Result in text:
The study on melatonin (van der Heijden, 2007) report a statistically significant increase of around 5 percent in the intervention group compared with the control group after treatment. The other study, on sleep hygiene practices (Hiscock, 2015), reports no increase in sleep efficiency.

Conclusion: Sleep interventions with the pharmaceutical melatonin increase sleep efficiency (SE) among children with ADHD, but the behavioral intervention does not.

Outcome	Sleep efficiency (SE) is the percentage of total sleep time in relation to time in bed.		
Design	**Alternatives**	**GRADE value**	**Comments**
Study design	(⊕⊕⊕⊕)	⊕⊕⊕⊕	2 RCTs, n = 170
Kriterier	**Alternatives**	**Mark possible deductions**	**Comments**
Risk of bias	No concerns (no deduction)		Selection bias in one of the studies.
	Some concerns (possible deduction)	x	
	Serious concerns (-1)		
	Very serious concerns (-2)		
Inconsistency	No concerns (no deduction)		Inconsistency in results between the two studies; one reports increases in SOL while the other reports decreases.
	Some concerns (possible deduction)		
	Serious concerns (-1)		
	Very serious concerns (-2)	-2	
Indirectness	No concerns (no deduction)		Different interventions in the two studies.
	Some concerns (possible deduction)		
	Serious concerns (-1)	-1	
	Very serious concerns (-2)		
Imprecision	No concerns (no deduction)		Different results reported from the two studies.
	Some concerns (possible deduction)	x	
	Serious concerns (-1)		
	Very serious concerns (-2)		

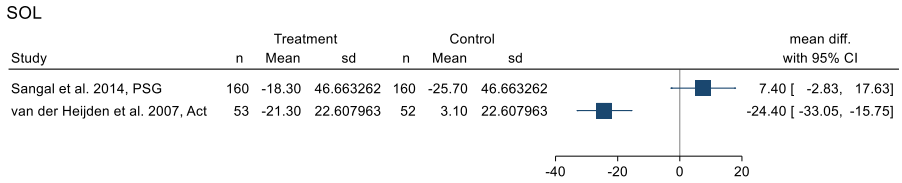
Other considerations (e.g. publication bias)	No concerns (no deduction)	x	
	Some concerns (possible deduction)		
	Serious concerns (-1)		
Does the number of Some concerns imply downrating?	No (no deduction)	x	
	Yes (-1)		
Other comments			
Summary			**Comments**
Certainty of evidence	High (⊕⊕⊕⊕)		-3 in downratings The certainty of the evidence is very low.
	Moderate (⊕⊕⊕◯)		
	Low (⊕⊕◯◯)		
	Very low (⊕◯◯◯)	⊕◯◯◯	

Statement:
Sleep interventions with the pharmaceutical melatonin increase sleep efficiency (SE) among children with ADHD but the behavioral intervention does not, but the evidence is very uncertain.

Outcome: Sleep onset latency, SOL

Result:
Can sleep interventions decrease sleep onset latency among children and adolescents with ADHD?
Two studies report changes in sleep onset latency (SOL) after pharmaceutical treatments, one on melatonin (van der Heijden, 2007) and one on eszopiclone (Sangal, 2014) and both compared with placebo. The melatonin study (van der Heijden, 2007) is on children with mean age 9 years, while the eszopiclone study (Sangal, 2014) includes both children and adolescents. One study uses polysomnography to measure the outcome, indicated as PSG in the forest plot, while the other uses actigraphy (Act in forest plot).

Forest plot



Result in text:
The study on melatonin reports a statistically significant decrease in SOL of nearly 25 minutes (van der Heijden, 2007) compared to placebo at 4 week follow-up, while the decrease in SOL in the high dose group of the pharmaceutical eszopiclone was lower than the decrease in the placebo group, leading to an increase in SOL for that pharmaceutical (Sangal, 2014).

Conclusion: Sleep interventions with the pharmaceutical melatonin may reduce sleep onset latency among children with ADHD, but not the pharmaceutical eszopiclone.

