Exogenous melatonin for sleep problems in individuals with intellectual disability: a meta-analysis

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Recent meta-analyses on melatonin has raised doubts as to whether melatonin is effective in treating sleep problems in people without intellectual disabilities. This is in contrast to results of several trials on melatonin in treating sleep problems in individuals with intellectual disabilities. To investigate the efficacy of melatonin in treating sleep problems in individuals with intellectual disabilities, we performed a meta-analysis of placebo-controlled randomized trials of melatonin in individuals with intellectual disabilities and sleep problems. Data were selected from articles published on PubMed, Medline, and Embase between January 1990 and July 2008. We examined the influence of melatonin on sleep latency, total sleep time, and number of wakes per night. Quality of trials was assessed using the Downs and Black checklist. Nine studies (including a total of 183 individuals with intellectual disabilities) showed that melatonin treatment decreased sleep latency by a mean of 34 minutes ($p<0.001$), increased total sleep time by a mean of 50 minutes ($p<0.001$), and significantly decreased the number of wakes per night ($p<0.05$). Melatonin decreases sleep latency and number of wakes per night, and increases total sleep time in individuals with intellectual disabilities.

Sleep problems are reported to occur in 13 to 86% of individuals with intellectual disabilities depending on study design, participant characteristics, and definition of sleep problems.[1] Such problems are often complex and usually more difficult to treat than in individuals without intellectual disability. When behavioral treatment for the sleep problems[2,3] is ineffective, sedatives are often prescribed. However, sedatives may induce serious side effects,[4] such as daytime sedation, increased risk of sleep related breathing problems, and behavioral problems. Where individuals with intellectual disabilities take other medications, the risk of drug interactions is increased. Therefore, melatonin may be an effective and safe treatment option for sleep problems in individuals with intellectual disabilities.

Melatonin, a hormone released by the pineal gland during darkness, is a chronobiotic drug with hypnotic properties.[5] Melatonin secretion is regulated by an endogenous pacemaker in the suprachiasmatic nucleus of the hypothalamus (biological clock). Information on the light/dark cycle through the retino-hypothalamic tract is needed to synchronize the circadian melatonin rhythm to 24 hours. Many pathophysiological conditions can disturb this complex regulatory system and cause dysfunction of the sleep–wake system.[6] Biological clock disturbances frequently occur in individuals with intellectual disability and consequently cause sleep-wake disturbances.[7,8] Low nocturnal melatonin levels have been found, for example, in Angelman syndrome, autism, and Rett syndrome. Recently an abnormal melatonin synthesis in autism spectrum disorders was discovered.[9]

Several placebo-controlled randomized trials with melatonin in individuals with intellectual disabilities have

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shown that melatonin improves sleep,[10–20] i.e. induces a significant reduction of sleep latency and an increase in total sleep time. Several reviews based on these trials, as well as on open studies and case reports, emphasize the benefits of melatonin in the treatment of sleep problems in individuals with intellectual disabilities.[7,8,21–23] These results, however, are not in line with results of three meta-analyses of individuals with sleep problems without intellectual disabilities.[21–23] Although the meta-analysis by Brzezinski et al.[24] showed a statistically significant improvement of sleep latency, sleep efficiency, and total sleep time, differences between the melatonin and placebo groups were small and seem to be of minor clinical importance. In the first meta-analysis by Buscemi et al.,[25] on the efficacy of melatonin in the treatment of primary sleep disorders, evidence was found that melatonin is not effective in treating most primary sleep disorders, except for the treatment of delayed sleep phase syndrome. In the second meta-analysis by Buscemi et al.,[26] no evidence for the effectiveness of melatonin in treating secondary sleep disorders was found. These results suggest that melatonin is not effective in individuals without intellectual disability. As stated above, this is in stark contrast to outcomes of controlled trials in individuals with intellectual disability. At present, no quantitative review has been published on the outcomes of placebo-controlled trials on the efficacy of melatonin in individuals with intellectual disabilities. Therefore, we investigated the efficacy of melatonin in the treatment of sleep problems in persons with intellectual disabilities, by performing a meta-analysis of placebo-controlled, randomized trials on melatonin in individuals with sleep problems and intellectual disabilities.

