auteurs	jaar	level of evidence	type	inclusie	omvang (aantal pat of aantal artikelen)	patgr	interventie	controle	uitkomstmaten en resultaat	conclusie
Cortese S, Brown TE, Corkum P, Gruber R, O'Brien LM, Stein M, Weiss M, Owens J.[1]	2013	1a	review		22	ADHD	melatonine			Promote healthy sleep habits. If sleep difficulties persist: try alternative dosages, dose regimen, formulations, or alternative ADHD medications, or add a sleep promoting medication (e.g., melatonin). Level: Adding melatonin: B (1 RCT rated as 1b); for other approaches: D (expert consensus).
Holvoet E, Gabriëls L.[2]	2013	1a	review		ND	ADHD	melatonine			Very little systematic research has been done into the possible impact of melatonin intake on puberty and the endocrine system. Therefore, treatment with melatonin in children with adhd and (c)soi is best reserved for children with persistent insomnia which is having a severe impact on daily functioning, particularly in cases where is an obvious phase-shift of the endogenous circadian rhythm
Ferracioli-Oda E, Qawasmi A, Bloch MH[3]	2013	1a	MA		19	PSD	melatonine		SOL, TST,	Despite these limitations, this meta-analysis demonstrated that exogenous melatonin administered to subjects with primary sleep disorders modestly improved sleep parameters including sleep latency, total sleep time and sleep quality. This finding corroborates the results of a previous meta-analysis conducted in the area several years ago that also demonstrated a significant benefit of melatonin. The benefits of melatonin compared to placebo appear smaller than that of available prescription sleep medications. However, melatonin should be considered in clinical practice due to its benign side-effect profile, cost and limited evidence of habituation and tolerance.

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Rossignol DA, Frye RE[4]	2011	1a	SR/MA		35/5	ASD			TST (+73) vs baseline/(44) vs placebo/SOL(-66) vs baseline/(-39) vs placebo	The meta-analysis found that the use of melatonin in ASD is associated with significantly improved sleep parameters (sleep duration and sleep onset latency). Furthermore, melatonin appears to improve daytime behavior in some individuals with ASD and has minimal to no side effects. However, additional studies are needed to examine melatonin metabolism in ASD, including the relationship between melatonin and serotonin in ASD. Some studies reported a higher daytime melatonin level in children with ASD, which could be related to slower melatonin metabolism; this finding needs further investigation. Studies examining optimal effective dosing, optimal timing of melatonin dosing, the potential differential effects of fastrelease and controlled-release melatonin, and its long-term adverse effects and safety in ASD are also needed.
Van Geijlswijk, Korzilius, Smits[5]	2010	1a	meta analyse	sleep disturbances	9 art, 4 child	CSOI / ADHD	melatonine		children: DLMO -1,13hr / SO -0,64hr / SOL -16,04 min / WUT -0,16 hr / TST +28,4 min	In 2 studies ADHD was diagnosed in 25% to 50% of the children, in the other 2 studies in children, ADHD was diagnosed in 100% of the participants. These individuals could fall under the category of circadian rhythm sleep disorder comorbid with ADHD. We suggest that an optimal melatonin therapy be based on 3 basic principles, namely, by identifying the appropriate patients (with a delayed biologic timing); by melatonin administration being based on biologic clock time, i.e., 3 to 6 hours before DLMO (CT 8-11); and by administering a small dose to avoid enhanced high melatonin levels during late night or early morning. To further optimize individual therapy, the results in which the administration time is advanced during the course of treatment should also be considered.
Braam W, Smits MG, Didden R, Korzilius H, Van Geijlswijk IM, Curfs LM[6]	2009	1a	meta analyse	sleep disturbances	9	ID	melatonine		SOL -34 / TST +50 / AW-	The results of this meta-analysis indicate that melatonin is effective and safe in the treatment of sleep problems in individuals with intellectual disability, at least in short-term treatment.