Outcome	Sleep onset latency is the time spent in bed before falling asleep, in minutes.		
Design	**Alternatives**	**GRADE value**	**Comments**
Study design	(⊕⊕⊕⊕)	⊕⊕⊕⊕	2 RCTs, n = 428
Kriterier	**Alternatives**	**Mark possible deductions**	**Comments**
Risk of bias	No concerns (no deduction)	x	No missing outcome data in one study but from around a fifth of participants in the other.
	Some concerns (possible deduction)		
	Serious concerns (-1)		
	Very serious concerns (-2)		
Inconsistency	No concerns (no deduction)		Inconsistency in results between the two studies; one reports increases in SOL while the other reports decreases.
	Some concerns (possible deduction)		
	Serious concerns (-1)		
	Very serious concerns (-2)	-2	
Indirectness	No concerns (no deduction)		Different measurement methods in the two studies.
	Some concerns (possible deduction)		
	Serious concerns (-1)	-1	
	Very serious concerns (-2)		

Imprecision	No concerns (no deduction)		Different results reported from the two studies.
	Some concerns (possible deduction)	x	
	Serious concerns (-1)		
	Very serious concerns (-2)		
Other considerations (e.g. publication bias)	No concerns (no deduction)	x	No evident publication bias.
	Some concerns (possible deduction)		
	Serious concerns (-1)		
Does the number of Some concerns imply downrating?	No (no deduction)	x	
	Yes (-1)		
Other comments			
Summary			**Comments**
Certainty of evidence	High (⊕⊕⊕⊕)		-3 in down ratings. The certainty of the evidence is very low.
	Moderate (⊕⊕⊕◯)		
	Low (⊕⊕◯◯)		
	Very low (⊕◯◯◯)	⊕◯◯◯	

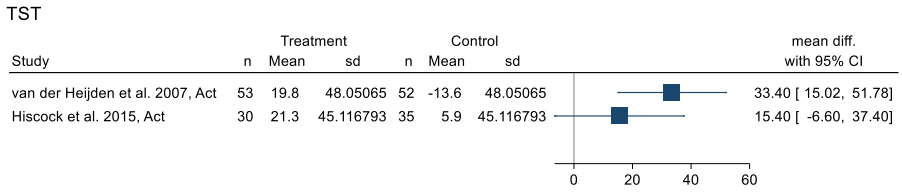
Statement:
Sleep interventions with the pharmaceutical melatonin may reduce sleep onset latency among children with ADHD, but not the pharmaceutical eszopiclone but the evidence is very uncertain.

Outcome: Total sleep time, TST

Result: Can sleep interventions increase total sleep time (TST) among children and adolescents with ADHD?

Two studies report changes in total sleep time (TST) after treatment, one with the pharmaceutical melatonin compared with placebo (van der Heijden, 2007) and the other on sleep hygiene practices and standardized behavioral strategies compared with standard care (Hiscock, 2015). Both studies involve children and measure the outcome with actigraph.

Forest plot



Result in text:
Both studies report larger increases in total sleep time (TST) in the intervention group than in the control group, with a statistically significant increase in the melatonin study (ref van der Heijden) of over 30 minutes. The reported increase in TST in the non-pharmaceutical study (ref Hiscock 2015) is around 15 minutes.

Conclusion: Sleep interventions increase total sleep time (TST) slightly among children with ADHD.

Outcome	Total sleep time (TST) measures the time awake after first falling asleep, in minutes. It is most frequently measured by actigraph.		
Design	**Alternatives**	**GRADE value**	**Comments**
Study design	(⊕⊕⊕⊕)	⊕⊕⊕⊕	2 RCTs, n = 170
Kriterier	**Alternatives**	**Mark possible deductions**	**Comments**
Risk of bias	No concerns (no deduction)		Selection bias present in one of the studies.
	Some concerns (possible deduction)	x	
	Serious concerns (-1)		
	Very serious concerns (-2)		
Inconsistency	No concerns (no deduction)	x	
	Some concerns (possible deduction)		
	Serious concerns (-1)		
	Very serious concerns (-2)		
Indirectness	No concerns (no deduction)		Different types of interventions in the two studies.
	Some concerns (possible deduction)		
	Serious concerns (-1)	-1	
	Very serious concerns (-2)		
Imprecision	No concerns (no deduction)		Imprecision present as both studies report broad
	Some concerns (possible deduction)		
	Serious concerns (-1)	-1	