METHOD

Search strategy

We performed a computerized search in the electronic databases PubMed, Medline, and Embase for trials on melatonin in individuals with sleep problems and intellectual disabilities, published between January 1990 and July 2008. Search terms used were, 'melatonin' and terms used to describe intellectual disabilities (i.e. 'developmental disability', 'intellectual disability', 'learning disorder', 'mental retardation', and 'neurodevelopmental disability'). In addition, a hand search was undertaken of reference lists of articles identified through this search.

Selection

All studies in which melatonin was used as an intervention in treating sleep problems in individuals with intellectual disability were initially selected and reviewed. Studies for the meta-analysis were included if (1) they used a randomized double-blind placebo-controlled design; (2) included individuals with any type of a diagnosis of intellectual disabilities; (3) provided quantitative data on at least one of the following primary outcome measures: sleep latency (time between laying down to sleep and the onset of sleep), total sleep time and number of wakes per night; and (4) results were reported in English. Methodological quality of each study was assessed by two independent reviewers using the Downs and Black checklist. [27]

Data extraction

Outcome variables in this study included, sleep latency, number of wakes per night, and total sleep time. The number of minutes in the time measurements was transformed to decimals. For each study, mean differences and standard deviations (SDs) between baseline and treatment were calculated. For this purpose, we used Elbourne et al.'s method[28] to compute SDs of the differences, imputing a correlation of 0.5, as these were not available from the studies.

Meta-analysis with Interactive eXplanations (MIX: version 1.4)[29] was used to perform the calculations. All measures were continuous; as association measure, the mean difference was applied. Following Sutton et al.,[30] the inverse variance method was used to weigh the number of participants in the studies. We used the random effects model; alpha level was 0.05 for each outcome. The numerical output consisted of the empirical value, the mean difference and 95% confidence interval (CI) of each study together with the z score and p value and the weight of the studies. As graphical output, standard forest plots were drawn containing mean differences and the 95% CI of each study, as well as of the pooled analysis.

In order to assess possible publication bias[31] we graphically inspected funnel plots, a scatter plot of treatment against the inverse standard error of each study,[29,32,33] and calculated the adjusted rank correlation test.[34] To test for statistical heterogeneity between studies, Galbraith plots[29] were inspected and the Tau-squared statistic, an estimate of the between study variance, was calculated (DerSimonian-Laird method in Bax et al.).[29] In order to save space, the funnel and Galbraith plots were not added.

RESULTS

Included studies

The computerized search strategy initially resulted in 276 references. Figure 1 shows the steps taken throughout the selection process. Screening these articles on selection criteria resulted in eight eligible studies. Reference tracking resulted in four additional studies, all involving individuals with intellectual disability and a specific etiological diagnosis (e.g. Angelman syndrome,[20] autism spectrum disorder,[16] ceroid lipofuscinosis,[12] and tuberous sclerosis),[11]

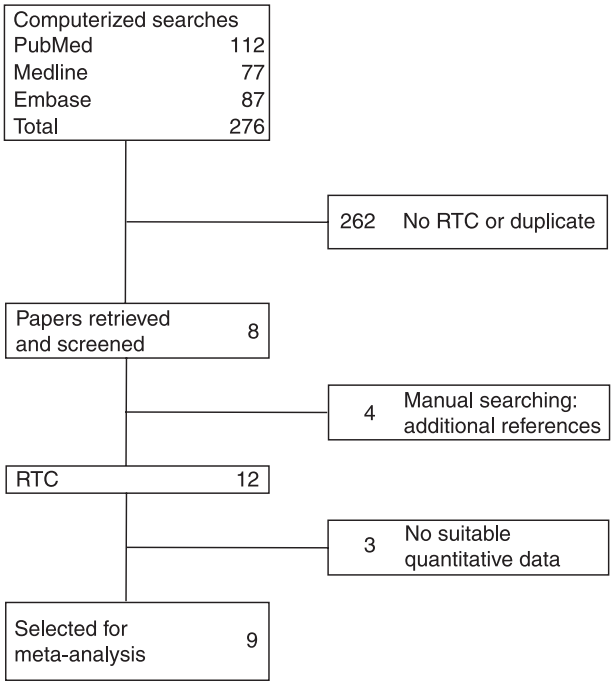

Figure 1: Study retrieval and selection. RCT, randomized controlled trial.

and, therefore, not found by general terms describing intellectual disability in the initial computerized search. From these 12 placebo-controlled trials, two studies were excluded because no suitable quantitative data were provided[14,17] and one study was excluded because it was single blind, and lacked suitable quantitative data.[12] One trial[16] was conducted on a sample of 11 children with autism spectrum disorder in which more than half also had intellectual disability. Therefore, we included nine studies, of which 7 were crossover[10,11,13,15–17,35] and 2 parallel[19,20], all double-blind and placebo-controlled studies and involving 183 individuals with sleep problems and intellectual disability, aged between 1 and 78 years. Tables I and II depict their demographic characteristics and study designs. All sleep studies were performed in the participants' home setting.

