USE OF MELATONIN IN PEDIATRIC NEUROLOGY

"WONDER DRUG OR IMAGINATION"

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SLEEP DISORDERS IN CHILDREN

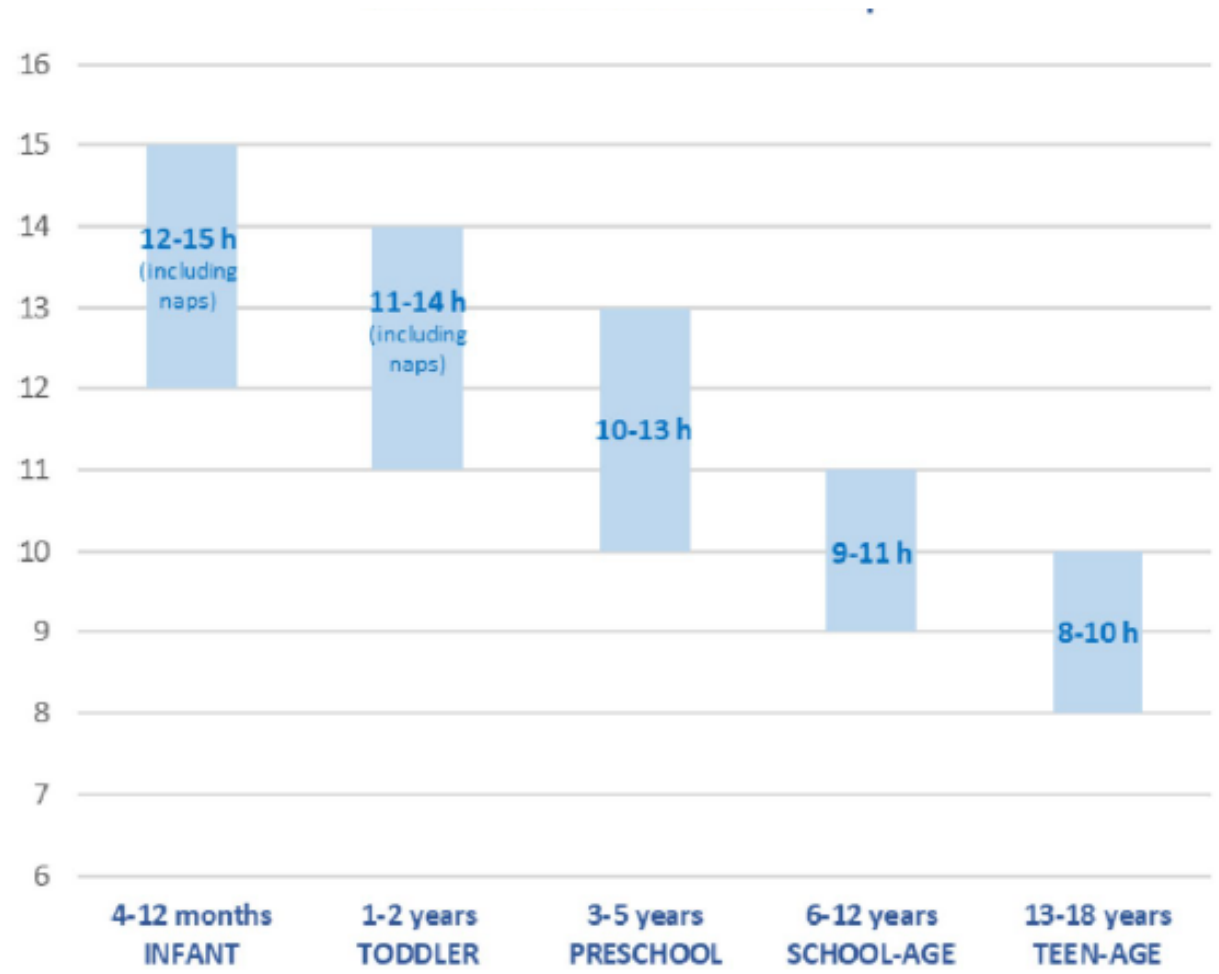
Sleep disorders are common in children

- Typically developing children 3-18.6%
- Children with neurological disorders up to 75%

Neurological disorders associated with higher prevalence include:

- Autism spectrum disorder (ASD)
- Attention deficit hyperactivity disorders (ADHD)
- Cerebral palsy
- Down syndrome

RECOMMENDED HOURS OF SLEEP



DEFINITION OF A SLEEP DISORDER

- Difficulty initiating sleep
- Difficulty maintaining sleep
- Early morning awakening with inability to return to sleep.