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Gringras P, Gamble C, Jones AP, Wiggs L, Williamson PR, Sutcliffe A, Montgomer YP, Whitehouse WP, Choonara I, Allport T, Edmond A, Appleton R; MENDS Study Group. [7]	2012	1b	RCT	severe sleep problems	included 146 (51-59 analysis)	NDD	melatonine ,5/2/6/(12) mg	placebo	TST (+22,4), SOL(-37,5/-45,3),WT(-29,9), behaviour, SAE	Only low doses of melatonin are required to alter the sleep phase in typically developing children, and, in this study, there was support for starting treatment with a low dose of melatonin with 18% of children needing only 0.5 mg melatonin. Our findings provide valuable evidence about the dosing, tolerability, and effect of using melatonin in children with neurodevelopmental and sleep disorders. They explain that although (standard) immediate release melatonin significantly reduces sleep onset latency, there is a more limited increase in total sleep time that might arise as a result of increasingly early waking time in the morning. Melatonin seemed tolerable in this population of children with a range of neurological and developmental disorders.
Cortesi F, Giannotti F, Sebastiani T, Panunzi S, Valente D.[8]	2012	1b	RCT	persistent insomnia	132	ASD	circadin	cbt/placebo	SOL (-30)	In our study, there was a significant trend for the combination group to produce higher improvement on sleep continuity and efficiency than in either melatonin or CBT groups with the strongest treatment response. Our resultsindicate that the greatest number and percentage of responders in the combination treatment group achieve a clinically significant change (63.38% of children with normative SE criterion of >85% and 84.62% of children with a SOL <30 min). In addition, this group produced fewer treatment dropouts than under other treatment conditions

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Van Geijlswijk, Van der Heijden, Egberts, Korzilius, Smits[9]	2010	1b	RCT		63	CSOI	dosefinding 0,05/0,1/0, 15 mg/kg	placebo	DLMO 65-105 min / SO 42-56 min /SOL 31-42 min	No dose–response relationship of melatonin with SO, SOL, and DLMO is found within a dosage range of 0.05–0.15 mg/kg. The effect of exogenous melatonin on SO, SOL, and DLMO increases with an earlier circadian TOA. The soporific effects of melatonin enhance the SO shift. This study demonstrates that melatonin for treatment of CSOI in children is effective in a dosage of 0.05 mg/kg given at least 1 to 2 h before DLMO and before desired bedtime.
Wirojanan J, Jacquemont S, Diaz R, Bacalman S, Anders TF, Hagerman RJ, Goodlin-Jones BL[10]	2009	1b	RCT		12	ASD/FXS	melatonine 3 mg 4 weken crossover	placebo	TST (+21 min), SO (-42 min), SOL(-28 min),WASO(-0,07)	In summary, the results of this study support the efficacy and tolerability of melatonin treatment for sleep problems in children with ASD and FXS. We conclude that melatonin can be considered a safe and effective pharmacologic treatment in addition to behavior therapies and sleep hygiene practices for the management of sleep problems in children with ASD and FXS.
Braam W, Didden R, Smits MG, Curfs LM.[11]	2008	1b	RCT	sleep disturbances	8	Angelman	melatonine 2,5/5 mg 4 weeks, followed bij open label 4 wks	placebo	SO -28 / SOL -32 / TST +56 / AW 3,1->1,6	This study indicates that it is possible that melatonin dose in Angelman syndrome should be lower than generally prescribed.
Braam W, Didden R, Smits M, Curfs L[12]	2008	1b	RCT	sleep disturbances	51 (29 V /22 P)	ID	melatonine 2,5/5 mg 4 weeks, followed bij open label 4 wks	placebo	SO -34 / SOL -29 / TST +48 / AW 0,4 / DLMO -2,01	In conclusion, the present study indicates that melatonin improves sleep in individuals with ID that suffer from chronic sleep disturbancesurbance, probably mainly because of its chronobiotic effects.
Damiani JM, Sweet BV, Sohoni P.[13]	2014	2a	review		5 x OL / 5xRCT / 1x SR (Rossignoil)	ASD	melatonine		SOL/SO/TST/AW/CSHQ	Data consistently support the efficacy of melatonin in decreasing sleep latency by up to 60 minutes in children with ASD. While less consistent, data generally suggest the potential of melatonin to increase TSD by up to 60 minutes. Melatonin has been well tolerated in children with ASD, but the substance is not regulated as a pharmaceutical, so selecting a product that has undergone quality testing is important.

