

The use of MElatonin in children with Neurodevelopmental Disorders and impaired Sleep: a randomised, double-blind, placebo-controlled, parallel study (MENDS)

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Executive summary

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Executive summary

Background

Circadian rhythms, including the sleep–wake cycle, are entrained by the transmission of light from the retina to the circadian pacemaker, situated in the suprachiasmatic nucleus (SCN) of the hypothalamus. Light perception is all that is required for synchronisation with the SCN. Melatonin (*N*-acetyl-5-methoxytryptamine) is a natural substance produced by the pineal gland in the evening in response to SCN signals, with concentrations peaking at approximately midnight and secretion being extremely low during daylight hours. The melatonin signal forms part of the system that can influence sleep-promoting and sleep–wake rhythm-regulating actions. The circadian clock is entrained not only by light but also by behavioural and social cues (zeitgebers). An inability to correctly interpret these zeitgebers in children with neurodevelopmental disorders can lead to abnormalities in circadian rhythm. Children with neurological or developmental disorders or both have a higher prevalence of sleep disturbances, which are frequently chronic and are usually far more difficult to treat than those in their ‘normally’ developing peers and may result in additional learning and behaviour problems. Disturbed sleep, and specifically discontinuous sleep with frequent awakenings, commonly results in disturbed sleep in their parents and siblings. This may have secondary detrimental effects on families, which may be physical, emotional and social – and, if chronic, may impair their ability to continue in employment or further education. Finally, chronic sleep disturbance in multiply disabled children is a frequent cause of families giving up their care.

Melatonin is unlicensed for use in improving sleep in children, whether or not a child has neurodevelopmental problems, and it is estimated that in the UK there are currently in excess of 6000 children being treated with melatonin. There are at least 50 preparations that are either imported into or manufactured within the UK. Current, and predominantly anecdotal, evidence, together with the rapidly increasing and largely haphazard use of melatonin prescribed by a range of paediatric specialties (community child health, neurology and psychiatry), justified the need to undertake a multicentre, randomised, placebo-controlled, parallel study of melatonin in children with neurodevelopmental delay and a range of neurological disorders and impaired sleep to confirm (or refute) the observation that the drug may increase the total duration of night-time sleep.

Objectives

The primary objective was to determine whether or not immediate-release melatonin is beneficial compared with placebo in improving total sleep time (TST) in children with neurodevelopmental problems, calculated using sleep diaries at 12 weeks compared with baseline. Secondary outcomes included TST calculated using actigraphy data, sleep-onset latency (SOL) (time taken to fall asleep), sleep efficiency, Composite Sleep Disturbance Index score, global measure of child’s sleep quality, Aberrant Behaviour Checklist, Family Impact Module of the Pediatric Quality of Life Inventory (PedsQL™), the Epworth Sleepiness Scale, number and severity of seizures and adverse events. Salivary melatonin concentrations and association of genetic variants with abnormal melatonin production were also investigated. The salivary melatonin analysis was undertaken primarily as an exploratory or hypothesis-generating approach. This was an attempt to enable biochemical phenotyping of those children with a genuinely delayed sleep phase and who might be expected to be better responders to melatonin.

Methods

Population

The population studied was a heterogeneous group comprising a large number of children with a wide range of neurological and developmental disorders, including those with specific genetic disorders but also those without a specific genetic or syndromic diagnosis. This group was chosen because it reflects the typical population who is currently prescribed melatonin in the UK.

Setting

Children were referred by community paediatricians and other clinical colleagues to the principal investigators in the participating sites in hospitals throughout England and Wales. Community paediatricians were informed that the paediatric population who could be referred for consideration of participation in MENDS (MElatonin in children with Neurodevelopmental Disorders and impaired Sleep) must be between the ages of 3 and 15 years and have sleep impairment and neurodevelopmental delay.

Screening

Following referral and at the initial screening visit (T-4W) children were assessed to determine whether or not they were eligible for recruitment into the study.