- It is often associated with disruption of Family and social wellbeing & Physical or academic lifestyle.

MANAGEMENT OF SLEEP DISORDERS

Non-pharmacological interventions

- First line: Ensure sleep hygiene
- Cognitive behavioral therapy
- Chronotherapy

Pharmacotherapy

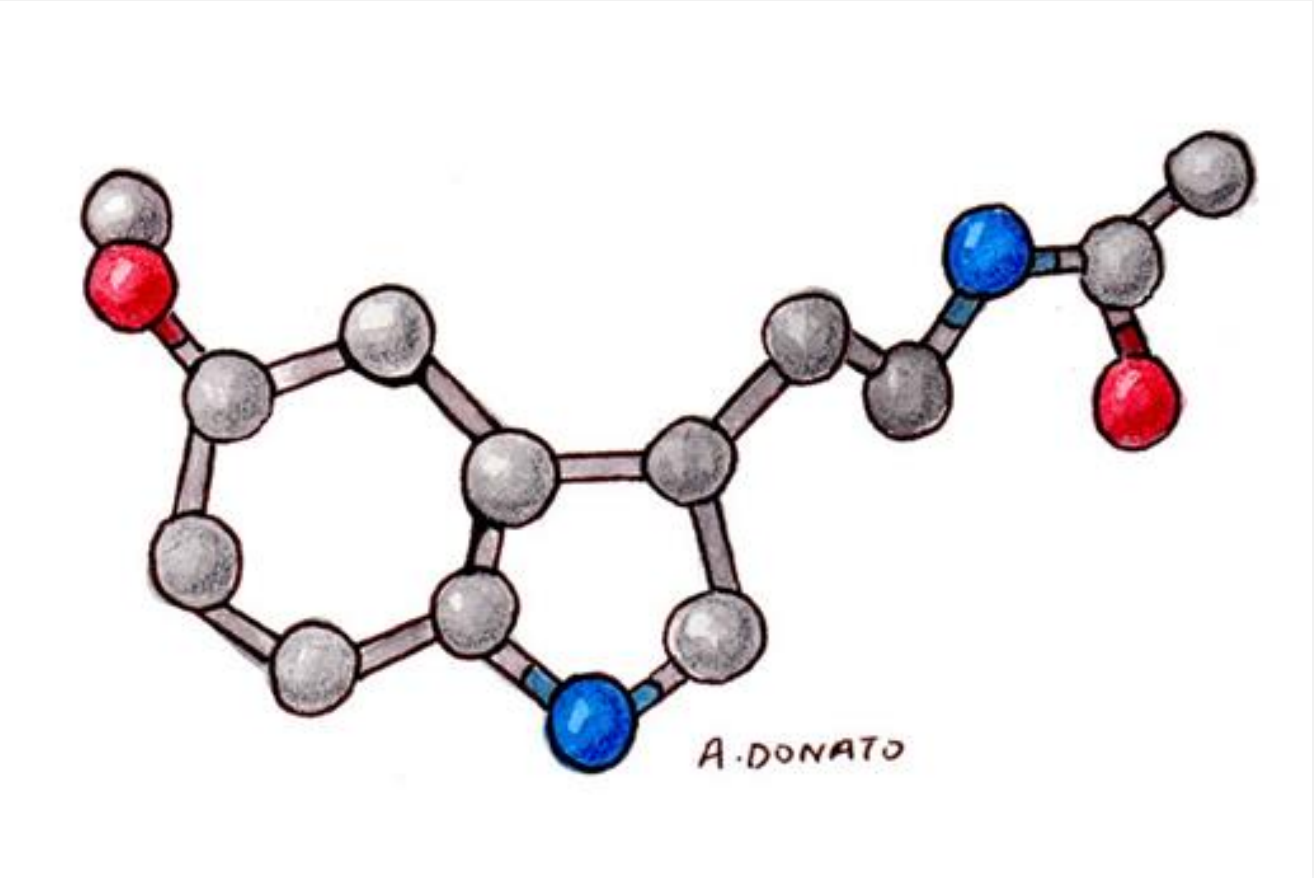
- Melatonin
- Benzodiazepines and others

