Melatonin for the management of sleep problems in children with neurodevelopmental disorders: a systematic review and meta-analysis

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Word count= 3212

ABSTRACT

Importance: Children with neurodevelopmental disorders have a higher prevalence of sleep disturbances. Currently there is variation in the melatonin use, hence an up to date systematic review is indicated to summarize the current available evidence.

Objectives: To determine the efficacy and safety of melatonin as therapy for sleep problems in children with neurodevelopmental disorders.

Data sources and study selections: PubMed, Embase, CINAHL, and the Cochrane Central Register of Controlled Trials from inception up to March 2017. Two reviewers performed data assessment and extraction. We assessed randomized controlled trials that compared melatonin with placebo or other intervention for the management of sleep disorders in children (<18 years) with neurodevelopmental disorders.

Data extraction and synthesis: We identified 3262 citations, and included 13 studies in this meta-analysis.

Main outcomes: Included total sleep time, sleep onset latency, frequency of nocturnal awakenings, and adverse events.

Results: Thirteen RCTs (n=682), met the inclusion criteria. A meta-analysis of 9 studies (n=541) showed that melatonin significantly improved total sleep time compared with placebo (MD 48.26 min, 95% CI: 36.78 to 59.73, I^2 =31%). In 11 studies (n= 581), sleep onset latency improved significantly with melatonin use (MD= -28.97, 95% CI -39.78 to -18.17). No difference was noted in the frequency of nocturnal awakenings (MD= -0.49, 95% CI -1.71 to 0.73). No medication-related serious adverse event was reported.

Conclusion: Melatonin appeared safe and effective for improving sleep in the studied children. The overall quality of the evidence is limited due to heterogeneity and inconsistency. Further research is needed.

Keywords: Melatonin, Developmental Disorders, Sleep disorders, Systematic Reviews, Meta-analysis, Randomized controlled trials.

What is already known on this subject

- Children with neurodevelopmental disorders have a higher prevalence of sleep disturbances.
- Previous studies suggested that melatonin might be beneficial for improving sleep disorders in these children.

What this study adds

- Evidence from this comprehensive systematic review and meta-analysis shows that melatonin may be effective for improving total sleep time and sleep latency in children with neurodevelopmental disorders.
- No serious adverse events were associated with the use of melatonin in these children.
- The overall quality of the evidence is limited due to heterogeneity and inconsistency.
- Further well designed, larger randomised controlled trials are needed to further conclude on these findings

INTRODUCTION

Children with neurodevelopmental disorders have a higher prevalence of sleep disturbances than their unaffected peers and this could potentially have a negative effect on learning and behaviour.[1] Recent studies suggest that the prevalence of sleep disorders in children with developmental disabilities ranges from 25% to 86%.[2] Melatonin is a neurohormone, well known for its effect on the regulation of the circadian sleep-wake rhythm. In physiologic conditions, it has a plasma concentration that follows a circadian rhythm, with low levels during the day and high levels at night. In humans, the peak secretion typically occurs at around 2 am, which explains the name "darkness hormone".[3] Melatonin appears to have other multiple actions other than sleep regulation. It has potent antioxidant action,[4] protects the organism from carcinogenesis and has an immune modulation effect.[5] Studies of melatonin production in children with sleep disorders were often limited by small sample sizes and were not entirely consistent, but reported abnormalities in melatonin production strongly indicate that nocturnal secretion of melatonin is often low in children with neurodisability and those with autistic spectrum disorders.[6]

 It has been suggested from previous studies that melatonin might be effective on improving total sleep time,[7, 8] time to sleep onset "sleep latency",[8, 9, 10] and number of awakenings.[7]

Many children with developmental disorders, such as autistic spectrum disorder, attention-deficit/hyperactivity disorder and intellectual disability, experience sleep disturbances and may potentially benefit from melatonin treatment.[11] In five studies assessed by Hollway et al, information was given on parental perception of the effect of melatonin on their family life.[2] Parents and caregivers reported that they spent less time and effort in getting their child to stay in bed, while daytime behaviour and alertness on the part of the child also improved.