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Barrett JR, Tracy DK, Giaroli G.[14]	2013	2a	review		5 art/4 gnm	ADHD	mel2x, zolp, Ltheanine, clonidine		SOL/TST / SAE	Alternatively, melatonin treatment seems to have positive effects on all primary sleep disorder characteristics, including sleep efficiency, and the majority of all secondary characteristics, such as nocturnal activity, sleep onset, and WASO.
Tordjman S, Najjar I, Bellissant E, Anderson GM, Barburoth M, Cohen D, Jaafari N, Schischman off O, Fagard R, Lagdas E, Kermarrec S, Ribardiere S, Botbol M, Fougerou C, Bronsard G, Vernay-Leconte J.[15]	2013	2a	review		3xCR/retro3x/OL6x/RCT7x /SR-MA 8x/div4x	ASD	melatonine		div	To develop therapeutic new perspectives in ASD, first it is necessary to restore some basic regular physiological rhythms such as circadian rhythms. Thus, prescribing small physiologic doses of melatonin could help to restore the impaired circadian melatonin rhythm in ASD which disturbs the sleep-wake rhythm, but more generally the synchronization of internal biological clocks, resulting in the absence of homogeneous and harmonious rhythmicity with the consequences previously described on social communication, stereotyped behaviors and adaptation to environmental changes.
Keegan LJ, Reed-Berendt R, Neilly E, Morrall MC, Murdoch-Eaton D.[16]	2013	2a	review		7	ABI	melatonine			There are potential benefits of melatonin for the management of sleep problems following paediatric ABI and it is suggested that treatment using a closely monitored n=1 trial approach occur and definitive RCTs should be conducted in order to establish the effectiveness of melatonin in the management of impaired sleep in children with an ABI
Grigg-Damberger M, Ralls F.[17]	2013	2a	review		20	ASD/NDD	melatonine			When behavioral therapies are incomplete, melatonin and other medications can be tried.

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Sánchez-Barceló EJ, Mediavilla MD, Reiter RJ.[18]	2011	2a	review		ND	div indicaties				Melatonin is beneficial not only in the treatment of dyssomnias, especially delayed sleep phase syndrome, but also on sleep disorders present in children with attention-deficit hyperactivity, autism spectrum disorders, and, in general, in all sleep disturbancesurbances associated with mental, neurologic, or other medical disorders.
Malow B, Adkins KW, McGrew SG, Wang L, Goldman SE, Fawkes D, Burnette C.[19]	2012	2b	open label		24	ASD	melatonine dose escalating 1-3 mg	-	SOL (-15,7) WASO / Seff / TST (+15)	Supplemental melatonin improved sleep latency, as measured by actigraphy, in most children at 1 or 3 mg dosages. It was effective in week 1 of treatment, maintained effects over several months, was well tolerated and safe, and showed improvement in sleep, behavior, and parenting stress.
Wright B, Sims D, Smart S, Alwazeer, A etal[20]	2011	2b	RCT	severe sleep problems	22	ASD	melatonine 1-10 mg 3 maanden crossover	placebo	SOL -47 min, TST +52 min, SAE (-), NW (_)	This study shows that melatonin improves sleep significantly in a group where behavior therapy has not been effective.
De Leersnyder H, Zisapel N, Laudon M.[21]	2011	2c	long term efficacy and safety	6-72 m	88	NDD	circadin (4-6 mg?)		SOL (-8 min) /TST (+1 hr) / WASO / WU (+ hr), SQ (+)	We conclude that prolonged-release melatonin remains a safe, effective therapy for the long-term treatment of sleep disorders in children with neurodevelopmental disease.