SLEEP HYGIENE MEASURES

- Limiting daytime naps to 30 minutes or within the standard based of the age of the child
- Avoiding stimulants such as caffeine close to bedtime
- Exercise to promote good quality sleep.
- Avoiding foods that can be disruptive right before sleep e.g. fatty or fried meals, spicy dishes, citrus fruit, and carbonated drinks
- Ensure adequate exposure to natural sunlight
- Establish a regular and relaxing bedtime routine
- Making sure that the sleep environment is pleasant
- Avoiding screen exposure 1-2hours before bedtime

WHAT IS MELATONIN

- Melatonin is the main hormone of the pineal gland.
- The synthesis and secretion of melatonin is enhanced by darkness and inhibited by light.
- The naturally occurring concentrations of melatonin vary considerably with age
- Infants before 3months of age secrete very low levels.
- Melatonin secretion increases and becomes circadian as the child develops



MODE OF ACTION OF MELATONIN

Stabilization of the sleep-wake rhythm is observed in 3-year-old children

Melatonin have generated interested because of its properties

- Effect in circadian rhythm
- Sedative, anxiolytic, anti-inflammatory and hypnotic effects
- Neuroprotective effects
- Antioxidant properties

MELATONIN USE IN CLINICAL PRACTISE

Melatonin dispensing is high and increasing in children with sleep disturbances

A 15-20-fold increase in melatonin prescription noted in Sweden

Despite high usage – Not FDA approved

- Conflicting and inconsistent evidence regarding efficacy
- No guidelines for use of Melatonin in neuro-atypical children

SHORT-TERM SIDE EFFECTS OF MELATONIN

Short-term use of melatonin appears to be safe and well tolerated.

Most common side effects reported include:

- Early morning awakenings
- Morning drowsiness
- Headaches
- Mood swings and irritability

LONG TERM SAFETY OF MELATONIN

- Currently there, is no evidence of serious long-term adverse effects
  - No effects on BMI
  - No effect on pubertal onset
  - No change in height
- Evidence is, however, insufficient evidence

Is melatonin safe to use long term in children with neurodevelopmental disorders?

SCENARIO

A boy of preschool age with autism and early developmental impairment is having severely disrupted sleep, taking 2–3 hours to fall asleep and several wakenings overnight. His parents are desperate for help as the whole family is exhausted. Your team has worked extensively with the family to optimise his sleep routine with minimal improvement. You now feel that he would benefit from melatonin. His parents ask you if there are any long-term effects of taking melatonin.

STRUCTURED CLINICAL QUESTION

In children with neurodevelopmental disorders and neurodisability (patient), what are the long-term side effects (outcome) of melatonin (intervention) to treat disordered sleep?

SEARCH

All searches were performed on 4 January 2024.

There was no Cochrane review covering melatonin use for neurodevelopmental disorders. There were several National institute for Health and Care Excellence guidelines related to melatonin use in our population, but none looked at the question of long-term side effects.

Inclusion criteria

EMBASE Search: (child* or P?ediatric) AND ((neurodevelopment* or intellectual disability or learning disability or autism) AND (adverse reaction* or toxicity or safety or interaction*) AND (Melatonin (Title))

Inclusion criteria was original research, experimental or observational studies, with greater than 2 years follow-up, children and young people with neurodevelopmental disorders as the participants, full text articles available, in English language. 73 results, 5 eligible for inclusion. Other studies mainly excluded due to short follow-up.

Relevant articles identified during the search also had forward and backward reference searching to look for other articles. One further article was identified. Articles were reviewed based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria.[1] 'Critical' outcomes included documentation of adverse events and side effects. Information about growth and puberty was classed as an 'important' outcome.

neurodevelopmental disorders; there was no difference in tolerability between melatonin and placebo.[5]

Once children are given melatonin, a large proportion continue this for many years. In follow-up studies of children taking melatonin, 65%–70% were still taking it after 3 years.[6–8] There has previously been concern that long-term melatonin could have adverse effects when taken long term, including alteration of pubertal onset.[9]

This Archimedes was performed to look at whether there was any evidence of safety concerns in long-term use of melatonin. Many studies claimed to look at 'long term' melatonin treatment, but had treatment periods of only 6 months. For this review we included only studies with at least 2 years follow-up and five studies were found that met this criterion.