Participants received melatonin or placebo each during 2 weeks[12,14] or 4 weeks,[10,15,16,19,20] separated by a 1-week washout period. In one study,[18] both study medication periods lasted 10 days, separated by a washout period of 3 to 5 days (to allow for weekends). In one study[35] for each 2-week interval during the 10-week trial, participants were randomized to receive placebo or melatonin for the first week with the alternate agent for the second week.

Various doses of melatonin were given. In four studies a fixed dose of 5mg melatonin was used.[11,13,16,18] In four studies the melatonin dose was based either upon individual weight (ranging from 2.5–7.5 mg)[10], or age (0.5 [<6y] or 1mg [≥6y][35] respectively 2.5 [<6y] or 5 mg [≥6y]).[19,20] In one study[15] melatonin was initiated at a daily dose of 3mg. Parents were allowed to increase this dose in case of inefficacy up to 9mg during the following 2 weeks in increments of 3mg/week. In only four studies explicit information was given about the type of melatonin used. Three studies used fast release melatonin[10,19,20] and in one study[18] a combination of 1mg fast and 4mg sustained release melatonin was given.

Time of administration of study medication also differed across studies, ranging from a fixed time of 6pm,[35] 8pm,[13] 7pm, or 8pm depending on age,[19,20] or 1 hour before set bedtime[10] to 20 to 30 minutes before the child's most desirable bedtime,[18] 20 minutes before each participant's

Table I: Characteristics of participants of included studies

		Sex		Age (y:mo)		
First author	*n*	Male	Female	Mean	Range	Diagnosis
Camfield et al.[35]	6	4	2	7:3	3:0–13:0	Mental disability
McArthur et al.[10]	9	0	9	10:1	4:0–17:0	Rett syndrome
O'Callaghan et al.[11]	7	3	4	11	2:0–28:0	Tuberous sclerosis
Dodge et al.[13]	20	NS	NS	7:5	1:1–12:0	Developmental disabilities
Coppola et al.[15]	25	16	9	10:6	3:7-16:0	Mental retardation/learning disability
Garstang et al.[16]	7	6	1	NS	5:0–15:0	Autistic spectrum disorders
Wasdell et al.[18]	50	31	19	7:5	2:1–18:10	Neurodevelopmental disability
Braam et al.[19]	51	28	23	22:2	2:0–78:0	Intellectual disability
Braam et al.[20]	8	3	5	10:4	4:0–20:0	Angelman syndrome

NS, not specified.

Table II: Trial designs of studies included in meta-analysis

First author	Study course (d)						Time of melatonin administration	Melatonin dose (mg)	
	Base	Period 1	Interval	Period 2	Interval	Period 3			
Camfield et al.[35]	7	14	7	14	7	14	6pm	0.5 or 1.0	Fixed, depending on age
McArthur et al.[10]	7	28	7	28			1h before fixed bedtime	2.5, 5, or 7.5	Fixed, depending on body weight
O'Callaghan et al.[11]	14	14	7	14			20min before usual bedtime	5	Fixed
Dodge et al.[13]	7	14	7	14			8pm	5	Fixed
Coppola et al.[15]	0	28	7	28			At bedtime	3, 6, or 9	depending result higher dose each week
Garstang et al.[16]	7	28	7	28			NS	5	Fixed
Wasdell et al.[18]	7	10	3–5	10			20–30min before desired bedtime	5	Fixed
Braam et al.[19]	7	28[a]					6pm (< 6y) or 7pm (≥6 y)	2,5, or 5	Fixed, depending on age
Braam et al.[20]	7	28[a]					6pm (< 6y) or 7pm (≥6 y)	2,5, or 5	Fixed, depending on age

