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Short communication

Protocol for a longitudinal study of melatonin therapy and cost effectiveness analysis in stimulant-treated children with ADHD and insomnia: An N-of-1 trial

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ABSTRACT

Background: Children with ADHD and sleep problems have more caregiver deficits and decreased school attendance than children with ADHD but without a sleep problem. We conducted an N-of-1 trial of melatonin for children with ADHD on stimulants. As a follow-up study, we aim to conduct a cost effectiveness analysis (CEA) of melatonin therapy by comparing costs of this condition (of using melatonin) to costs of the baseline condition (usual care with no N-of-1 trial).
Methods: The CEA will compare participants who remained on melatonin vs those who chose to cease melatonin. Costs will be determined by medication cost to the caregiver(s), school/work absences, other sleep remedy costs, and health service utilization costs, including incidentals like parking. These costs will be determined at baseline, end of 6-week trial, and 6 months post-trial. We will also calculate Quality-Adjusted Life-Years (QALY) based on responses to PedsQL or SF-12v2 for patients and caregiver(s) and assess differences between remaining on melatonin or not; and assess the intermediate-term effectiveness and adverse effects of melatonin at 6 months.
Discussion: We hypothesize that shorter sleep-onset-latency will be associated with improved QALYs for patients and caregivers. We also expect that targeting melatonin to positive responders will be cost effective both for individuals and society. Cost per QALY for positive responders to melatonin is useful for doctors when creating treatment plans since melatonin is not an over-the-counter pharmaceutical in Australia.
Trial registration number: ACTRN12614000542695.

1. Background

Approximately 5% of children and adolescents have ADHD [2]; of those, up to 85% [3] will experience problems with sleep. It has been shown that children with ADHD and sleep problems have more caregiver deficits, poorer quality of life, poorer family functioning, and decreased school attendance than children with ADHD but without a sleep problem [4].

Craig et al. [5] found that up to 12% of functional and social impairment variance can be attributed to sleep problems rather than ADHD itself, and that these sleep problems have a significant negative impact on children's functioning and quality of life. Poor sleep management has also been shown to negatively impact response to ADHD medication [6].

Sung, et el, first looked at the effects of sleep problems in children with ADHD and further effects on the family in 2008 using a cross sectional survey [7]. That study found that primary caregivers of children with moderate to severe sleep problems were 2.7 times more likely to be clinically depressed, stressed, or anxious, in comparison to primary caregivers of children without sleep problems.

Abbreviations: ADHD, Attention Deficiency/Hyperactivity Disorder; QALY, Quality-adjusted life-year; DSM, Diagnostic and Statistical Manual of Mental Disorders; GP, General Practitioner; ICUR, Incremental cost-utility ratio; CEAC, Cost Effectiveness Acceptability Curve.

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Moreover, Sung et al. reported that a higher percentage of primary caregivers of children with ADHD and sleep problems (along with their spouses) were more likely to be late for work [7] than caregiver(s) of children with ADHD but without sleep problems. These findings are important for shedding light on the economic impact on the family of children with sleep disorders because lateness to work can correlate to missing wages. Although not recorded in the Sung et al. survey, there can also be added stress that accompanies fear of being late to work. Another economic factor in relation to the effects of poor sleep patterns was reported by Pelayo and Yuen: "high costs for direct consumption of medical care [can be] offset by early diagnosis and treatment of pediatric sleep disorders" [8]. Importantly, the Sung study also found that less than half of affected children's primary care doctor enquired about the child's sleep patterns (both before and after prescribing ADHD medications) [7].

The aim of this study is to conduct a longitudinal study and a cost-effectiveness analysis that examines correlation between increased amount of children's sleep and parental quality of life.

Longitudinal study aims:

1. Assess how many patients on melatonin at follow-up, and if not on still melatonin, why not.
2. Determine whether patients in our study population had any intermediate-term adverse effects from the melatonin at follow-up, which has been studied in other pediatric populations [10,11]

Health Economics Aims:

1. To assess change in quality of life of caregiver(s) using the QualityMetric's SF-12v2 health survey with one-week recall period (acute) and changes in quality of life of patients using the PedsQL between control and intervention, during the 6-week trial.
2. To assess intermediate term (6 months) differences in quality of life between patients and caregiver(s) whose child remained on melatonin to those who chose to cease taking regular melatonin for any reason.
3. To estimate the costs associated with melatonin treatment compared to standard care across four groups at end of 6-week trial, and at 6 months post-trial. See definition of four groups, and cost variables in Methods.
4. To determine the incremental cost per QALY for parent(s) across four groups, as defined in Methods.