Two of the identified studies included patients with neurodisability, two included those with ASD, and one included only those with attention deficit hyperactivity disorder and normal IQ.

None of these were RCTs looking at long-term melatonin use. Two studies were follow-up studies after an initial RCT, lasting 2–3 weeks in one and 13 weeks in the other, followed by an open label phase, where all participants were offered melatonin and followed up prospectively. The first used daily diaries and the other three monthly questionnaires. Long-term sleep outcomes were generally compared with measures at baseline and not with the initially untreated control group. The remaining three were retrospective cohort studies.

All of the studies were positive about the effects of melatonin on sleep outcomes and parental perception of its use, including behavioural and educational effects, with side effects and adverse events only a minor outcome of interest.

The main side effects noted in the studies were irritability, drowsiness or excessive sedation. Fatigue, anxiety, bed-wetting, dizziness, mood swings and sleep maintenance insomnia were also reported. The incidence of side effects varied greatly, depending on how the question was asked, between 84% in Malow's study[10] to 0% in Carr's study.[11] Carr also used a Likert Score to ask about a range of possible symptoms, with irritability scoring the greatest with a mean of 0.27 with a range between 0, never to 4, very often. Up to 4% of children stopped taking the melatonin due to side effects.

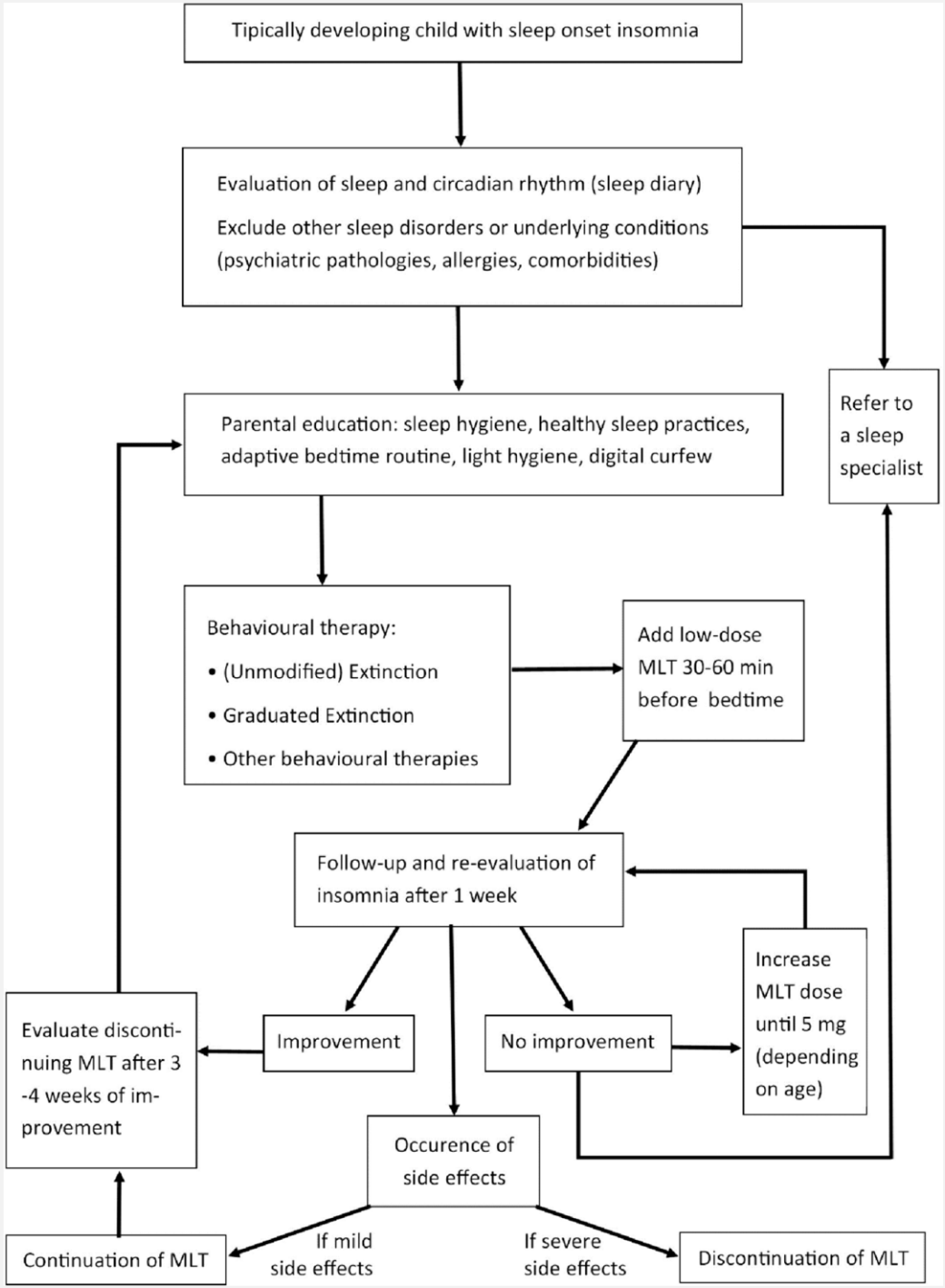
Two studies comprising only 70 children looked at effects on puberty and found no adverse effects.[10 11] One study looked at effect on growth and found no change in body mass index, but height outcomes were not presented.[10] None of the papers covered effects on education, cognition, social interaction, mood or attention span objectively, other than