[a]Parallel study. NS, not specified,

usual bedtime,[11] or even at bedtime.[15] In one study, time of administration was not specified.[16]

Studies differed in terms of the patients examined. In five studies, a heterogeneous group of patients with intellectual disabilities with different etiologies was included.[13,15,18,19,35] Four studies were performed in patients with a specified diagnosis, in which sleep problems have a relative high prevalence. These were, Angelman syndrome,[20] autism spectrum disorders,[16] Rett syndrome,[10] and tuberous sclerosis.[11] In all nine studies, sleep parameters were measured using sleep diaries. In two studies, data from actigraphic recordings were available. [10,18]

Melatonin decreased sleep latency by a mean of 34 minutes (p<0.001), significantly decreased mean number of wakes per night (p=0.024), and increased total sleep time by 50 minutes (p<0.001). Figures 2, 3, and 4 summarize the means and SDs for sleep latency, total sleep time, and number of wakes per night for melatonin and placebo groups for the trials that provided data on this outcome.

The mean quality score on the Downs and Black checklist[27] from the two reviewers of the included studies was 25.28 out of 32 (SD=3.03; range 19–31). Intraclass correlation (mean measures, two-way random effects model using an absolute agreement definition) between the two reviewers was 0.90 (p=0.002; 95% CI: 0.59–0.98).

Graphical examination of the funnel plots showed no substantial effect of publication bias. This finding was corroborated by the adjusted rank correlations, for sleep latency, 0.19 (p=0.55); total sleep time, 0.00 (p=1); and number of night awakenings 0.25 (p=0.39). Publication bias did not substantially affect the results of the meta-analyses.

Inspection of Galbraith plots showed that there was some indication of statistical heterogeneity. For sleep latency and total sleep time two studies[16,18] had smaller variances than the other studies; for number of night awakenings this was the case for one study;[16] however, the Tau-squared measure of heterogeneity was 0 for all three sleep parameters. As a result we conclude that heterogeneity of the studies did not affect the outcomes of the meta-analyses.

Adverse effects

Specified reports on adverse effects were given in four studies.[13,18–20] Adverse effects were minor and their incidence in both melatonin and placebo phases were the same. In one study on children with Angelman syndrome,[20] parents of one child reported an increase in night wakes in the fourth treatment week. Two studies reported that no significant adverse side effect was observed,[10,15] while in another three studies no information on side effects was given.[11,16,35]

DISCUSSION

This meta-analysis showed that melatonin treatment significantly decreased sleep latency, increased total sleep time, and reduced the number of wakes per night in individuals with sleep problems and intellectual disability. It confirms earlier findings from case reports and open and