2. Methods

2.1. Study design and procedure

In order to answer the question about patient and caregivers' quality of life, the effectiveness of melatonin as a sleep supplement for children with ADHD and sleep problems must be determined. We are currently conducting the Melatonin in Youth: N-of-1 trial in a stimulant-treated ADHD Population study (MYNAP) [1].

This trial is a series of individual double-blind N-of-1 randomized controlled trials [9]. The schema of the study design for the MYNAP trial is shown below as Fig. 1, with each period accounting for one week of time (so six weeks total).

2.2. Participant recruitment

This study has recruited caregivers of Australian children aged 6–17 who have been diagnosed with ADHD using DSM IV or DSM V criteria and who are currently attending school full-time. The full inclusion/exclusion criteria were as follows:

Inclusion Criteria.

1. Children and adolescents between 6 and 17 years
2. Diagnosis of ADHD according to DSM- IV or V criteria
3. On a stable dose of stimulant medication (e.g., Ritalin®, Ritalin LA, Concerta®) for at least 1 month prior to the study. The dosage will need to remain constant during the study (6 weeks) for the data to be included in analysis.
4. Sleep Onset Latency of ≥45 min, ≥3 nights/week, for ≥1 month as confirmed by parent/guardian.
5. If previously on melatonin, have ceased it at least two weeks previously.
6. Informed consent form by parent/guardian for participants under age 16, assent by child (if 12–16 years), or informed consent form by the child if over 16)

Exclusion Criteria.

1. Children with co-morbid psychiatric/neurological diagnoses that may affect sleep, including:
   - Autism/pervasive development disorder
   - Brain injury
   - Cerebral palsy

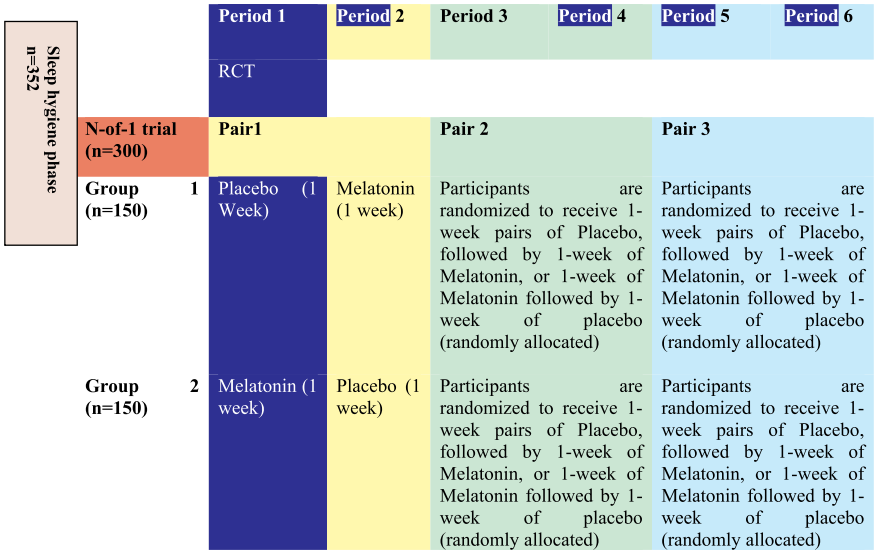

Fig. 1. Schema of study design.