MELATONIN IN TYPICALLY DEVELOPING CHILDREN

Melatonin has been shown to be effective

European guidelines use melatonin as first line pharmacotherapy

- Duration of therapy is however not clear
- Dosage regimen also not clear


Tipically developing child with sleep onset insomnia
Evaluation of sleep and circadian rhythm (sleep diary)
Exclude other sleep disorders or underlying conditions (psychiatric pathologies, allergies, comorbidities)
Refer to a sleep specialist
Parental education: sleep hygiene, healthy sleep practices, adaptive bedtime routine, light hygiene, digital curfew
Behavioural therapy:
• (Unmodified) Extinction
• Graduated Extinction
• Other behavioural therapies
Add low-dose MLT 30-60 min before bedtime
Follow-up and re-evaluation of insomnia after 1 week
Increase MLT dose until 5 mg (depending on age)
Evaluate discontinuing MLT after 3-4 weeks of improvement
Improvement
No improvement
Occurence of side effects
Continuation of MLT
If mild side effects
If severe side effects
Discontinuation of MLT

SLEEP DISTURBANCES IN CHILDREN LIVING WITH ASD

40% - 86% of children living with ASD experience sleep disorders

Children with ASD have abnormal sleep architecture as measured by polysomnography (PSG).

Disrupted sleep in children with ASD is associated with problematic daytime behaviour - higher rates of aggression, self-injury, anxiety, hyperactivity, and inattention

low melatonin levels

MELATONIN USE IN ASD

Studies report conflicting results

Studies show

- Improved sleep duration
- Enhance sleep quality
- Reduced sleep latency
- Increased morning alertness

SLEEP DISTURBANCES IN CHILDREN WITH ADHD

Sleep disturbances and disorders occur in 70% - 85% of children with ADHD

Unhealthy sleep practices

- Genetic predisposition and Neurotransmitter imbalance

Comorbid conditions

Side effect of stimulant treatment

MELATONIN USE IN ADHD

The association between ADHD and sleep disturbances has been extensively investigated.

Meta-analysis and RCTs show

- improved sleep duration
- enhanced sleep quality
- reduced sleep latency
- increased morning alertness

Evidence supports behavioural interventions and melatonin.

