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Feasibility of 3-month melatonin supplementation for brain oxidative stress and sleep in mild cognitive impairment: protocol for a randomised, placebo-controlled study

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ABSTRACT

Introduction Melatonin has multiple proposed therapeutic benefits including antioxidant properties, synchronisation of the circadian system and lowering of blood pressure. In this protocol, we outline a randomised controlled trial to assess the feasibility, acceptability and tolerability of higher dose (25 mg) melatonin to target brain oxidative stress and sleep disturbance in older adults with mild cognitive impairment (MCI).

Methods and analysis The study design is a randomised double-blind, placebo-controlled, parallel group trial. Forty individuals with MCI will be recruited from the Healthy Brain Ageing Clinic, University of Sydney and from the community, and randomised to receive either 25 mg oral melatonin or placebo nightly for 12 weeks. The primary outcomes are feasibility of recruitment, acceptability of intervention and adherence to trial medication at 12 weeks. Secondary outcomes will include the effect of melatonin on brain oxidative stress as measured by magnetic resonance spectroscopy, blood pressure, blood biomarkers, mood, cognition and sleep. Outcomes will be collected at 6 and 12 weeks. The results of this feasibility trial will inform a future conclusive randomised controlled trial to specifically test the efficacy of melatonin on modifiable risk factors of dementia, as well as cognition and brain function. This will be the first trial to investigate the effect of melatonin in the population with MCI in this way, with the future aim of using this approach to reduce progression to dementia.

Ethics and dissemination This protocol has been approved by the Sydney Local Health District Ethics Committee (X18-0077). This randomised controlled trial will be conducted in compliance with the protocol published in the registry, the International Conference for Harmonisation on Good Clinical Practice and all other applicable regulatory requirements. The findings of the trial will be disseminated via conferences, publications and media, as applicable. Participants will be informed of results of the study at the conclusion of the trial. Eligible authors will include investigators who are involved in

Strengths and limitations of this study

► This is the first study to investigate the effect of melatonin on brain oxidative stress in a population with mild cognitive impairment.
► The study uses a higher dose of 25 mg, which allows the role of melatonin as an antioxidant to be explored.
► The study examines many pathways to dementia, rather than a single outcome.
► This study is a pilot study and will not have the power to give definitive efficacy information.
► This study is not investigating the effects of melatonin withdrawal, which could be affected if melatonin were incorporated into treatment.

the conception and design of the study, the conduct of the trial, the analysis of the results, and reporting and presentation of study findings.

Trial registration number Australian and New Zealand Clinical Trials Registry (ANZCTRN 12619000876190).

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BACKGROUND

Neurodegenerative dementias represent a significant socioeconomic burden, currently affecting 46.8 million people worldwide, with numbers expected to double every 20 years.[1] Due to this rising incidence and the current lack of a cure, there has been increased focus on developing novel, preventative measures to slow cognitive decline in those who are at risk of developing dementia. It is believed that the neurobiological changes associated with the most common form of dementia, Alzheimer's disease (AD), commence 20–30 years prior to clinical diagnosis,[2] suggesting

there is a long prodromal phase. Therefore, preventative approaches targeting multiple modifiable risk factors for cognitive decline, early in the disease course, will likely have the best chance at modifying the clinical trajectory of AD.

Mild cognitive impairment (MCI) is defined as cognitive decline greater than the average for an individual's age and education level, without significantly affecting daily activities.[3] As MCI is considered a prodromal phase for dementia, those with MCI can be considered a key population group to target with prevention strategies, to decelerate the rate of cognitive decline, and potentially prevent or delay dementia onset. This subgroup has a high rate of conversion to dementia, with an estimate of 53.7% developing AD and 15.7% developing other forms of dementia within 5 years.[4] Recent studies have estimated that approximately 35% of dementia risk is attributable to modifiable health and lifestyle factors such as midlife obesity, low educational attainment, diabetes, midlife hypertension, hearing loss, later life depression, physical inactivity, smoking and social isolation.[5] Sleep and circadian disturbances are also common in the population with MCI, and are also increasingly recognised as potential risk factors for dementia[6]; thus, they may also be viable secondary prevention targets.[7]

Oxidative stress levels, characterised as the imbalance between the oxidant/antioxidant state of brain cells, have been shown to be involved in the progression of many neurodegenerative diseases including dementia.[8] Individuals with MCI have increased brain oxidative stress compared with those who are cognitively normal.[9] Furthermore, antioxidant treatment in animal models has demonstrated significant improvements in AD-like disease processes.[10] Importantly, dietary supplementation has been shown to modify brain oxidative stress levels in older adults,[11] which signifies that this pathway can be exogenously modified and targeted for dementia interventions.