The results of a systematic review conducted by Appleton et al in 2004 suggested that melatonin might be effective in reducing sleep latency in children with neurodevelopmental disabilities.[10] Since that review, there have been a number of clinical trials that have investigated the effect of melatonin on the sleep pattern in children with neurodevelopmental disorders. Currently in the UK, there is variation in the guidance on the use of melatonin between clinical commissioning groups. An up to date systematic review using the Cochrane Collaboration format is indicated to summarise the current evidence on the use of melatonin compared with placebo for the treatment of sleep disorders in children with neurodevelopmental disorders. This review evaluated the effect of melatonin on total sleep time, sleep

onset latency, frequency of nocturnal awakening, early-morning awakening time, parental perception of the effect of melatonin treatment on their child's behaviour, and adverse events.

MATERIAL AND METHODS

Study selection and search strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and meta-analysis (PRISMA) criteria. A study protocol was conducted and is available online under this registration number: PROSPERO CRD42015024170.

We searched the following databases from inception to March 2017, that was then updated January 2018: PubMed, Embase, CINAHL and the Cochrane Central Register of Controlled Trials (CENTRAL). Reference lists from retrieved articles were inspected to identify additional citations that may have been missed by the electronic searches. We also searched for current unpublished ongoing clinical trials on the following websites: www.clinicaltrials.gov and www.controlled-trials.com. The search strategy included these terms: Melatonin (All Fields) AND (Neurodevelopmental disorder* OR Neurodevelopmental disabilit* OR Developmental delay* OR Behaviour disorder* OR Attention deficit hyperactivity disorder OR ADHD OR Autistic spectrum disorder or autism or Asperger syndrome OR Communication disorder* OR Sleep OR Sleep disorder* OR Insomnia OR Sleep quality OR Sleep difficult*OR Sleep disturbance* OR Sleep problem*) (see Appendix 1).

We applied no language restriction, and English translation was to be considered for relevant studies when needed.

Study characteristics

We included randomized controlled trials (RCTs) that compared melatonin to either placebo or any other intervention. The unit of analysis was the participating child that needed melatonin for sleep disorder. Cluster randomized trials were not included.

Participants were patients below 18 years of age with neurodevelopmental and sleep disorders. Interventions of the included trials included the therapeutic use of melatonin for sleep disorder. Melatonin should have been compared with placebo or any other intervention.

The primary outcome measure was total sleep time. Secondary outcome measures included: sleep onset latency, frequency of nocturnal awakening and early-morning awakening time, parental perception of

the effect of melatonin treatment on their child's behaviour, quality of life for both children and families and adverse events.

Data extraction and quality assessment

Using the above search strategy, papers that appeared to be potentially relevant were identified by two reviewers (IA, MG). We obtained full-text versions of all studies that were included in the review for assessment. We used a data extraction form that included risk of bias assessment, demographic information, methodology, intervention details, and reported outcomes. Two reviewers (IA, MG) extracted the data independently from each eligible study and compared the extracted data for any differences, which was resolved by discussion. Any disagreement was discussed and where necessary resolved by consultation with the third author (AA). We used the Cochrane Collaboration's Review Manager (RevMan, version 5.3) for data processing and analysis.

The criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions were used to assess the risk of bias.[12] Two reviewers (IA, MG) independently assessed the risk of bias for each study. Any disagreement was resolved by discussion or by involving a third reviewer (AA). We assessed the risk of bias according to the following criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other bias.[12] We graded each potential risk of bias as being at low, high or unclear risk. We contacted the authors of published studies for further clarification or to provide additional information when required.

Statistical analysis

We used the Cochrane Collaboration's Review Manager (RevMan) software (version 5.3) for statistical analysis. We performed meta-analysis for the outcomes that were amenable for pooled data synthesis using the random-effects model. We calculated the mean difference (MD) and corresponding 95% confidence intervals (CIs) for continuous outcomes measured using the same units. Narrative description was used to synthesize trial outcome data where data cannot be combined or significant heterogeneity exists

Assessment of Subgroups and Statistical Heterogeneity

Heterogeneity was assessed by the visual inspection of the forest plots and was tested using the I^2 statistic, in which $I^2 > 50\%$ indicated significant heterogeneity.[13]

Planned subgroup analyses were based on: a) type of neurodevelopmental disability, b) dosage of

melatonin, c) duration of treatment, d) age and e) the method used for sleep times measurements. We used sensitivity analyses to explore the impact of including only non-crossover studies in the analysis. All analyses were also subjected to fixed-effects model analysis to explore differences that would indicate heterogeneity. We used the GRADE system [14] to assess the quality of the body of evidence associated with specific outcomes (total sleep time, sleep onset latency, frequency of nocturnal awakening, early-morning awakening time). A funnel plot was to be used to investigate the potential of reporting and publication biases when at least 10 studies contributed to an outcome.

