

## Is Melatonin likely to help children with neurodevelopmental disability and chronic severe sleep problems?

### Scenario-

A girl aged 3 years and 6 months has neurofibromatosis with significant visual impairment and mild to moderate learning difficulties. She has always been difficult to settle to sleep and has frequent nocturnal awakenings.

A sleep programme with specific behavioural management techniques has been used as have sedative medications such as Trimeprazine, which caused deterioration in concentration and daytime sleepiness. Should she be tried on Melatonin?

### Structured clinical question-

In a preschool child with visual impairment and mild to moderate learning difficulties in whom conventional treatments have failed (patient) is Melatonin (intervention) likely to improve her sleep pattern (outcome)?

### Search Strategy and outcome-

**Secondary sources-**DARE, Clinical Evidence Dec 2000, Medicines for Children RCPCH 1999- None

Cochrane Library -Systematic Reviews- 0, Abstracts of Reviews of Effectiveness- 0, Controlled Trials Register –6 papers of which 2 relevant.(Same papers found through search detailed below)

**Primary Sources-** Medline 1966 to July 2003

Melatonin AND Sleep disorders AND limit to:Children <0 to 18 years> Human, English language

This gave 95 references –all titles checked – 16 considered – 6 included. 9 excluded as 3 non-systematic reviews, 2 other conditions, 1 non-delayed children, 1 slow-release melatonin, 2 abstracts only

Embase 1980 to present- Searched with same strategy- no additional papers

**Summary-** 7 papers-See table

Citation	Study group	Level of evidence	Outcomes	Key results	Comments
Jan et al 1994	15 children aged 6 months to 14 yr mean 6.8yr most multiply disabled 5 with epilepsy 9 visually impaired Melatonin 2.5mg to 5mg	Double blind placebo controlled trial  (Level 1b-)	Sleep charts  Parental interview	No adverse effects  No response in 2/15  1 child-ceased effect even with 20mg after 6/12	6 (40%) not randomised.  Type of sleep disturbance described

O'Callaghan et al 1999	7 Children age 2-28yr with Tuberose Sclerosis with Epilepsy +SLD Randomised to placebo or 5mg Melatonin 20 min prior to bedtime	Crossover Randomised double blind trial;  (Level 1b-)	Sleep diary Total sleep time Sleep onset latency No. awakenings	Mean improvement in total sleep time of 0.55hr (CI 0.088-1.01)  No effect on fragmented sleep	Short treatment time for any adverse effects to become apparent.  No effect noted on seizure frequency (95% CI 0% to 41%)
Dodge N et al 2001	20 children with moderate to severe developmental disabilities (4/20 visual impairment) Age range 1-12 years  36 recruited but only 20 completed study	Randomised double blind placebo controlled trial  (Level 2b-)	Sleep latency Duration of sleep No. awakenings  Sleep log and parental questionnaire	Sleep latency improved in all but 2 children on MLT (p<0.05)- more marked in those with greater sleep latency on baseline measure.  Duration of sleep improved with MLT but no different from placebo . No change in number of wakenings	No side effects reported (95% CI 0% to 17%)  Large drop out rate but no reported differences in diagnosis, age, epilepsy etc in those not completing. No baseline data for type or severity of sleep problems in those dropping out.
Camfield et al 1996	6 children aged 3-13 yr Blind with at least moderate learning disability, using 0.5 – 1mg melatonin	'n-of1' double blind placebo trial.  (Level 2b)	Sleep diary. Average numbers hours sleep per 24 hours.  Number of wakenings between 9pm-7am.  Number of nights without wakening between 10pm –7 am.	Found MLT to be ineffective in 5/6	Low dose used. Timing in relation to desired sleep time may have been too long. No adverse effects noted. (95% CI 0% to 46%) No information about blinding or randomisation
Palm I. et al 1997	8 aged 3-23yr (6 children aged 18 or less) All functionally blind	Open study  (Level 4)	Sleep diaries for 6 week prior to treatment and several	"Dramatic" response in all 8 Loss of effect in 1 after 6-8 months	No side effects reported (95% CI 0% to 37%)

	M/S learning disabilities 0.5-2mg melatonin age dependent		months during treatment  MLT levels in 7 children	MLT levels showed delayed peak	
Sheldon S 1998  Published as research letter	6 children 9 months-18 yr multiple neurological deficits and chronic sleep disorders with 5mg at bedtime	Open study  Consecutive recruitment  (Level 4)	Wrist Actigraph. Changes in sleep onset latency, Nocturnal awakenings Total sleep time	Marked improvement in all 3 measures in 5/6	Study stopped due to increased or new seizure type activity on melatonin in 4/6 (67%: 95% CI 23% to 96%) No info on types of AE meds used
Ross,C 2002	46 patients, 1y to 18y, with neurodevelopmental disorders	Retrospective case review (Level 4)	Overall improvement	Sleep improvements in 34 patients	Diary (28 patients) Imputed from case notes (18 patients)
			Median total time sleep interruptions (before vs. after)	9h pre-treatment 5h on-treatment Median reduction 2.75h (95% CI 6.25h to 0h)	26 patients also had epilepsy.
			Median total number sleep interruptions (before vs. after)	7 pre-treatment 3.5 on-treatment Median reduction 1.5 (95% CI 3.5 to 0.5)	No adverse effects noted (95% CI 0% to 7.7%)

### Comments-

Most studies had small numbers of participants with significant drop out rates or non randomisation in larger studies. Very few of the studies give p values or confidence intervals – they appear far too small to give statistically meaningful effects. One of the trials (by Camfield) is very different in design, an ‘N-of-1’ study. These trials are designed for each individual patient, and allow for interpersonal variation in drug effect. Classically an N-of-1 trial has three blocks, during each block the patient receives sequentially therapy and placebo under double blind conditions with an appropriate washout period. Response in 2 or 3 blocks is considered positive, less than this due to chance alone.

Even allowing for the difficulty of recruitment and objective assessment of outcomes in children with multiple difficulties, there is currently little good quality evidence for the effectiveness of Melatonin. The startling increase in seizures noted by the Sheldon paper is of great concern, especially in the UK where Melatonin is often given in an uncontrolled way with overseas imports of the drug. However, this should be balanced against the lack of effect in the other reviewed studies and benefits seen in other case reports (e.g. Peled 2001). Given the data we have reviewed, the estimate of side effect frequency is about 4% (95% CI 1% to 10%).

A large multicentre placebo controlled RCT is needed to try to clarify which children and what types of sleep disorder are most amenable to treatment, and to define the likely side effect profile. We understand a trial is currently underway, and will update this Topic when the results are available.

### **Clinical bottom lines-**

1. Melatonin may be effective in sleep onset difficulties, but not in fragmented sleep or early morning wakening, though evidence is poor quality.
2. There is little evidence regarding Melatonin's long term safety profile.
3. Melatonin should be used with caution in any child with epilepsy in view of increased seizure frequency in one study; 'N-of-1' methods may be considered.

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