- Uncontrolled major depression
- Migraines
- Posttraumatic stress disorder
- Psychosis or schizophrenia
- Seizure disorder (i.e. seizure in the last 12 months)

2. Children with any of the following disorders of sleep:
   - Untreated obstructive sleep apnoea
   - Untreated sleep related breathing disorder (any form of trouble during sleep associated with breathing, such as need for oxygen, underlying lung disease outside of stable asthma)
   - Untreated narcolepsy
   - Sleep related movement disorders (head banging or body rocking that results in insomnia)
   - Parasomnias (current, regular sleep walking or night terrors)
   - Adjustment insomnia (acute – related to hospitalisation, travel etc)
   - Insomnia due to drug use, or mental health issue
   - Secondary enuresis
3. Known allergy or hypersensitivity to melatonin or other study drug ingredients; Mannitol, Dextrose, Cellulose, Crospovidone, Calcium Carbonate, Xylitol, Dicalcium Phosphate, Vegetable Stearic Acid, Vegetable Magnesium Stearate, Silica
4. Children on immunosuppressive drugs, blood pressure drugs, SSRIs or anticoagulant drugs;
5. Children not on regular sedatives or hypnotics whose caregiver(s) do not agree not to commence these treatments regularly during the course of the trial.
6. Caregiver(s) of children on sedatives or hypnotics who do not agree not to alter the daily dose of these for the duration of the trial.
7. Patients with active or uncontrolled hormonal disorders, or diabetes, or active liver disease, or abnormal kidney function or untreated kidney disease, or any blood clotting disorders;
8. Participants who disagree to not driving or operating heavy machinery within 8 h of ingestion of study medication;
9. Breastfeeding or pregnant adolescents
10. Adolescent girls 12 years and above who are menstruating and sexually active
11. Children whose parent/primary caregiver does not understand English or have a phone.

Participants were recruited by a number of mechanisms. We sent informational e-mails with a brochure advertising our study to local pediatricians/GPs with an interest in ADHD. Further, we created a strong presence on social media (Facebook, Twitter, Instagram) to recruit interested parent groups. For example, we made posts on Facebook Groups like 'ADHD Parent Support Group Australia' in order to advertise our study with links in the posts to initial interest forms on our study's website. Lastly, we reached out to ADHD coaches and national leaders in ADHD parent support, to pass information about our study to their clientele.

We gained informed consent using an ethics-committee-approved consent form to be signed by the parent/caregiver of participants and the patients' doctors, and assent form from the child if 12–16 years old. Children 16 or over could sign the consent form themselves.

2.3. Data collection

The aims of this study are to determine how melatonin use affects both quality of life and its economic impact. Thus, we will be collecting separate data points for these separate outcomes. During the 6-week study, patient's caregivers were asked to fill out an online sleep diary every night for their child using a secure online portal. Caregivers were asked to fill out a QualityMetric's SF-12v2 [19] health survey and a PedsQL [18] survey on behalf of their child, if their child was unable to fill it out on his/her own, at the end of each week of the 6-week trial. Caregivers were also asked to fill out both of these surveys six months after the trial ended. In order to perform the cost effectiveness analysis, we asked about costs to the family in caregiver online surveys at baseline and at 6 months post-trial.

2.4. Outcome measurements

The timing of outcome assessments for specific outcome measures is shown in Fig. 2.

1. Baseline assessment as part of the main trial baseline e-CRFs (Case Report Forms)
2. Weekly assessment during main trial by e-CRF
3. Six-week assessment as part of the main trial final e-CRFs
4. Postal 6-month CRFs and sleep diary (or e-CRF)

Ongoing melatonin use is defined as taking melatonin 4 or more times per week over the previous month.

Outcome Measures for Health Economics and Intermediate-term Follow-up:

1. Out of pocket cost of melatonin & any other sleep-related medications, at baseline and recalling a 4-week period at 6 months

This will be obtained from a survey based on that used in Genereaux et al., 2015 to determine direct and indirect out-of-pocket costs to patients' families [12,13]. Questions will include, but are not limited to:

"How many days of employed work have your family's income-earners had to miss over the past (12 weeks, 6 months) due to the child's absence from school?", "How much money has your family had to pay out of pocket for melatonin?", "How much money has your family had to pay for any medication during the past (12 weeks, 6 months) for your child with ADHD and sleep problems?" "What health care services has your child utilized in the past (12 weeks, 6 months) weeks (if any)?"