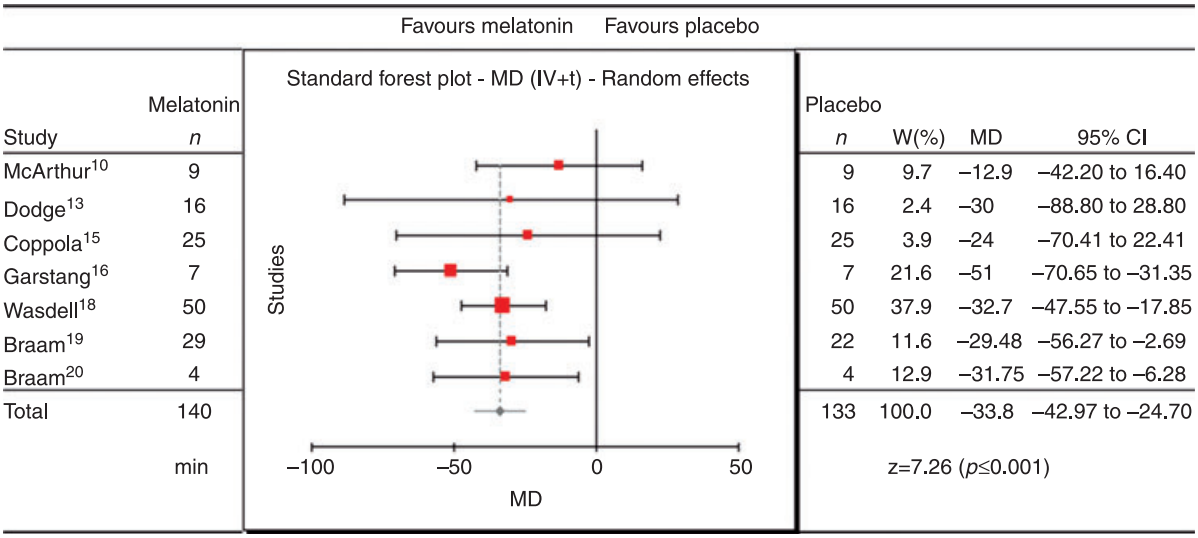

Figure 2: Effects of exogenous melatonin on sleep latency. t=estimate of the between study variance where the weight (W) given to each study is calculated by the inverse sum of the within study and between study variance estimates. The z-statistic determines the size of the effect of melatonin when all studies are combined. MD, mean difference; IV, inverse variance; CI, confidence interval.

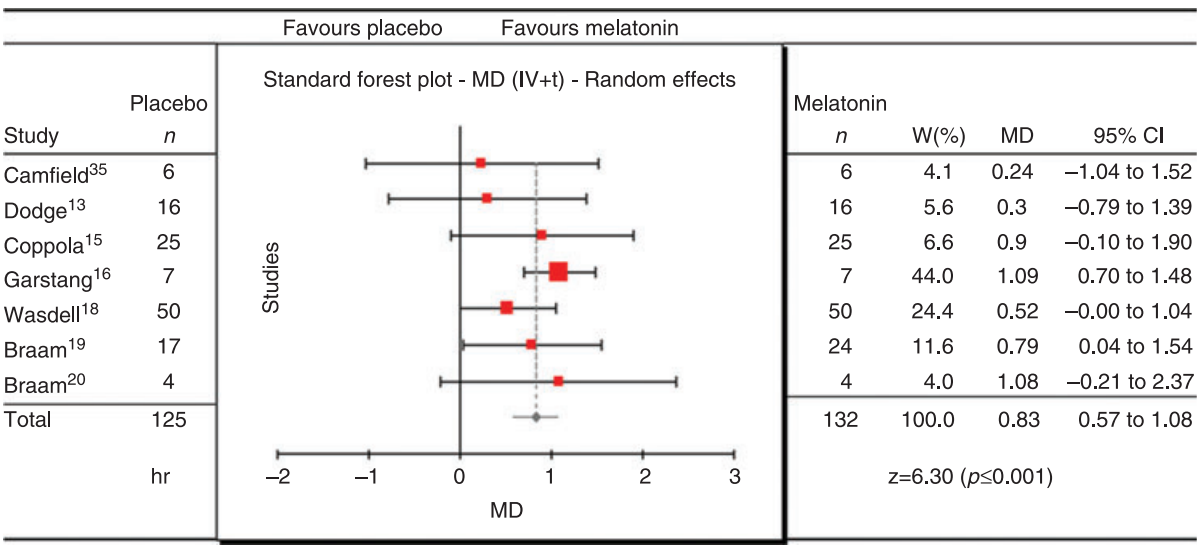

Figure 3: Effects of exogenous melatonin on total sleep time. t=estimate of the between study variance where the weight (W) given to each study is calculated by the inverse sum of the within study and between study variance estimates. The z-statistic determines the size of the effect of melatonin when all studies are combined. MD, mean difference; IV, inverse variance; CI, confidence interval.

randomized controlled studies, summarized in several reviews,[7,8,21–23] with similar positive outcomes.

Getting to sleep a mean of 30 minutes earlier is a statistically significant difference, but one might ask whether this is of a meaningful benefit to the individuals and their parents or caregivers. In five studies information was given on parental perception of the results.[15,16,18–20] Parents and caregivers reported that they spent less time and effort in getting their child to stay in bed, while daytime behavior and alertness on the part of the child also improved. Furthermore, compared to placebo, melatonin improved ratings on several functional and health dimensions as well as on ratings of severity and impact of sleep disorder on family stress.