RESULTS

Identifying studies and quality assessment

We identified 3262 citations from the database searches of the pre-specified websites. Seven more citations were identified from searching other resources. 3217 studies were excluded from screening of titles and abstracts. We screened full paper copies of 52 citations that were potentially eligible for inclusion in the review. From the full texts, seventeen studies were excluded as duplicates, fifteen studies were excluded as non-RCTs, three studies included adults' data, two studies were excluded because melatonin was not used for sleep disorder and two studies assessed children with no neurodevelopmental disorders. We included 13 studies [15-26] involving a total of 682 children in this systematic review. A flow chart detailing the studies' selection process is shown in Figure 1.

Characteristics of eligible studies

All the included studies were prospective RCTs (see Table 1). Participants were children below18 years of age that had both neurodevelopmental and sleep disorders. The studies were conducted in Europe, North America and Iran. Eight studies were crossover RCTs.[17, 18, 20, 22, 24-27] The enrolled children were described in the primary studies to have the following neurodevelopmental disabilities: neurodevelopmental disorder,[15, 17, 24] autistic spectrum disorders,[16, 18, 19, 27] attention-deficit hyperactivity disorder (ADHD),[21, 23, 25] Fragile X Syndrome,[26] Rett syndrome [20] and mental retardation.[22] Sleep data was recorded either by using sleep diaries (7 studies),[17, 18, 19, 21, 22, 25, 27] using actigraph (4 studies),[19, 20, 23, 24, 26] or both (2 studies).[15, 16] The melatonin used was fast release melatonin in 10 studies,[15, 17, 18, 20-23, 25-27] and two studies used a combination of the slow and fast melatonin preparations.[16, 24] One further study used slow release melatonin [19]. The dosages used ranged from 0.1 -12 mg. Escalating dose of melatonin according to

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response was used in three of the included studies.[15, 19, 27] Duration of melatonin treatment ranged

from one to 13 weeks.

Study ID	Country of the study	Type of participants' disorder	Number of Children (n)	Age group	Type of melatonin and doses	Sleep diary or actigraph record
Appleton 2012.[15]	UK	Neurodevelopmental disorder	n=110	3-15 years and 8 months	0.5-12 mg slow release	Both diary and Actigraph
Cortesi 2012.[16]	Italy	Autism spectrum disorders	n=134	4-10 years	1-mg fast-release and 2-mg controlled-release	Both diary and Actigraph
Dodge 2001.[17]	USA	Moderate to severe developmental disability	n=20	1-12 years	5 mg fast release melatonin	Sleep diary
Garstang 2006.[18]	UK	Autistic spectrum disorder	n=11	4-16 years	5 mg fast release melatonin	Sleep diary
Gringras 2017.[19]	USA & Europe	Autistic spectrum disorder	n=125	2-17.5 years	2-5 mg slow release melatonin	Sleep diary
McArthur 1998.[20]	USA	Girls with Rett syndrome	n=9	4-17 years	2.5 -7.5 mg fast release melatonin	Actigraph
Mostafavi 2012.[21]	Iran	Attention-deficit hyperactivity disorder (ADHD).	n=50	7-12 years	3 or 6 mg fast release melatonin	Sleep diary
Niederhofer 2003.[22]	Austria	Mental retardation	n=20	14-18 Years	0.1-0.3 mg fast release melatonin	Sleep diary
Van der Heijden 2007.[23]	Netherland	Attention-deficit hyperactivity disorder (ADHD).	n=105	6-12 years	3 or 6 mg fast release melatonin	Actigraph
Wasdell 2008.[24]	Canada	Neurodevelopmental disabilities	n=50	2-18 years	1 mg fast, 4 mg sustained release melatonin	Actigraph
Weiss 2006.[25]	Canada	Adolescents With ADHD	n=19	6-14 years	5 mg fast release melatonin	Sleep diary
Wirojanan 2009.[26]	Canada	Autism, Fragile X Syndrome, or Autism and Fragile X Syndrome	n=12	2-15.3 years	3 mg fast release melatonin	Actigraph

