

POSITION STATEMENT

PRESCRIBING OF MELATONIN

Prescribing Recommendations:

New initiation of melatonin for sleep disorders in children and adolescents with ADHD – **RAG status 'Red'**

Management of sleep disorders in children with ADHD already established on melatonin – **refer to local commissioning arrangements for ongoing review and supply**

Management of sleep disorders in adults with ADHD (new initiation and patients already established on treatment) – **RAG status 'Black'**

Management of sleep disorders in children and adults with neurodevelopmental disorders – **RAG status 'Amber 0'**

There are five meta-analyses and two good quality RCTs in the literature that relate to the use of melatonin in the cohorts where melatonin has been recommended for use in the position statement.

Meta-analyses and systematic reviews

Abdelgadir et al [1] published a 2018 systematic review and meta-analysis focussing on the management of sleep problems in children with neurodevelopmental disorders. The objective of the study was to determine the efficacy and safety of melatonin as therapy for sleep problems in children with neurodevelopmental disorders. Thirteen randomised controlled trials (n=682) met the inclusion criteria. A meta-analysis of nine studies (n=541) showed that melatonin significantly improved total sleep time compared with placebo (mean difference (MD)=48.26 min, 95% CI 36.78 to 59.73, I²=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. [1]

The authors concluded that Melatonin appeared safe and effective in improving sleep in the studied children. However, they stated that the overall quality of the evidence was limited due to heterogeneity and inconsistency and further research is needed. [1]

Ferraciolli-Oda et al, 2013, published a meta-analysis regarding the use of melatonin for the treatment of primary sleep disorders. The authors looked at the efficacy of melatonin compared to placebo in improving sleep parameters in patients with primary sleep disorders. Adults and children were included in the study. Nineteen randomised placebo-controlled trials involving 1683 participants were included. Ten studies were crossover in design and nine were parallel. To be eligible for inclusion, studies were required to have at least ten participants for parallel designs and five for crossover designs. Trial duration ranged from seven to 182 days. Melatonin doses ranged from 0.1mg to 5mg across the 19 studies. The primary outcome measures were mean improvement in sleep onset latency, total sleep time and sleep quality (sleep efficacy was considered the same as sleep quality). [2]

The analysis showed that melatonin was more effective than placebo in decreasing sleep onset latency (mean difference = 7.06minutes [95% CI 4.37 to 9.75]; 15 trials; $I^2 = 56\%$), increasing total sleep time (8.25minutes [1.75 to 14.75]; 13 trials; $I^2 = 44\%$) and improving sleep quality (standardised mean difference = 0.22 [0.13 to 0.32]; 14 trials; $I^2 = 0\%$). Similar effects were reported in random-effects analysis for total sleep time and sleep quality; sleep onset latency was further reduced (mean differences = 10.18 [6.1 to 14.27]). Sleep quality and sleep onset latency were improved on both subjective and objective measures. Total sleep time was only increased on subjective measure and not objective. Higher melatonin dose was and longer trial duration were both associated with improved outcomes for sleep onset latency and total sleep time, but not sleep quality. The authors concluded that the effects of melatonin were modest but did not appear to dissipate with continued use. [2]

Systematic reviews of several smaller trials, including **immediate and prolonged-release formulations** of melatonin have observed longer total sleep times for melatonin treatment. **Braam et al, 2009**, published a meta-analysis of 9 studies conducted in patients with intellectual disabilities (including a total of 183 people, both children and adults), melatonin treatment increased total sleep time by a mean of 50 minutes ($p < 0.001$), decreased sleep latency by a mean of 34 minutes ($p < 0.001$), and significantly decreased the number of wakes per night ($p < 0.05$). [3] Another systematic review, **Rossignol et al, 2011**, of melatonin studies specifically in autism spectrum disorders identified 18 studies of various designs. [4] Thirteen were uncontrolled studies and all of these reported improvements in some aspects of sleep, with one study reporting improvements over 12 and 24 months of

follow-up. Six studies reported improved daytime behaviour with melatonin use. [4] Meta-analysis of five randomised, double-blind, cross-over trials indicated significant improvements in sleep duration (73 minutes) and sleep onset latency (66 minutes) for children with ASD. [4] It should be noted that there is an overlap of the studies included in the two reviews and, as noted by the authors of the MENDS study, there are several methodological issues, including differences in trial designs of the included studies, measures of sleep improvements, and the exclusion criteria employed. [5]

Randomised controlled trials

The MENDS study was a randomised double-blind placebo-controlled trial conducted in 19 hospitals across England and Wales. 114 children aged between 3 years and 15 years 8 months, with a range of neurological and developmental disorders (40% with autism spectrum disorder [ASD], none with ADHD) and whose sleep could not be improved by non-pharmacological intervention alone, were randomised to receive **immediate-release** melatonin 0.5mg capsules or placebo 45 minutes before the normal bedtime. The melatonin dose could be up titrated at weekly intervals: 2mg, 6mg and then 12mg in those not settling to sleep within an hour of administration. [5]