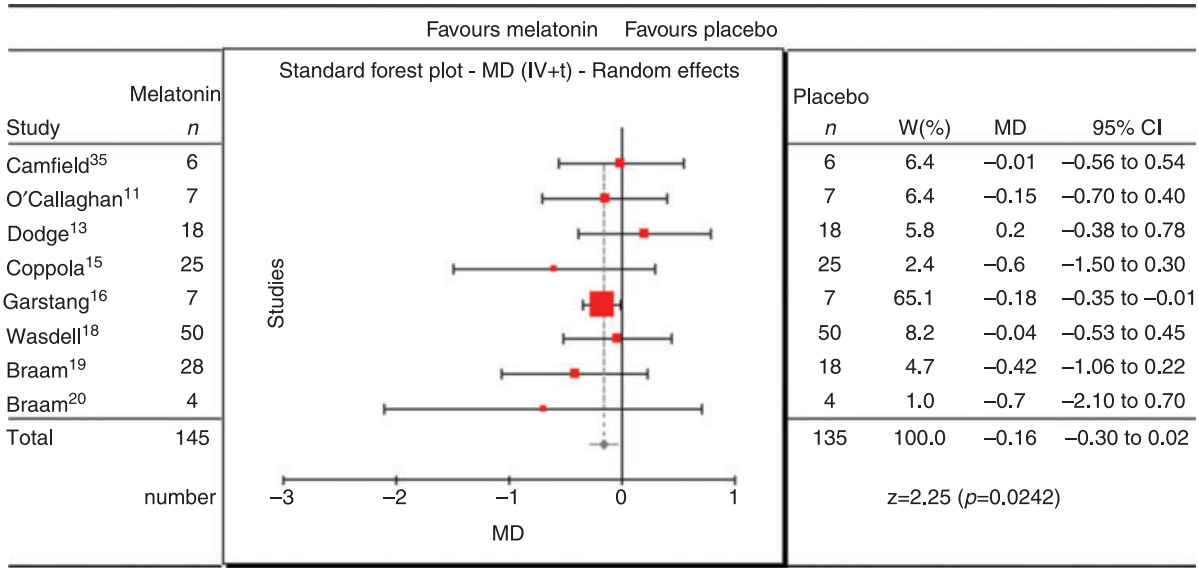

Figure 4: Effects of exogenous melatonin on night wakes. t=estimate of the between study variance where the weight (W) given to each study is calculated by the inverse sum of the within study and between study variance estimates. The z-statistic determines the size of the effect of melatonin when all studies are combined. MD, mean difference; IV, inverse variance; CI, confidence interval.

Across studies, timing of melatonin administration was different and various doses of melatonin were given. Both could have influenced the efficacy of melatonin. Melatonin is a chronobiotic drug with hypnotic properties.[5] However, none of the included studies specifically mentioned which of these two properties was the main object of the study. This is an important issue, because time of administration of melatonin can influence the effect of melatonin therapy. Difference in timing of melatonin administration, however, did not affect the results of the meta-analysis. Outcomes of studies with fixed times of administration were similar to those of studies with varying times of administration. There was also no association between melatonin dose and the effect on sleep parameters in the studies that were included in this meta-analysis. This is in line with results of a randomized study[17] (not included in this meta-analysis), that compared the efficacy of three different melatonin doses (i.e. 1, 3, and 5mg) in adults with intellectual disability, given 30 minutes before the desired bedtime. It showed no difference in effectiveness among these three melatonin doses. Another study of elderly persons with sleep problems,[36] without intellectual disability, comparing 0.3 and 3.0mg of melatonin given half an hour before each participant's fixed bedtime, found that the lower dose was more effective. This suggests that the positive effect of exogenous melatonin in these two studies mainly resulted from its chronobiological effect. This is in contrast to results of a study on individuals with sleep problems and intellectual disability,[15] in which parents and caregivers were allowed to increase the dose up to 6mg or even 9mg in subsequent phases, in case of inefficacy of the 3mg dose in the first phase of the study. In the last phase of the study, in 17 out of 24 (70.8%) participants, dose had been increased. Because in this study melatonin was given at bedtime, the tendency to increase the dose suggests that the positive effect of exogenous melatonin in this study mainly resulted from its hypnotic effect.