Wright 2011.[27]	UK	Autism Spectrum Conditions	n=17	4-16 years	2-10 fast release melatonin	Sleep diary

Table 1. Characteristics of included studies

Risk of bias

The risk of bias assessment across all 13 included studies is shown in Figure 2 and Figure 3. Eight studies gave sufficient details about randomization and allocation to be assessed as having a low risk of selection bias.[15, 16, 19, 21, 23-25, 27] Only one study was classified as high risk for random sequence generation.[26] Eleven studies were classified as low risk for participants and personnel blinding.[15-17, 20-27] Six studies adopted good measures to reduce the risk of bias in outcome assessment by using actigraph to measure the sleep times.[15, 16, 21, 23, 24, 26] In 10 studies, there were enough outcomes assessments data to be classified as low risk,[16, 19-27] and all the 13 studies included in the review were of low risk for reporting bias.

Effect of melatonin

Total sleep time

Nine studies (n=541) provided sufficient data for this outcome and these were included in the data synthesis.[15-19, 23, 24, 26, 27] There was a statistically significant higher total sleep time in the melatonin group compared with the placebo group (MD= 48.26 minutes, 95% CI 36.79 to 59.73) (Figure 4). There was mild heterogeneity among the studies (I^2=31%). A sensitivity analysis using the fixed effects model made no significant difference to the results. Analysing only the non-crossover RCTs also made no significant difference to the results: melatonin remained superior in improving total sleep time (MD=51.26, 95% CI 42.56 to 59.96).

Sleep onset latency

Sleep onset latency was defined as the time taken to fall asleep by most of the studies' authors. All the 13 included studies assessed this outcome, however we included only 11 studies (n=581) that provided sufficient data in a suitable format to be included in the data synthesis.[15-20, 23-27] The pooled data synthesis showed that sleep onset latency is significantly improved by the use of melatonin (MD= -28.97, 95% CI -39.78 to -18.17) (Figure 5). There was severe heterogeneity among the included

individual studies (I^2=82%) (Figure 5). A funnel plot for this outcome showed asymmetry of the studies' distribution. This would indicate under reporting of smaller studies (Figure 6).

Frequency of nocturnal awakening

The frequency of the times that participants got awake after starting sleep was measured and data were suitable for meta-analysis in 6 studies (n=277).[16-18, 24, 25, 27]

The results showed that there was no significant difference between participants receiving melatonin or placebo (MD= -0.49, 95% CI -1.71 to 0.73). There was severe heterogeneity among the included individual studies (I^2=95%) (Figure 7).

Adverse events

Eleven studies reported on melatonin adverse events.[15-19, 21, 22, 24-27] There was no reported difference from the primary studies between melatonin and placebo groups, but there was not suitable data to allow meta-analysis on this outcome.

Child's behaviour

The parental perception of the effect of melatonin treatment on their child's behaviour for both children and families was reported in seven studies.[15, 18, 21, 23-25, 27] The direction of changes in children's behaviour favoured melatonin in four of these studies,[15, 18, 24, 27] and parents felt their children behaviour improved with melatonin treatment compared with placebo. However, studies that assessed children with ADHD reported no differences in behaviour between children received melatonin and those who received placebo treatment.[21, 23, 25]

Other outcomes

There wasn't enough data to allow a report on early-morning awakening time.

Subgroup analysis

Outcome: total sleep time

Subgroup analysis was done for the outcome total sleep time based on the type of neurodevelopmental disorders. Only studies that assessed children with neurodisabilities,[15, 17, 24] and autistic spectrum disorders[16, 18, 19, 27] could be grouped for data synthesis, and the pooled estimate showed a significantly higher total sleep time in the participants who received melatonin compared with placebo, in both neurodisabilities group (MD= 27.91, 95% CI 4.23 to 51.60) and autistic spectrum disorder

group (MD= 61.30, 95% CI 50.48 to 72.13) (Figure 8).

Outcome: Sleep onset latency

There was heterogeneity among the included studies noted on the initial analysis. This was improved when subgroup analysis was done according to neurodevelopmental disabilities diagnoses that is stated by the primary studies (MD= -26.09, 95% CI -32.13 to – 20.05) ($I^2 = 0$ %) (Figure 9).