Melatonin is an endogenous hormone secreted from the pineal gland that has a major role in the synchronisation of the body's circadian rhythm. This also strongly influences sleep–wake cycles, with melatonin secretion initiating a cascade of physiological events that cause increases in sleep propensity.[12] It has been shown to have many properties including antioxidant, anti-inflammatory, antihypertensive, anxiolytic and antiapoptotic effects.[13–15] These properties have all been suggested as possible mechanisms by which to slow neurodegeneration, cognitive decline and dementia.[16 17] Melatonin also affects mood, behaviour, sleep efficiency and total sleep time, which are independently associated with dementia risk.[18–20] Additionally, animal studies have demonstrated that the administration of melatonin may interrupt the production and accretion of both neurofibrillary plaques and tangles, and has prevented the death of cells exposed to toxic levels of amyloid-beta, which are pathological signs of AD.[21] It is timely therefore to propose a study to investigate the use of melatonin as a possible preventative

treatment, given that it may potentially curtail neurodegenerative pathways.

The varying effects of exogenous melatonin have been previously examined in different populations. To date, evidence for the effectiveness of melatonin in dementia has been limited to improvements in sleep efficiency and total sleep time, with any cognitive benefits being attributable to improved sleep rather than a direct effect of melatonin.[22] This lack of a direct effect may be due to the late stage of disease studied, where neurodegeneration was potentially too advanced and therefore irreversible. Consequently, intervention in the earlier stages of disease prior to extensive cognitive decline, for example, in those with MCI, may be more impactful. The current evidence for an antineurodegenerative effect of melatonin in the prodromal phase of dementia including in MCI is very limited and may be dose dependent. Currently, the dosage in humans that would be required to target brain oxidative stress has not yet been established. Previous retrospective studies in MCI have included varying doses of melatonin (3–24 mg) and have shown improvements in[22 23 24] cognition, mood and sleep. The only randomised controlled trial (RCT) investigating melatonin's effect at a 6 mg dose in patients with MCI was only for a 10-day duration and included just 10 participants with both MCI and AD, which showed a decrease in depressive symptoms, enhanced sleep–activity rhythms, improved sleep quality and ability to remember previously remembered items.[18] The results of this trial demonstrated improved rest–activity rhythm and enhanced sleep quality but other sleep quality indices, such as total sleep time and wake within sleep were not different between melatonin and placebo arms. However, this small, preliminary study also showed an improvement in memory and mood with melatonin compared with placebo.

Based on these preliminary data, we outline a proposal to determine the feasibility of a 12-week randomised, parallel group, double-blind, placebo-controlled clinical trial of 25 mg melatonin in MCI. This dose selection has been made after triangulating evidence related to melatonin efficacy, pharmacology and toxicology. We believe this should provide sufficient antioxidant effect while minimising adverse events (AEs). The duration of the study has been chosen to examine the longer term effects of melatonin, while providing preliminary data for a longer study in the future. The study specifically aims to provide viability, feasibility and safety data, as well as preliminary efficacy data in order to power a larger definitive trial. The current study is the first to investigate melatonin as a possible preventative treatment due to its potential to target pathophysiological pathways involved in neurodegeneration.

METHODS
Study design
The study will use a parallel group, individually randomised, double-blind design with one intervention

and one control arm, using a 1:1 allocation ratio. Data collection time points will be baseline, 6 weeks and 12 weeks, with 12 weeks as the main time point of interest. Participants will be recruited from the Healthy Brain Ageing (HBA) Clinic, University of Sydney and from the community. After screening for eligibility, providing informed consent and undergoing baseline procedures, participants will be randomised to either the melatonin or placebo group. Excluded participants and reasons for exclusion will be recorded. Assessments will include MRI and magnetic resonance spectroscopy (MRS); questionnaires relating to mood, sleep and chronotype; blood collection; 24-hour central aortic pressure; pulse wave velocity and analysis; and cognitive tests. Actigraphy data will also be collected for 7–14 days prior to the baseline visit. Participants will complete these measurements again at the 12-week follow-up, with the questionnaires also administered at the 6-week follow-up. The current protocol has been prepared in accordance with Standard Protocol Items: Recommendations for Interventional Trials statement[25] (online supplemental file 1) and the WHO Trial Registration Data Set (online supplemental file 2).