Patient groups in studies included in this meta-analysis were very heterogeneous. In five studies a mixed population of patients with intellectual disabilities was included,[13,15,18,19,35] and four studies examined specified groups with disorders in which sleep problems have a relative high prevalence (i.e. Angelman syndrome,[20] autism spectrum disorder,[16] Rett syndrome,[10] and tuberous sclerosis).[11] In Angelman syndrome, Rett syndrome, and tuberous sclerosis, epileptic seizures are frequent and nocturnal seizures can cause poor sleep maintenance. This could have influenced the efficacy of melatonin treatment. Results of melatonin in these three studies, however, were in line with the results in the studies with a mixed population of patients with intellectual disability. This can, at least in part, be caused by an anticonvulsant effect of melatonin.[37]

Three recent meta-analyses on the efficacy of melatonin in individuals without intellectual disability found that there is no evidence that melatonin is effective in treating most sleep disorders,[25,26] or only found small differences that seem to be of minor clinical importance.[24] There are

several possible explanations for this discrepancy between positive results with melatonin in individuals with sleep problems and intellectual disability and lack of positive results in individuals without intellectual disability. The first is that many studies in individuals without intellectual disability were performed in a sleep laboratory using polysomnography. Visual inspection of the standard forest plots, as presented in the three meta-analyses in individuals without intellectual disability, suggests that the change in sleep latency in studies in which measurements were performed in a sleep laboratory using polysomnography is smaller compared with studies that were performed under home conditions. Re-analyzing the data presented in these studies shows that the mean change in sleep latency in the studies using polysomnography is 10.1 minutes, whereas change in sleep latency in studies performed under home conditions is 16.8 minutes. The inclusion of a substantial number of studies using polysomnography in the meta-analyses in individuals without intellectual disability may have contributed to the smaller decrease in sleep latency compared with our meta-analysis, in which all studies were performed under home conditions.

A second explanation is the inclusion of studies on individuals with non-circadian rhythm sleep disorders, or no sleep problems at all, in the meta-analyses in individuals without intellectual disability. A circadian rhythm sleep disorder (CRSD) is defined as a persistent or recurrent pattern of sleep disturbance due primarily to alterations in the circadian timekeeping system or a misalignment between the endogenous circadian rhythm and exogenous factors that affect the timing or duration of sleep.[38] Exogenous and endogenous factors can contribute to misalignment between the timing of internal circadian rhythms and the desired (from the parent's or caregivers perspective) time for sleep.[39] In individuals with intellectual disability both endogenous as well as exogenous factors play an important part, whereby sleep problems caused by endogenous factors can be difficult to treat because they are externally maintained, for example by co-sleeping. In individuals with intellectual disability the prevalence of circadian rhythm sleep disorders is much higher than in individuals without intellectual disability.[7,8] Because melatonin is more effective in CRSD than other sleep disorders, it could be more effective in individuals with sleep problems and intellectual disability, than in some individuals with sleep problems without intellectual disability.

A third possible explanation for differences in results between studies in sleep problems in patients with and without intellectual disability may lie in the type of intellectual disability, i.e. the neurodevelopmental disorder, itself. First, maintaining a 24-hour circadian rhythm is based on a complex regulation system and many pathophysiological factors can disrupt this system.[6] Second sleep maintenance, i.e. getting back to sleep in case of wakes or arousals at night, has to be learned. Children with autism and patients with moderate or severe intellectual disability are easily aroused up to a stage that it becomes more difficult to fall asleep again independently. Also, low nocturnal melatonin levels can have a causal relation with sleep maintenance problems. For example, in Angelman syndrome, nocturnal melatonin levels are low.[40] The same applies to persons with autism, in whom, recently, an abnormal melatonin synthesis, leading to low nocturnal melatonin levels, was found.[9] It is possible that increasing a low melatonin level to a more normal physiological level, leads to less arousals that interfere with sleep maintenance. This is supported by results of a study that found that response to melatonin treatment in patients with intellectual disability with lower endogenous melatonin levels was better than in such patients with higher melatonin levels.[17]

Except for two parallel studies[19,20] all other studies were crossover studies. A crossover design is inappropriate when evaluating the efficacy of melatonin[41] because of the possibility of a carry-over effect. In two studies included in this meta-analysis, specific attention was given to this possibility, by analyzing the results by grouping the participants according to the drug-order.[15,18] Both studies found tendencies to carry-over effects on some parameters in participants who received placebo following melatonin. Laakso et al[17] in a study on individuals with sleep problems and intellectual disability (not included in this meta-analysis because no suitable quantitative data were provided), found tendencies to carry-over effects on all parameters in participants who received placebo following melatonin. A carry-over effect was also found in a study on individuals[41] with sleep problems without intellectual disability in participants who received placebo after melatonin. Although carry-over effects may have influenced the results in the crossover studies included in this meta-analysis, this does not threaten the validity of the conclusions of these studies, nor of this meta-analysis. After all, carry-over effects only lead to smaller differences in efficacy between melatonin and placebo groups, and as a result, to a smaller statistically significant difference in melatonin efficacy than in parallel studies.