2. Name and dose of melatonin, & sleep-related medications, at Baseline, during 6-week trial, and at 6 months post-trial
3. Name, dose and cost of ADHD medications, at Baseline, during 6-week trial, and at 6 months post-trial
4. Days absent from school, days absent from work, at Baseline, during 6-week trial, and recalling a 4-week period at 6 months post-trial
5. Health service utilization (GP visits, hospitalisations (days, length of stay), emergency (without overnight stay), paediatrician) using a diary at baseline, and recalling a 4-week period at 6 months post-trial (NB: hospitalisation also during 6-week trial)
6. Questionnaire on known (and unknown) adverse events related to melatonin use at during 6-week trial, recalling a 4-week period at 6 months post-trial, such as headache, dizziness, abdominal discomfort, irritability, confusion, depression, and nausea
7. Questionnaire to parent on school performance of child at baseline, end of 6-week trial only, and recalling a 4-week period at 6 months post-trial
8. Sleep diary (1-week) at Baseline, and 6 months post-trial, including questions such as "how long did it take for your child to fall asleep", "how many times did your child wake up during the night?"
9. PedsQL [18] (children) at Baseline, weekly during 6-week trial, and 6 months post-trial

The PedsQL Measurement Model [18] measures health-related quality of life (HRQOL) in children and adolescents. It is a 23-item measure that takes 4 min to complete and is developmentally appropriate to different age groups. It contains 4 Multidimensional Scales, namely, Physical Functioning, Emotional Functioning, Social Functioning, School Functioning and 3 Summary Scores, namely, Total Scale Score, Physical Health Summary Score, Psychosocial Health Summary Score.

Assessment	Who?	Baseline	Weekly (6-week trial)	6-mths
Melatonin (non-trial, name, dose)	C	x	x	x
Melatonin Cost (out of pocket)	C	x		x
Sleep-related medications (Name, dose, out of pocket cost)	C	x	x	x
ADHD medications, (Name, dose, out of pocket cost)	C	x	x	x
School absence (child) (is reason for school absence due to lack of sleep)	C	x	x	x
Work absence (both parents)	P	x	x	x
Health Service Utilisation (*via a diary*):				
GP visits	C	x		x
Hospital admissions (overnight in ward)	C	x	x	x
Hospital length of stay	C	x	x	x
Emergency Dept visit (without overnight stay)	C	x		x
Pediatrician visits	C	x		x
School Performance	C	x	x*	x
Adverse Events (known, unknown, related to melatonin?)	C	x	x	x
Sleep Diary (1 week)	C	x		x
PedsQL	C	x	x	x
SF-12 (v2) 4-week recall	P	x		x
SF-12 (v2) 1-week recall	P		x	
Household income	P	x		x

*End of trial only
C= child; P=parent/guardian

Fig. 2. Schedule of assessments.

10. QualityMetric's SF-12v2 [19] health survey with one-week recall period (acute) for parent during the 6-week trial. SF-12v2 is a measure of physical and mental health. It contains eight health domains, namely: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health and each survey provides psychometrically based physical component summary (PCS) and mental component summary (MCS) scores. The SF-12v2 ratings will be transferred to SF-6 score values that are used in the QALY calculations.

We define participants as a 'melatonin responder' if their averaged sleep-onset latency (SOL) over all melatonin treatment periods is less than their averaged SOL over all placebo treatment periods by a minimally clinically important difference of 15 min[17] (Group A).

Group B is defined as a decreased SOL with either melatonin or placebo of at least 15 min compared to baseline, but similar effect for both.

Group C is defined as uncertain response (no consistent response in either direction to melatonin or placebo).

Group D is defined as SOL on placebo is less than their SOL on melatonin by a minimally important clinical difference of 15 min.

Costs will be determined based on cost of medication to parents, school absences, work absences, costs of medicines indicated for sleep problems, and health service utilization, including incidental costs such as parking, at the end of the 6-week trial and 6 months later.

2.5. Economic analysis

The within trial economic analysis will be conducted on an intention-to-treat basis. This means that all patients will be analyzed within the group to which they were allocated for that period of the study, regardless of, for example, whether or not they had taken the melatonin or placebo as expected. With regards to handling missing data, we will conduct a sensitivity analysis using various missing data methods. These methods will include: complete-case analysis for cost outcome measures, and last observation carried forward for clinical measures.