Participants and setting

Participants with MCI will be recruited from the specialist HBA Clinic at the Brain and Mind Centre, University of Sydney, Sydney, Australia. Advertisements may also be displayed in health magazines, websites or newspapers that are targeted towards older adults. Larger general practices and community centres in the general area will also be advised of the trial and will be requested to advertise the trial for potential participants. Online recruitment platforms and social media advertising will also be used, including the StepUp for Dementia Research recruitment tool. This is an online self-registration service that enables volunteers with memory problems or dementia, carers of those with memory problems or dementia, and healthy volunteers to register their interest in taking part in research. The purpose of StepUp for Dementia Research is to allow such volunteers to be identified by researchers as potentially eligible for their studies. Researchers can then contact volunteers, in line with the volunteers' preferred method of contact, to discuss potential recruitment into a study.

Recruitment, eligibility and consent

Research staff will contact interested and provisionally eligible participants to explain details of the study, that is, objectives, benefits, risks and requirements. They will then obtain verbal consent to telephone screen the participant. The telephone screen will consist of the MoCA-Blind,[26] Memory and Ageing Telephone Screen (MATS),[27] the Wechsler Adult Intelligence Test-III Digit Span subtest,[28] the Oral Trail Making Test Part A and Part B[29] and the Delis Kaplan Executive Function System Letter Fluency.[30] Participants will also be asked if they meet the inclusion or exclusion criteria, including their

medications. Lastly, participants will be asked about the extent of their cognitive impairment and their functional autonomy. Following this step, the participant will receive a detailed information statement to read prior to their medical screening, which will be conducted via telehealth. They will also be encouraged to discuss the study with their family and general practitioner prior to agreeing to participate and to call or email the study team if they have any questions or concerns about the study prior to medical screen. During the medical screen, participants, and if applicable their carers, will be given ample time to discuss the study with the study team prior to electronically signing the consent form via the online data capture system, REDCap. The medical screening will be conducted by a medical officer who will record the participant's medications and medical history. The medical officer will decide if the participant is fit to participate in the trial, or if they need to be referred on for further examination.

Eligible participants are those: (1) aged between 60 and 80 years old; (2) diagnosed with MCI as defined by a cut-off score of ≤33 on the MATS[27] and/or performance 1.5 SDs below age-matched peers on: Wechsler Adult Intelligence Test-III Digit Span subtest, Oral Trail Making Test Part A and Part B, or Delis Kaplan Executive Function System Letter Fluency; (3) stability of at least 4 weeks on permitted medications (ie, any medication not listed in the exclusion criteria below) and (4) fluent in English. The cut-off score for the MATS was selected in accordance with Rabin et al[27] for the best specificity and selectivity of MCI. The other cognitive tests will allow for the assessment of non-memory domains. These tests are validated and easily administrated via telehealth and can detect non-amnestic MCI using the widely used definition of 1.5 SDs below the mean normative value for their age and education.[31] The MATS also includes questions about subjective cognitive complaints, which will be used to assess any lack of functional autonomy, as required by MCI criteria of Petersen et al.[31] All de-identified scores on screening, accompanied by any answers suggesting a lack of functional autonomy, will be forwarded on to a clinical neuropsychologist who will inform the study investigator if someone requires further testing for a dementia diagnosis for possible exclusion from the study. The clinical neuropsychologist will also examine the participant at baseline. Participants will be excluded if they (1) have suspected dementia with a score of <18 on the MoCA-blind; (2) have a history of cerebrovascular events (eg, stroke, transient ischaemic attack) associated with persisting cognitive changes; (3) are a shift-worker or have engaged in transmeridian travel within 14 days of assessment; (4) have any neurological disorders (eg, Parkinson's disease, epilepsy, multiple sclerosis); (5) have had a head trauma with associated loss of consciousness >30 mins; (6) have a current psychiatric disorder including: bipolar disorder (I and II) and schizophrenia; (7) are currently regularly taking benzodiazepines, sedatives, antipsychotics or hypnotics; (8) have current

substance abuse or dependence (alcohol and/or other illicit substances); (9) have any significant systemic illness or medical condition that may hinder compliance with the protocol; (10) have a contraindication to MRI scanning such as pacing devices, coronary or peripheral artery stents, cochlear implants or renal insufficiency; (11) are experiencing a current major depressive episode (not excluded if receiving treatment using antidepressants for maintenance of depression or subthreshold depression unless a medication listed in 7 and 12); (12) are currently taking monoamine oxidase inhibitors or melatonergics. Participants will be asked not to take excluded medications for the duration of the trial, and will not undergo study assessments within 2 weeks of travel across more than two times zones.