This is the first meta-analysis of melatonin in individuals with sleep problems and intellectual disabilities. Quality of the studies included was thoroughly assessed. Nevertheless there were some limitations. First, conclusions in this meta-analysis are based on nine studies with relatively small numbers of participants. In connection with this limitation it should, however, be noted that this reflects the difficulties in recruitment of participants in these type of studies. Second, most studies in this meta-analysis included only or mainly children, and meta-analyses in individuals

with sleep problems without intellectual disability have included mainly adult participants. Because there is a physiological decrease in melatonin amplitude with age, we specifically looked into this possible bias. Given the fact that melatonin amplitude decreases with age, one might expect that because of these lower levels, if related to sleep problems at all, exogenous melatonin in adults would have resulted in a better therapeutic result than in children. However, outcome of studies in adults with sleep problems and intellectual disability included in this meta-analysis was less favorable than studies in with children intellectual disability. Therefore, it is unlikely that the difference in results between this meta-analysis and the meta-analyses in patients with sleep problems without intellectual disability can be explained by the inclusion of different age-groups, although differences in melatonin receptor sensitivity[42] cannot be ruled out as the causative factor.

The included studies were of short duration (10–28 days), so that neither information on the effectiveness of long-term melatonin therapy, nor any indication on the time needed to resolve the sleep problems, can be given. However, in one long-term follow-up study,[43] in which children with intellectual disability were followed every 3 months for up to 3 years 9 months after a randomized trial,[18] all parents remained satisfied with the results and adverse reaction to melatonin therapy and development of tolerance were not evident.

Polysomnography, the criterion standard to establish the effects of melatonin on sleep, was not used in the included studies in this meta-analysis, because many children and adults with intellectual disability do not tolerate this procedure. However, the other methods (i.e. actigraphy and sleep diaries) are reliable methods to establish shifts in sleep-wake rhythm.[44] In seven out of the nine included studies in this meta-analysis diaries to collect sleep parameters were used, while in two studies sleep diaries as well as actigraphy were used. In one of these two studies[18] the primary outcome measure was felt to be best measured by the caregiver-completed diaries, while in the other study[10] actigraphy was said be more reliable at monitoring sleep parameters than caregiver diaries. Diary measures obviously have measurement errors, but are frequently used in non-clinical settings. Sleep diaries based on observations by others, however, yield more satisfactory data than sleep diaries based on self-report.[45] Besides, parents of sleep-disturbed infants can be accurate reporters of actigraphically-assessed sleep onset and sleep duration. Sadeh et al.[46] showed an 85.3% agreement rate between actigraphic sleep-wake scorings and those of polysomnography. Therefore, we believe diary measures based on observations by parents and other caregivers can be used in assessing sleep parameters.

Publication bias and heterogeneity are major concerns for meta-analysis.[31,34] We included only studies that had good methodological quality as indicated by the Downs and Black checklist.[27] In addition, we examined publication bias and statistical heterogeneity and found that they did not substantially bias the outcomes of the meta-analyses reported. However, as can be seen from the low number of participants in some of the included studies, the statistical power is intrinsically not very high. As a result, the outcomes of this meta-analysis should only cautiously be applied in clinical practice. We advocate that more methodologically sound placebo-controlled randomized trials on melatonin should be conducted in the future, as this is of major importance for treating sleep problems in individuals with intellectual disability.

CONCLUSION

In spite of the heterogeneity of the studies, regarding patient groups, melatonin preparations, dosage, and timing of administration, 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. Although melatonin can be prescribed safely in individuals with sleep problems and intellectual disability, prescribers should realize that melatonin is a non-licensed drug in most countries, and that its long-term treatment effects are still unknown. Therefore, we advise the prescription of melatonin in individuals with sleep problems and intellectual disability preferably when it has been tried to assess the biological clock by (salivary) dim light melatonin onset measurements[47] and in randomized clinical trials. Future studies should assess melatonin dose and timing, circadian rhythm parameters, and quality of life of patients with intellectual disabilities and their caregivers.

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