Subgroup analyses on the dosage of melatonin, duration of treatment, and age were not feasible as there was no suitable available data.

GRADE Assessment

The GRADE quality of evidence for the outcomes: total sleep times, sleep onset latency and frequency of nocturnal awakening were downgraded to moderate because of inconsistency and heterogeneity of the studies.

DISCUSSION

Summary of the findings

The results of this systematic review and meta-analysis show that melatonin significantly improves total sleep time by about 48 minutes when used for children with neurodevelopmental disabilities. Children with autistic spectrum disorder showed an improvement in their sleep times by a mean of 61 minutes more sleep with melatonin treatment. Sleep onset latency was improved by a mean of about 29 minutes. The frequency of night-time awakening was not different between patients who received melatonin and those who received placebo. There was heterogeneity between the studies so it is difficult to conclude on these results. Getting to sleep earlier by around 30 minutes and having an extra 48 minutes of sleep might be statistically significant but its clinical significance needs to be evaluated further. Parents and caregivers reported that melatonin improved the rating on health issues and improved sleep and family stress.[29]

The doses of melatonin used varied between the primary studies and no consistency was noted. The dosages used ranged from 0.1 -12 mg. Escalating dose of melatonin according to response was used in two of the included studies.[15, 19, 27] Duration of treatment ranged from 1 week to 13 weeks with no consistent pattern noted among the studies. Both subjective (sleep diary), and objective (Actigraph) measures of sleep were used for assessment of sleep among the primary studies. With sleep diary,

periods could be missed when a child is awake and not disturbing the family.[15] Actigraphy might pick up restless sleep and artefact movements as being awake.[15] However actigraphy has become an important assessment tool in sleep research and is considered a sensitive and objective tool of assessment in clinical efficacy of interventions in sleep medicine.[30]

Most of the included studies on this meta-analysis (eight out of thirteen) were crossover RCTs. The washout periods between melatonin and placebo treatment groups varied between studies. Only one study had no washout period,[27] and the remainder of the crossover studies had 3-7 days as a washout period. Some authors believed that there could be a carry on effect of melatonin on sleep parameters and circadian rhythm.[15, 29, 31] A recent systematic review on the pharmacokinetics of melatonin showed that the maximum concentration of melatonin after supplementation would be reached after approximately 50 min with oral immediate-release formulations.[31] The elimination half-life of both oral and intravenous melatonin was about 45 min. Kunz et al, in a study involving 14 adults, showed that exogenous melatonin appeared to normalize circadian variation in human physiology.[32] This effect outlasted the period of melatonin administration and diminished only slowly over time. Even if this carry-over observation might have influenced the results, it is unlikely to have affected the validity of the conclusion of the meta-analysis.[29]

The results of this systematic review are similar to previous systematic reviews with comparable improvements in sleep times and sleep latency when melatonin was used for children with various neurodevelopmental disorders.[10, 28, 29]

There are some potential limitations of the current study. Some of the included studies had modest sample sizes. This could represent difficulties in recruitment of patients. There were some differences in the detailed study designs such as the different doses of melatonin used by the primary studies. This heterogeneity could have had an impact on the overall results.

Implications for Policy and Practice

There are variations in current practice and guidelines on the use of melatonin as an adjunct therapy to enhance sleep in children with neurodevelopmental disabilities. The evidence from this study on the use of melatonin in this group of children would help guide current practice and recommendations for future research. Furthermore, no significant adverse events of melatonin were reported by the primary studies.

Implications for Research

Using the GRADE criteria the overall quality of the evidence was judged to be moderate. Therefore the strength of our conclusions is limited. Higher quality, adequately powered parallel RCTs investigating the efficacy and safety of melatonin for improving sleep disorders in children with neurodevelopmental disorders is warranted.

CONCLUSIONS

In conclusion, the results of this study suggest that melatonin improves total sleep time and sleep onset latency with less disturbed night sleep in children with neurodevelopmental disorders. This conclusion is limited by heterogeneity and small sample sizes in the primary studies.

FOOTNOTES

Data sharing statement: Data extraction form and protocol available by request to

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LIST OF FIGURES

SUPPLEMENTS

     i.   **APPENDIX 1:** Search strategy