	Very serious concerns (-2)		confidence intervals, of around 40 minutes.
Other considerations (e.g. publication bias)	No concerns (no deduction)	x	
	Some concerns (possible deduction)		
	Serious concerns (-1)		
Does the number of Some concerns imply downrating?	No (no deduction)	x	
	Yes (-1)		
Other comments			
Summary			**Comments**
Certainty of evidence	High (⊕⊕⊕⊕)		-2 in downratings. The certainty of the evidence is low.
	Moderate (⊕⊕⊕◯)		
	Low (⊕⊕◯◯)	⊕⊕◯◯	
	Very low (⊕◯◯◯)		

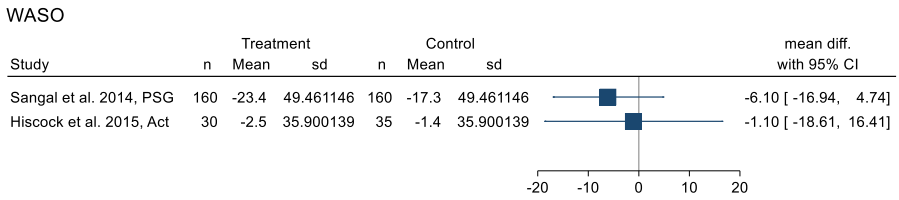
Statement: Sleep interventions may increase total sleep time (TST) slightly among children with ADHD.

Outcome: Wake after sleep onset, WASO

Result: Can sleep interventions decrease wake after sleep onset, WASO, among children and adolescents with ADHD?

Two studies report changes in wake after sleep onset (WASO), one on the pharmaceutical eszopiclone compared with placebo (Sangal, 2014) and another on sleep hygiene practices and standardized behavioral strategies compared with standard care (Hiscock, 2015). The study on the pharmaceutical eszopiclone include children and adolescents, while the non-pharmaceutical study only includes children aged 5-12 years. The pharmaceutical study measures the outcome with polysomnography (PSG in the forest plot) while the non-pharmaceutical use actigraph (Act) measurements.

Forest plot



Result in text:
Both studies report modest decreases in wake after sleep onset (WASO) after the intervention compared with the no intervention group (i.e. placebo and standard care, respectively): 6 minutes for the pharmaceutical eszopiclone (Sangal, 2014) and 1 minute for the study on sleep hygiene practices and standardized behavioral strategies (Hiscock, 2015). No changes in WASO are statistically significant.

Conclusion: Sleep interventions result in little to no reduction in wake after sleep onset, WASO, among children and adolscents with ADHD.

Outcome	Wake after sleep onset measures the time awake after first falling asleep, in minutes.		
Design	**Alternatives**	**GRADE value**	**Comments**
Study design	(⊕⊕⊕⊕)	⊕⊕⊕⊕	2 RCTs, n = 385
Kriterier	**Alternatives**	**Mark possible deductions**	**Comments**
Risk of bias	No concerns (no deduction)		Possible selection bias in one study as measurement only from subgroup of children. Missing outcome data from one fifth of participants in the other study.
	Some concerns (possible deduction)	x	
	Serious concerns (-1)		
	Very serious concerns (-2)		
Inconsistency	No concerns (no deduction)	x	
	Some concerns (possible deduction)		
	Serious concerns (-1)		
	Very serious concerns (-2)		
Indirectness	No concerns (no deduction)		Different treatment modalities and
	Some concerns (possible deduction)		
	Serious concerns (-1)	-1	

	Very serious concerns (-2)		measurement methods in the two studies.
Imprecision	No concerns (no deduction)		Considerable imprecision with wide confidence intervals.
	Some concerns (possible deduction)		
	Serious concerns (-1)	-1	
	Very serious concerns (-2)		
Other considerations (e.g. publication bias)	No concerns (no deduction)	x	
	Some concerns (possible deduction)		
	Serious concerns (-1)		
Does the number of Some concerns imply downrating?	No (no deduction)	x	
	Yes (-1)		
Other comments			
Summary			**Comments**
Certainty of evidence	High (⊕⊕⊕⊕)		-2 in downratings. The certainty of the evidence is low.
	Moderate (⊕⊕⊕◯)		
	Low (⊕⊕◯◯)	⊕⊕◯◯	
	Very low (⊕◯◯◯)		

Statement: Sleep interventions may result in little to no reduction in wake after sleep onset, WASO, among children and adolescents with ADHD.