A within-trial, cost–utility analysis will be conducted. It will estimate any potential incremental gain in utility, measured in quality-adjusted life years (QALYs), as well as the incremental change in costs between those who continue melatonin and those who do not. Responses to the SF-12v2 will be converted into SF-6D utility values using the Australian utility algorithm [14] in order to calculate QALYs [15]. PedsQL responses will be converted into utility values using a mapping algorithm. The primary outcome will be the incremental cost–utility ratio (ICUR) with incremental costs, benefits and net monetary benefits also reported, where the ICUR is estimated as per the following equation:

$$ICUR = \frac{C_1 - C_0}{QALY_1 - QALY_0}$$

Where C_1 and C_0 are the costs for the intervention and control groups respectively and $QALY_1$ and $QALY_0$ are the quality adjusted life years for the intervention and control groups respectively.

In order to estimate the mean incremental cost and incremental effect (QALY gain) associated with melatonin, regression analysis will be

undertaken. The system of a seemingly unrelated regression method will be used, which is generally robust to skewed data and to allow for any correlation between costs and effects [16]. The cost and QALY regressions will be run simultaneously, with allocation to intervention included as an explanatory variable along with baseline demographic and sleep descriptive variables being included (as covariates) only where an a priori expectation exists that the covariate might be associated with cost and/or QALY scores.

Assuming that neither melatonin nor placebo is both more costly and less effective, the ICUR will be reported. However, if either the incremental cost and/or incremental effect is negative, owing to the potential for misinterpretation, the incremental net benefit will be calculated at the cost-effectiveness threshold (λ) value of $50,000 per quality adjusted life year (QALY) [15]. Additionally, in order to estimate the level of uncertainty associated with the decision as to whether or not melatonin is cost-effective, the non-parametric bootstrap technique with 5,000 replications sampled (with replacement) will be used to estimate the probability that the intervention is cost-effective at a λ of $50,000 per QALY. In addition, the probability of the intervention being cost-effective at alternative threshold values will be presented using a cost-effectiveness acceptability curve (CEAC) [16,17].

2.6. Limitations

There are many possible confounding factors to rating quality of life of caregiver in relation to their child's sleep patterns. Perception of quality of life could be influenced by a wide variety of factors, for example daily stressors of home life, caring for other children, etc. However, given that these surveys will be taken over a short period of time (initially within a total of 6 weeks from each other), the survey is taken in the same context as filling out the sleep diary at the 6 month follow-up, and that we will recruit enough participants to account for variance, we will accept that the change in answers to the questions on the survey is at least partially due to the child's changed sleep patterns.

3. Discussion

The relevant stakeholders for this research are caregivers of children with ADHD, who have trouble sleeping, doctors of children with ADHD, and the patients themselves. We hope that this research will generate new knowledge about the societal effects of ADHD and sleep troubles. ADHD is a very prevalent disease that not only effects the person with symptoms, but those caring for them and society at large. Moreover, the associated effects of poor sleep for children with ADHD, and the further effects on caregivers, seems to not be adequately addressed at this time. We hypothesize that caregivers' and patients' quality life will improve when their child's sleep onset latency is decreased using melatonin. This study is replicable in other countries with easy access to home internet and a reliable pharmacy to administer the melatonin and placebo medications.

This outcome will be significant because this information can be used as part of development of management plans for poor sleep, if present, when a patient is first diagnosed with ADHD. This is especially important in Australia (where this study took place), because melatonin requires a prescription from one's doctor in that country. Caregivers should be made aware of the common association between ADHD and insomnia and what options they have to manage their children's sleep problems, including ones that will improve their own perceived quality of life. We hope that those doctors with an interest in ADHD treatment will use this knowledge in creating a treatment plan for their patients.

Ethics approval and consent to participate

This study has been cleared by:

Human Medical Research Ethics Committee of The University of Queensland in accordance with the National Health and Medical Research Council's guidelines (Ethics approval number 2012000999) and Mater Human Research Ethics Committee (#2012000999 (HREC/14/MHS/28).

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Declaration of competing interest

The authors have no competing interests to declare.

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