Inclusion criteria

- Children aged from 3 years to 15 years and 8 months at screening.
- Children with a neurodevelopmental disorder diagnosed by a community paediatrician, paediatric neurologist or paediatric neurodisability consultant.
- Children with an Adaptive Behaviour Assessment System (ABAS) questionnaire score with a percentile rank <7.
- Children with a reported minimum 5-month history of impaired sleep at screening as defined by:
 - not falling asleep within 1 hour of 'lights off' or 'snuggling down to sleep' at age-appropriate times for the child in three nights out of five and/or
 - less than 6 hours of continuous sleep in three nights out of five.
- Children whose parents were likely to be able to use the actigraph and complete sleep diaries.
- Children who were able to comply with taking the study drug.
- Families who were English speaking.

Exclusion criteria

- Children treated with melatonin within 5 months of screening.
- Children who had been taking a benzodiazepine (other than as the child's rescue or emergency medication for epilepsy) or other psychoactive drug for <2 months.
- Children receiving a beta-blocker (minimum of 7 days' washout required).
- Children receiving a sedative or hypnotic drug, including choral hydrate, triclofos and alimemazine tartrate (Vallergan[®], Sanofi-Aventis) (minimum of 14 days' washout required).
- Children with a known allergy to melatonin.
- Children with a regular consumption of alcohol (more than three times per week).
- Children for whom there are suggestive symptoms of obstructive sleep apnoea syndrome (OSAS) (such as combinations of snoring, gasping, excessive sweating or stopping breathing during sleep), physical signs supportive of OSAS (such as very large tonsils/very small chin) or results of investigations suggesting OSAS (such as overnight pulse oximetry or polysomnography), for which the child should be referred to appropriate respiratory or ear, nose and throat colleagues for specific assessment and treatment.
- Girls or young women who were pregnant at the time of screening (T-4W).

- Children who are currently participating in a conflicting clinical study or who have participated in a clinical study involving a medicinal product within the last 3 months.

Following registration, and before randomisation, patients who met the inclusion and exclusion criteria outlined above and who were able to give informed consent entered a 4- to 6-week behaviour therapy period in which a behaviour therapy advice booklet was provided. Sleep was measured using daily sleep diaries and actigraphy. After this period the sleep diaries were reviewed to determine if the sleep problem fulfilled the eligibility criteria. At this time (T0W), possible participants for the interventional stage of the study were reassessed. Patients whose parents/carers had completed sleep diaries for an average of 5 out of 7 nights at baseline (T0W) and whose children still met the inclusion and exclusion criteria were then randomised to receive either melatonin or placebo and were followed for 12 weeks at which point the study terminated (T+12W).

Interventions

At randomisation, children were allocated to receive either active melatonin (Alliance Pharmaceuticals) or matching placebo capsules in doses of 0.5 mg, 2 mg, 6 mg and 12 mg for a period of 12 weeks. The starting dose was 0.5 mg and the dose could be escalated through 2 mg and 6 mg to 12 mg at weekly intervals during the first 4 weeks at the end of which the child was maintained on that dose. The decision to increase the dose was based on a review of set criteria. The dose could also be reduced if the patient's parents/carers felt that the child was experiencing any unwanted side effects from the medication. The capsules could be swallowed whole or opened and the contents mixed with the following vehicles: water, orange juice, semi-skimmed milk, strawberry yoghurt and strawberry jam.

Results

The first patient registered was on 11 December 2007, the first patient randomised was on 28 January 2008, the last patient registered was on 7 May 2010 and the last patient randomised was on 4 June 2010.

A total of 275 children were screened to enter the trial at T-4W; 263 (96%) children were registered and completed the 4- to 6-week behaviour therapy period and 146 (56%) of these children were randomised at T0W, of whom 110 (75%) contributed data for the primary outcome.

The mean difference in TST between the two treatment groups, adjusting for mean baseline total sleep time, was 22.43 minutes [95% confidence interval (CI) 0.52 to 44.34 minutes; $p=0.04$] in favour of the melatonin group when using the sleep diaries and slightly less when using actigraphy (13.33 minutes; 95% CI -15.48 to 42.15 minutes). Although the difference between the treatment groups was statistically significant when diaries were used, the 95% CI does not contain the minimum clinically important difference of 60 minutes.

