Melatonin to assist in the management of sleep disorders in children with neuro-developmental disorders

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Health Technology Description

Melatonin is a hormone produced by the pineal gland located in the brain. It plays an important role in the regulation of sleep and circadian rhythm, and thus has been suggested to be a potential treatment for various sleep disorders due to this physiological function. Synthesis and secretion of endogenous melatonin are stimulated by darkness and inhibited by light. Secretion reaches a peak between the age of one to three years, after which the levels gradually decline especially at puberty. Although melatonin can be isolated from the pineal glands of animals, synthesised melatonin is preferable for use in treatment as it contains less potentially harmful impurities. Melatonin is not licensed in the UK but can be prescribed on a named patient basis. Available forms include: capsules, tablets, liquids, sustained-release preparations and sprays. Exogenous melatonin ingested orally is expected to have relatively short duration of effect as it is rapidly eliminated from the body (half-life 30 to 60 minutes).

Epidemiology

Neuro-developmental disorders are clinically and aetiologically diverse conditions, the commonest of which include: attention deficit hyperactivity disorder (ADHD) that affects up to 5% of school-age children, autistic spectrum disorders (estimated prevalence 18.7 - 44.2 per 10,000 children in Scotland according to existing registers and 116.1 per 10,000 children in South Thames using active population screening), and learning disabilities associated with genetic or neurological conditions. Sleep disorders including difficulty in falling asleep, waking at night and waking too early in the morning are very common among children with neuro-developmental disorders. The prevalence of parentally reported sleeping problems in ADHD is estimated to be 25 to 50%, although more objective measures give inconsistent and generally milder sleep abnormalities. Sleep disorders in ADHD are frequently complicated by the use of stimulant medications. Two-thirds of children with autism are estimated to exhibit sleep problems at any one time and between 44 to 86% of children with severe learning disability have been reported to experience sleep disorders. Management of sleep disorders usually involves identification and elimination of extrinsic causes such as other medical conditions and implementation of behaviour measures including good sleep hygiene. These interventions are not always effective and may not be practical. Use of sedative and hypnotic medications in children has undesirable daytime effects and there were concerns over safety.
Clinical effectiveness

A systematic review by Phillips and Appleton specifically addresses the use of melatonin in children with neurodevelopmental disabilities and sleep impairment. It included three small placebo-controlled, randomised controlled trials (RCTs). Another comprehensive systematic review was found that covers both adults and children and all forms of sleep disorders. It is not described here further as no additional RCTs relevant to the population of interest were included.

Two studies included in the review by Phillips and Appleton reported a statistically significant reduction in sleep onset latency (the time between going to bed and actual onset of sleep) by approximately 10 to 30 minutes (baseline 42 and 72 minutes respectively) during melatonin treatment compared to placebo. One of these two trials (n=9) included children with Rett syndrome (a genetic neurodevelopmental disorder) and used melatonin 2.5 – 7.5 mg one hour before bedtime; the other (n=20) included children with moderate to severe developmental disability and administered melatonin 5 mg at 8 pm. No significant effects on total sleep time, number of night-time awakenings, and parental opinions on children’s sleep performance and daytime behaviour were observed in these two trials. Melatonin demonstrated no significant difference over placebo for all outcomes reported in the third trial (n=6) that included children with moderate to severe learning disability and administered melatonin 0.5 – 1 mg at 6 pm. One RCT, excluded from the review, compared fast-release to sustained-release melatonin in children with severe neuro-developmental difficulties. The study failed to produce quantitative results due to frequent medical problems unrelated to treatment among study subjects.

Safety

Use of melatonin appears to be well tolerated in the aforementioned short-term trials (all <3 months). No serious adverse events were reported, although an isolated case of severe mood swings and another case of severe migraine were mentioned. Contrary to a widely cited small cohort in which four of the six children with neurological disabilities had increased seizure activity after melatonin treatment, no change in seizure frequency was observed among the limited number of trial patients. There was no report of serious adverse effects in two uncontrolled studies with longer follow-up (2 years or longer; n=67 in total). Anticonvulsant medications had to be adjusted on occasion and there was one case of discontinuation of treatment due to excessive sedation. There is a lack of evidence regarding long-term effect of melatonin on puberty.
Economic implications

No published economic evaluation examining the cost effectiveness of melatonin treatment in children was found. Despite the limited clinical effectiveness evidence and the lack of cost effectiveness evidence, the use of melatonin appears to be rising. The number of items prescribed within primary care in Scotland increased from 1,833 during 2001-2 to 8,645 during 2005-6. A similar increase was observed in England. By 2004, 239 UK hospital/trust pharmacies had requested melatonin. The average cost per prescribed item in Scotland during 2005-6 was £15.63. Among the available formulations, tablets are the cheapest and controlled-release capsules of the same strength cost nearly double.

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Ongoing research

An ongoing double-blind, cross over RCT led by Dr Barry Wright at Limetrees Child, Adolescent & Family Unit, York aims to recruit 32 children with autism and sleep problems by the end of 2007. This study will compare melatonin (starting 2 mg and titrating in 2 mg steps to up to 10 mg) to placebo over a 3-month period for each treatment with a one-month washout period. Another double-blind RCT funded by the NHS Health Technology Assessment Programme is due to start in January 2007. The trial, led by Dr Richard Appleton at Royal Liverpool Children’s NHS Trust, is expected to enrol 172 children with neuro-developmental disorders and impaired night-time sleep and will compare melatonin (starting 0.5 mg per day, with weekly increments through 2 mg and 6 mg and increasing to a maximum of 12 mg) to placebo. The results of the study are due to be published in early 2010.

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