MELATONIN USE IN CEREBRAL PALSY

Prevalence is 20-24% in children with CP

Muscle spasms and pain

Comorbid conditions

Improvement in sleep quality

Reduction in sleep disturbances

MELATONIN IN NEURODEVELOPMENTAL DISABILITIES

Sleep disorders occur in 13-86% of individuals with NDD

Melatonin

- Decreased sleep latency by a mean of 34mins
- Increased total sleep time by a mean of 50mins
- Less significantly decreased the number of awakenings per night

MELATONIN IN SYNDROMES

Down syndrome – improved sleep quality and duration

Angelman syndrome – sleep onset insomnia and sleep maintenance problems

- Melatonin levels are low, and melatonin treatment is effective

Tuberous sclerosis complex – multiple night awakenings and reduced total sleep time

- Melatonin reduce SOL and improve total sleep

Rett and Sanfilippo syndrome – melatonin has been found to be effective for sleep disorders

Magenis syndrome is characterized by daytime somnolence, night waking and early wakings- Caused by an inverted circadian melatonin rhythm

EFFECT OF MELATONIN IN PERINATAL ASPHYXIA

Renders neuroprotection through

- Strong anti-apoptosis properties
- Antioxidant and free radical scavenger action
- Anti-inflammatory properties
- Anti-excitatory effects

Potential to limit damage during the latent phase (6-15hours)

Reduce secondary phase of neuronal death

Crosses physiological barriers including the blood brain barrier

MELATONIN USE IN HYPOXIC ISCHEMIC ENCEPHALOPATHY

Neurodevelopmental outcomes

- No statistical differences in the cognitive scale at six months
- No statistical differences for the other components of neurologic development

Death in the neonatal period

- Certainty of evidence of this was low for a very small sample size

No long term follow up studies

MELATONIN USE IN HYPOXIC ISCHEMIC ENCEPHALOPATHY

Melatonin is considered safe in the neonatal population

Side effects

- Hypnotic and sedative properties

Doses as high as 10mg/kg/dose

MELATONIN USE IN REFRACTORY EPILEPSY

Melatonin has been investigated as an adjuvant therapy in epilepsy

Improvements have been noted

- Reduction in seizure frequency
- Improved sleep and quality of life

Data is still inconclusive about its efficacy

MELATONIN USE IN HEADACHE

Patients with tension type headache are commonly afflicted with insomnia and daytime sleepiness

Sleep disturbance is associated with emotional and psychological disturbances

A bidirectional relationship appears to connect tension-type headache and circadian dysregulation

Data for use in for treatment in headaches is insufficient

MELATONIN IN ANAESTHESIA

Anxiolytic – there is conflicting evidence for the use of melatonin as a pre-op anxiolytic in children

Anesthetic induction - Evidence for induction compliance was conflicting

- One study found no difference between melatonin and midazolam
- Another showed lower induction compliance

Sedation – use of different sedation scales

- Melatonin was as good a sedative as midazolam

MELATONIN IN CONSCIOUS SEDATION

Melatonin has been used to induce sleep in EEG laboratory

- Melatonin can induce sleep in high percentage
- Melatonin does not interfere with EEG interpretation, nor does it hide epileptic abnormalities
- Sleep onset was shorter when melatonin was compared to chloral hydrate

Brainstem auditory evoked potentials – reduced the need for general anesthesia

Brain magnetic resonance imaging– successfully performed brain MRI in 50% of cases

Randomised Controlled Trial

ANNALS OF MEDICINE & SURGERY

OPEN

Melatonin versus chloral hydrate on sleep induction for recording electroencephalography in children: a randomized clinical trial

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Background: Electroencephalography (EEG) plays an essential role in the diagnosis of seizures. EEG recording in children is done with partial sleep deprivation and sedative drugs. To compare the effectiveness of melatonin and chloral hydrate on sleep induction and EEG recording in children.

Materials and methods: In a parallel blinded randomized clinical trial study, 78 patients (6 months–5 years) were included to record EEG. Patients were randomly divided into two groups to receive melatonin (0.4 mg/kg) or chloral hydrate (0.5 ml/kg). After receiving the sedative drug, the start and duration of sedation, recovery time, side effects, and epileptiform waves in the EEG were recorded. The data was analyzed using SPSS version 16, and the significance level was determined to be less than 0.05.