The outcome of SOL measured the time taken for a child to go to sleep from 'snuggle-down time'. This was calculated using both the actigraphy data and the sleep diary. The mean difference between the treatment groups, adjusting for mean baseline SOL, was -37.49 minutes (95% CI -55.27 to -19.71 minutes; $p<0.0001$) in favour of the melatonin group using the sleep diary and -45.34 minutes (95% CI -68.75 to -21.93 minutes; $p=0.0003$) using actigraphy. Both measures showed that the time taken to fall asleep by children in the melatonin group was statistically

and clinically significantly less than that in the placebo group. The difference in sleep efficiency between the two treatment groups, adjusted for baseline, was not statistically significant, with an average improvement of 4.03% in the melatonin group (95% CI -0.6 to 8.67%; $p = 0.0869$).

The paucity of salivary melatonin data precludes any meaningful analysis and the genetic analyses are 'work in progress'.

Conclusions

On average, the children treated with melatonin slept for 23 minutes longer than those in the placebo group; however, the upper limit of the CI was < 1 hour, the minimum clinically worthwhile difference specified at the outset of the trial. Melatonin is effective in reducing SOL in children with neurodevelopmental delay, reducing this time by a mean of 45 minutes; a reduction of 30 minutes was specified a priori to be clinically worthwhile.

Implications for health care

Sleep disorders are a common presentation in children with a wide variety of neurodevelopmental conditions. Medication should not be the first-line intervention and, in common with previous studies, our behavioural run-in period was successful, with many children no longer meeting eligibility criteria for the study after a relatively short period with a specific evidence-based behaviour therapy advice booklet and monitoring, but no direct work with psychology or other sleep behavioural specialists. However, it is possible that the relatively large 'dropout' of patients in the 4- to 6-week behaviour intervention (therapy) phase may also reflect parental perceptions of their child's sleep problem. The process of formally observing and documenting their child's sleep pattern in sleep diaries may have unmasked a significant gap between their perceived interpretation of their child's sleep problem and their child's actual sleep problem. It would be relatively easy to test this hypothesis in a future randomised controlled trial of behavioural intervention compared with no intervention in this type of population.

Melatonin is more effective than placebo for children with neurodevelopmental delay who have trouble falling asleep. This is a common presenting complaint and melatonin reduces this period by an average of 37 minutes. This is helpful for families desperate to settle their child with neurodevelopmental delay and who may then benefit from a calmer evening either for themselves or for siblings and other family members. However, we found no evidence that this reduction in sleep latency measurably improved the quality of life of families or children's behaviour over the 3-month period. It did seem to reduce parents' reports of daytime fatigue, which is an interesting finding that should be further explored.

Although the children fell asleep earlier, they gained very little extra total night-time sleep. An extra 23 minutes of sleep over the whole night is small and was deemed not to be clinically significant for our study. The increase does, of course, vary with individuals and its value is likely to be cumulative. In addition, some families may actually consider that an additional 23 minutes is of benefit.

Recommendations for research

- The MENDS study compared melatonin only with placebo. There are a number of other licensed and unlicensed medications for children with sleep problems, including hypnotics and sedatives, and head-to-head trials may help clinicians and families decide which option is likely to be the safest and most helpful.
- Further studies need to be undertaken to try and establish the most appropriate dose and formulation (fast or slow release) of melatonin, incorporating the child's age, weight and

24-hour endogenous melatonin profile, including dim-light melatonin onset and whether they are a fast or slow metaboliser of the drug.

- We were not able to undertake measures of cognition directly. Given that these may reflect important end points around learning potential, they will be important to explore in future intervention trials, however difficult.
- Future studies should be undertaken over a longer period of time and should include both appropriate quality of life and economic evaluations.

Trial registration

This trial is registered as ISRCTN05534585.

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Publication

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