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Van Geijlswijk, Mol, Egberts, Smits[22]	2011	2c	long term efficacy and safety	1-4,6 jaar	51	CSOI	melatonine		SDQ en CSHQ score, Tanner Stages	In conclusion, we found that melatonin was still used by 81% of children, after a mean term of usage of 3.1 years. Six (10%) children stopped therapy successfully, two others adopted a delayed sleep pattern after cessation. One girl quit melatonin therapy because of apathy and weight gain, one boy quit because of loss of response. One girl was forced to stop therapy by her GP after 6 months. The CSHQ results indicate that the sleep habits in melatonin users are better than in PS without medication, but worse than in NPS. Social development assessed by SDQ indicates a normal development. Puberty onset, as assessed by Tanner scores, seems to be undisturbed after 3.1 years of exogenous melatonin usage in this limited population.
Hoebert M, van der Heijden KB, van Geijlswijk IM, Smits MG.[23]	2009	2c	long term efficacy and safety	CSOI na 3,7 jr	94	ADHD	melatonine			No serious adverse events or treatment related co-morbidities were reported. Sixty-five percent of the children still used melatonin daily and 12% occasionally. Temporal discontinuation of treatment resulted in a delay of sleep onset in 92% of the children. Nine percent of the children could discontinue melatonin completely because of improvement of sleep onset insomnia. Long-term melatonin treatment was judged to be effective against sleep onset problems in 88% of the cases. Improvement of behaviour and mood was reported in 71% and 61% respectively. We conclude that melatonin remains an effective therapy on the long term for the treatment of CSOI in children with ADHD and has no safety concerns regarding serious adverse events or treatment related co-morbidity. Discontinuation of melatonin treatment usually leads to a relapse of sleep onset insomnia and in resuming melatonin treatment, even after several years of treatment.

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Guénolé F, Godbout R, Nicolas A, Franco P, Claustrat B, Baleyte JM.[24]	2011	3a	review		4 case reports, 3 retrospective studies, 2 open-label clinical trials, and 3 RCT)	ASD	melatonine			Melatonin appears to be useful for the treatment of sleep problems in ASD.
Doyen C, Mighiu D, Kaye K, Colineaux C, Beaumanoir C, Mouraeff Y, Rieu C, Paubel P, Contejean Y.[25]	2011	3a	review		17	ASD	melatonine			The dosage used in clinical studies for children varied from 0.5 to 10 mg taken at the desired bedtime, some reports advocating doses of 10 mg or higher. The most common doses employed were 2.5–5 mg, starting with low doses and increasing gradually. Given its relatively short half-life, melatonin should be given 30 min before the desired bedtime. In addition to acting as a hypnotic, it also has a chronobiotic (phase-shift) effect and for individual with delayed sleep phase syndrome it is proposed by researchers, but not all, to be given several hours before bedtime. Physiological doses (500 microg) are effective in causing phase shifts, but doses of 1–3 mg are more commonly used because of sedative effects. It is necessary to monitor closely the child for adverse effects because children with autism may be unable to verbally describe side effects. It is important to use the same formulation, as the bioavailability of melatonin may vary widely among manufacturers. Attempts should be made to discontinue melatonin once a sleep cycle is established for 6 weeks or more, although long-term use appears safe and may be necessary
Hollway JA, Aman MG[26]	2011	3a	review	sleep disturbances	58 art	NDD	melatonine en trazodon/mirtazepine/ramelteon			Melatonin appears to be the most widely assessed agent and safest choice for children with developmental disabilities. Trazodone, mirtazapine, and ramelteon hold promise but require further study.