The primary endpoint was total sleep time measured by sleep diaries at 12 weeks compared with baseline. Melatonin significantly improved total sleep time compared with placebo by 22.43 minutes (95% CI 0.52 to 44.34 minutes; $p = 0.04$). When measured using actigraphy (non-invasive method of monitoring rest and activity cycles) rather than diaries the difference in total sleep time was smaller and not statistically significant (13.33 minutes, 95% CI -15.48 to 42.15 minutes). Melatonin statistically significantly reduced the time to fall asleep (sleep onset latency) compared with placebo by 37.49 minutes when measured using diaries (95% CI -55.27 to -19.71 minutes; $p < 0.0001$) and by 45.43 minutes using actigraphy (95% CI -68.75 to -21.93 minutes; $p = 0.0003$). However, melatonin also statistically significantly reduced the wake up time compared with placebo by 29.9 minutes (95% CI -46.3 to -13.6 minutes; $P < 0.001$). The study found that children given melatonin fall asleep earlier, but after three months' treatment also wake up earlier. The major effect of melatonin was on sleep latency, rather than total sleep time. The long term cumulative effect of short increases in total sleep time for children is unclear. [5]

NICE has published a Summary of Evidence for unlicensed or off-label use of melatonin for sleep disorders in children and young people with attention deficit hyperactivity disorder (ADHD). The main study reviewed by NICE was by **Van der Heijden et al, 2007**. The study

was a 4-week, randomised, double-blind, study, 105 children aged 6-12 years and who were medication-free at baseline. The patients were randomised to receive unlicensed (immediate-release) melatonin 3mg or 6mg (n=53), or placebo (n=52) at 7pm each evening. From the data available (data were missing for 24% of patients), it was estimated (using actigraphy) that the primary endpoint of sleep onset was advanced by melatonin by 26.9 +/- 47.8 minutes in contrast to a delay of 10.5 +/- 37.4 minutes with placebo ($p < 0.0001$). There was an increase in mean total sleep time of 19.8 +/- 61.9 minutes with melatonin and a decrease of 13.6 +/- 50.6 minutes with placebo ($p = 0.001$). There was also a significant decrease in sleep latency and nocturnal restlessness, and increase in sleep efficiency; however, there was no significant difference reported in behaviour, cognitive performance and quality of life. At trial end, all participants were eligible to receive melatonin in a longer term extension study. After a mean follow-up of 3.7 years, 61 (64.9%) children used melatonin daily and 11 (11.7%) used it occasionally (in most cases only using melatonin when they could not sleep). Parental satisfaction with melatonin was reported to be high, with a majority agreeing that melatonin improved their child's behaviour and mood. [6]

In a smaller study reviewed by NICE, **Weiss et al, 2006**, 19 children aged 6-14 years, on concurrent medication to treat ADHD (e.g. methylphenidate) and who failed to respond to a 10-day sleep hygiene programme were randomised into a 30-day cross-over study with melatonin 5mg and placebo. A 5mg dose of short-acting melatonin given 20 minutes before bedtime statistically significantly reduced sleep onset latency by 15.7 minutes ($p < 0.01$). Sleep duration was statistically increased when measured by parents (increased by 15 minutes; $p < 0.01$) but not when measured by actigraphy. In 17 children responding well to melatonin, continued use for up to 90 days resulted in a statistically significant improvement in sleep duration of 23 minutes from baseline. [6]

References

- [1] Abdelgadir et al, "Melatonin for the management of sleep problems in children with neurodevelopmental disorders: a systematic review and meta-analysis," *Archives of Disease in Childhood*, p. Epub ahead of print, 2018.
- [2] Ferracioli-Oda et al, "Meta-analysis: melatonin for the treatment of primary sleep disorders," *PloS one*, vol. 8, no. 5, p. e63773, 2013.

- [3] Braam et al , "Exogenous melatonin for sleep problems in individuals with intellectual diasbility: a meta-analysis.," *Developmental Medicine and Child Neurology*, vol. 51, no. 340, 2009.
- [4] Rossignol et al, "Melatonin in autism spectrum disorders: a systematic review and meta-analysis.," *Developmental Medicine and Child Neurology*, April 2011.
- [5] Appleton et al, "The use of melatonin in children with neurodevelopmental disorders and impaired sleep: a randomised, double-blind, placebo-controlled parallel study (MENDS).," *Health Technology Assessment*, vol. 16, no. 40, 2012.
- [6] National Institute for Care and Health Excellence, "Evidence summary: sleep disorders in children and young people with attention defecit hyperactivity disorder: melatonin," National Institute for Care and Health Excellence, Manchester, 2013.

Version Control

Version Number	Date	Amendments Made	Author
Version 1.0	September 2017	New document	AG
Version 1.1	February 2018	Wording amended for Children with ADHD already established on melatonin	AG
Version 1.2	July 2018	New indication and associated RAG status added. Changes to formatting and update to background information.	AG

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