Randomisation and blinding

Randomisation will occur after completion of baseline assessment and will be on a 1:1 basis to either the melatonin intervention group or to the placebo group. A randomisation sequence has been computer generated by an unblinded investigator (NSM) who will not otherwise be involved in the trial and will not have any contact with participants. The sequence will be stored in a password-protected online secure system, only accessible by the unblinded investigator. A unique participant randomisation number will be assigned sequentially, in ascending order and will comprise a 2-digit number prefixed by 'R' (eg, R01, R02 and so on). Once a randomisation number has been allocated to a participant, it may not be reused. The unblinded investigator will give the randomisation list to the study pharmacist who will hold the list for the duration of the trial. To ensure the participant's anonymity, documents will use the participant's unique participant screening and randomisation numbers. Participants will be informed of their allocated treatment only after study completion and the dissemination of study results.

To maintain allocation concealment, once a participant has been randomised, the study coordinator will send the study prescription to the study pharmacist who will prepare the appropriate treatment (active drug or placebo) according to the randomisation outcome and will arrange a courier to deliver to the participant. The only people to be unblinded are the pharmacist and the unblinded investigator, both of whom will not have any direct contact with participants. Treatments will look identical to the participant, and in the case of a serious AE (SAE) where codes need to be broken, the dispensing pharmacist or unblinded investigator will be contacted, and drug allocation will be unblinded for that participant only. The dispensing pharmacist will then be able to inform study staff whether the participant was on the active treatment or placebo at the time.

Investigational product

Participants will be randomly allocated to receive nightly 25 mg melatonin or matching placebo capsules for the entire 3-month study period. Participants will be provided instructions on how to store the melatonin and to take it before habitual bedtime. All investigational products will be provided by a compounding pharmacy that will prepare the melatonin and matching placebo, ensuring that the capsules are identical in size, shape, taste and colour. Participants will be instructed to take one capsule 30–60 min before bed. At baseline and 6-week visits, the study medical officer will provide a prescription for the blinded study drug to the compounding pharmacy/pharmacist who will prepare the investigational product. The study pharmacist will record all treatments supplied on the medication-dispensing forms along with the original script.

Primary outcomes

There are three equal primary outcomes: (1) to assess the feasibility of recruitment by determining the percentage (and associated CIs) of people who meet inclusion and exclusion criteria and could potentially join the study; (2) the acceptability of intervention by totalling the number of people who agree to be randomised (and take part in the trial) as a fraction of all potential participants; and (3) medication adherence as assessed by the number of people who correctly adhere to the study medication as instructed. Adherence will be measured by the study coordinator who will count the pills returned at each visit and via an adherence card that participants must tick off every day once they take their medication. The results will be used to inform progression to a definitive RCT. Thus, the number of eligible patients who attend a screening visit, the proportion who agree to be randomised and the proportion who adhere to the trial medication as instructed for the 3-month period will all be recorded.

Secondary outcomes

Secondary outcomes include brain oxidative stress, sleep–wake disturbance, mood, vascular function, cognition and safety. The schedule of study procedures is shown in table 1. Effect sizes and variability (means, SDs, CIs) of melatonin and placebo on each of the following measurements will be recorded:

Biomarkers

(a) The concentration of glutathione in the anterior and posterior cingulate measured via MRS, chosen as glutathione is the primary indicator of oxidative stress in the brain.[32] The involvement of the cingulate cortex in the earliest stages of MCI and AD has been emphasised in neuropathological, functional and volumetric studies.[33] Further, atrophy in both the heterogeneous subdivisions: the anterior and posterior cingulate cortex has been linked to MCI.[33] Moreover, hypometabolism and hypoperfusion in the posterior cingulate occur before any other region in patients with MCI.[34] Due to the inherent difficulties in using MRS to examine the hippocampus due to its proximity to the lateral ventricles and low signal-to-noise ratio, and as such the in vivo concentration of cingulate

glutathione is being examined, as per Duffy *et al*.[35] Additionally, there is evidence for increased oxidative stress in the brains of people with MCI.[36] We will use an established spectroscopy sequence[35] using a 32-channel head array. Analysis will be processed using a software program (LCModel).[37] (b) Blood markers of oxidative stress and inflammation (including glutathione and C reactive protein), glucose and melatonin levels. Fasted bloods will be taken in the morning at baseline and 3 months.