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Cortesi F, Giannotti F, Ivanenko A, Johnson K[27]	2010	3a	review	sleep disturbances	ND	ASD				Melatonin has been more extensively studied in children with insomnia than any other sleep-promoting medication. Initial research in children with neurodevelopmental disorders demonstrated reductions in sleep latency and improvements in total sleep time and sleep efficiency when melatonin was administered close to bedtime. Melatonin was shown to be effective in a dose range from 3 to 6 mg in children with ASD. Controlled-release melatonin was found to be superior to behavioral intervention in a controlled study of children with ASD using actigraphy. Melatonin in this study was highly effective in reducing sleep onset latency, night-to-night variability in bedtime, waking after sleep onset, and in increasing sleep duration. There is evidence to support use of extended release formulations of melatonin for sleep maintenance insomnia in children (2 studies).
Bruni O, Novelli L[28]	2010	3a	review	dyssomnia/parasomnia	28 systematic reviews, RCTs, or observational studies	CSOI	melatonine	{{}}		Melatonin for dyssomnia in otherwise healthy children may be more effective at improving sleep-onset time, total sleep time, and general health compared with placebo. Evidence of improvements in dyssomnia with melatonin is slightly stronger in children with physical disabilities, learning disabilities, epilepsy, or attention-deficit disorder. Little is known about the long-term effects of melatonin, and the quality of the product purchased could be variable as melatonin is classified as a food supplement. Melatonin for dyssomnias in children with attention-deficit disorder, epilepsy, neurodevelopmental disabilities, or physical disabilities One large RCT added, which found that melatonin modestly improved total night-time sleep and decreased sleep latency compared with placebo. [50] However, little is known about the long-term effects of melatonin. Categorisation changed from Unknown effectiveness to Trade off between benefits and harms.

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Bendz LM, Scates AC[29]	2009	3a	review	CSOI	20 art: ADHD: 4; RCT (n = 5), safety studies (n = 1), long-term follow-up studies (n = 1), post hoc retrospective analyses (n = 1), meta-analyses (n = 2), review articles (n = 9), and letters (n = 1)	ADHD	melatonine		SO (~0.5–2 h, SOL (~20 min), TST (~0.33–1 h)	Available data suggest that melatonin is a well-tolerated and efficacious treatment option for pediatric patients with chronic SOI and ADHD. Regulated melatonin products and larger, well-designed trials to establish optimal dosing regimens and long-term safety are needed.
Wasdell MB, Jan JE, Bomben MM, Freeman RD, Rietveld WJ, Tai J, Hamilton D, Weiss [30]	2008	3b	RCT	sleep disturbances	50	NDD	CR 5 mg (en hoger), followed by 3 month open label	placebo	SOL (P->M -34,7) TST(+20,4)	Overall, the therapy improved the sleep of 47 children and was effective in reducing family stress. Children with neurodevelopmental disabilities, who had treatment resistant chronic delayed sleep phase syndrome and impaired sleep maintenance, showed improvement in melatonin therapy.
Andersen IM, Kaczmarska J, McGrew SG, Malow BA.[31]	2008	4	open label	sleep disturbances	107	ASD	melatonine 0,75-6 mg			The majority of parents reported an improvement in their child's sleep with melatonin treatment. Parents of 27 children (25%) no longer reported sleep concerns at follow up visits after initiation of melatonin. Parents of 64 children (60%) reported improved sleep; however, they continued to have concerns regarding sleep during follow up clinic visits. The majority of parents reported an improvement in their child's sleep at the first follow-up clinic visit after initiation of melatonin. This response was sustained during later follow-up visits in most children, although 18 children had only 1 documented follow-up visit after initiation of melatonin. In 7 children, melatonin was reported by parents to initially improve sleep, although sleep problems returned after 3–12 months, despite dose escalation. Parents of 14 children (13%) continued to report sleep problems as a major concern. One child's parent reported worse sleep after starting melatonin (1%), and 1 child had an undetermined response (1%).

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