Results: A total of 78 children, including 34 girls (43.6%) and 44 boys (56.4%) (average age of 27.15 ± 17.15 months), were examined. Success in the induction of sedation was reported by melatonin in 36 patients (92%) and chloral hydrate in 37 patients (95%), which was similar between the two drugs ($P = 0.5$). The start time ($P = 0.134$) and the duration of sedation ($P = 0.408$) were alike between the two drugs. However, compared to the chloral hydrate, the recovery time in the melatonin group was significantly shorter ($P < 0.001$). Side effects were not seen in melatonin, while six children (15%) using chloral hydrate had mild side effects ($P = 0.013$). Epileptiform waves in EEGs were reported to be similar and positive for melatonin in 18 children (50%) and chloral hydrate in 16 children (43%) ($P = 0.410$).

Conclusion: The findings show that using melatonin in the dose prescribed in this study had similar effects to success in inducing sedation with the minimum quantity of chloral hydrate. Regardless of the start time and duration of sedation, the shorter recovery time and the absence of side effects are the advantages of using melatonin.

Keywords: child, chloral hydrate, electroencephalography, hypnotics and sedatives, melatonin, seizures

HIGHLIGHTS

- This trial demonstrated that melatonin had similar effects to chloral hydrate in inducing sleep.
- Melatonin had the advantage of causing a shorter recovery time and fewer side effects.
- The onset time and duration of sedation are similar when using melatonin and chloral hydrate.

COST OF MELATONIN

- The cost of melatonin, one month supply of 2mg tablets ranges from R278.68 – R405.06

WESTERN CAPE EDL QUIDELINE

ANNEXURE B

USE OF MELATONIN IN CHILDREN WITH SLEEP DISORDERS

INDICATIONS:

- Children from subspecialist clinics (neurology, developmental paediatrics and child psychiatry) with an underlying developmental, psychiatric or neurological diagnosis such as ADHD, Learning difficulties and Autism, who present with a reported minimum 3 month history of impaired sleep at screening

Or

- Newly acquired sleep disorders as part of an associated acute medical in-patient condition

who meet the definition below, (consultant prescribed)

Sleep disorder 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.

Intervention

Sleep hygiene*
Behavioural interventions

↓ No response / Not effective

Initiate melatonin 2mg (Circadin®) and, if no response, increase by 2mg up to a maximum of 10 mg (specialist prescribed in context of specialist / subspecialist services as above / code list)

Monitor with sleep diaries.

Use for a minimum of one month.
Once sleep has settled continue at minimum effective dose.
Consider discontinuing melatonin once sleep has settled (after 6 months)

↓

If relapse occurs repeat re-introduction as above.

PROPOSAL FOR MELATONIN STUDY AT TYGERBERG HOSPITAL

- Melatonin is prescribed for sleep disorders at Tygerberg Hospital
- Most patients have ASD
- The Western Cape protocol is used - advocates interrupting therapy after 6months

RESEARCH QUESTION

- Describe the use, side effects and duration of melatonin therapy in neuro-atypical children attending the Pediatric neurology and neurodevelopmental clinic at Tygerberg Hospital?

OBJECTIVES

Main objective

- Describe the use of melatonin in neuro-atypical children at Tygerberg hospital over an 18month period.

Secondary objectives

- Describe the population of patients receiving melatonin.
- Describe the dose, duration and side-effects of melatonin use.
- Describe the experience of the parents of children using melatonin with regards to melatonin benefits.
- To determine if melatonin therapy was interrupted, the reason for interruption, who interrupted it and if it was successful.

METHODOLOGY

Study design

This is a retrospective descriptive study.

Study setting

Pediatric neurology and neurodevelopment out-patients clinic.

Study population

Children and adolescents less than 13 years receiving melatonin therapy for sleep disorders attending the pediatric neurology and neurodevelopmental services at Tygerberg hospital.

METHODOLOGY

Sample size

An estimated 60 patients on melatonin therapy attending Pediatric neurology and neurodevelopmental clinic.

Data collection

Pediatric neurology and neurodevelopmental clinic records will be reviewed for patients on melatonin and captured on REDCap.

STRENGTHS AND LIMITATIONS

Strengths

- There is no data on melatonin use in Low to middle income countries.
- There is conflicting data and no global guidelines on the use of melatonin in children.
- Data can inform pharmacy and guide on resource allocation.

Limitations

- Retrospective study based on data already available.
- Small cohort of patients.
- Single enter and can not be generalized for other centers.

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