Vascular markers

(c) Seated blood pressure and heart rate[38]; (d) pulse wave velocity and pulse wave analysis for the assessment of arterial stiffness and central aortic pressure (Sphygmocor, Atcor Medical, Sydney, Australia)[39]; (e) 24-hour ambulatory central aortic pressure and arterial stiffness (Oscar 2, SunTech Medical, Model 250, North Carolina, USA).[40]

Sleep and circadian measures

(f) Rest–wake activity (non-parametric and cosinor analysis) using actigraphy, a wrist-worn accelerometer collected over 2 weeks, accompanied by a sleep log (Phillips Actiware V.6, Respironics, Murrysville, Pennsylvania, USA).[41] Parameters measured will include sleep midpoint, sleep onset latency, wake after sleep onset, sleep efficiency and sleep offset. Cosinor variables will include: cosinor phase, cosinor amplitude, cosinor SD, cosinor mean and cosinor intercept. Non-parametric variables will include: interdaily stability, intradaily variability, relative amplitude, L5, L5 onset, M10 and M10 onset. Actigraphy will be processed R packages: 'mice' for imputation,[42] 'nparACT' for non-parametric analysis[43] and 'psych' for cosinor analysis.[44] (g) Subjective sleep quality (Pittsburgh Sleep Quality Index, Insomnia Severity Index[45]), Leeds Sleep Evaluation Questionnaire,[46] where an increase in total score indicates positive impacts on sleep.

Mood

(h) Depressive symptoms (Geriatric Depression Scale[47]); (i) anxiety symptoms (Geriatric Anxiety Scale[48]). All sleep, circadian and mood questionnaires will be completed online by the participant on REDCap.

Cognition

(j) Encoding, recall and recognition in a single modality (California Verbal Learning Test[49]); (k) set shifting and executive function (Oral Trail Making Test)[50] (l) memory, processing speed and executive functioning (Cambridge Neuropsychological Test Automated Battery; Paired Associated Learning; Rapid Visual Processing and Multitasking Test)[51]; (m) verbal fluency (Delis, Kaplan Executive Functioning System Verbal Fluency Alternate). Cognitive tests will be administered via telehealth by an appropriately trained neuropsychologist.

Safety

(n) Raw AE reports supplied by patients will be coded using the latest version of MedDRA by a sleep physician and the medical principal investigator (PI) and reported as tabulated raw counts. (o) Safety and exploratory outcome (Leeds Sleep Evaluation Questionnaire), where a decrease in total score indicates negative impacts on sleep and daytime functioning. Safety will be collected via phone, email and online questionnaire.

All data collection personnel including phlebotomists, neuropsychologists and medical officers will be adequately qualified and trained for the role.

Where possible, aspects of the trial will be conducted via telehealth and online assessments (including screening, questionnaires, AE collections and cognitive assessments). The 24-hour blood pressure cuff will be set up on the participant by the study coordinator at each visit. They will send it back to the site the next day in a prepaid envelope. The actigraphy watch will be sent in the mail with a prepaid return envelope with detailed instructions. The study coordinator will also contact the participant to explain the procedures. This procedure is currently in use at the HBA Clinic at the University of Sydney. Participants will be asked to attend face-to-face visits for assessments that are unable to be collected in this manner (eg, MRIs, blood collections and pulse wave analysis). If unable to attend due to COVID-19 restrictions, these tests will be omitted until it is safe to introduce them to the remaining participants. Once restrictions are lifted, we will aim to maintain as many of the assessments via telehealth and online as possible.

Table 1	Schedule of study procedures			
List of interventions	**Screening**	**Baseline**	**Follow-up**	**Follow-up**
Week(s)	−2	0	6	12
Cognitive assessment	X			
Informed consent	X			
Inclusion/exclusion criteria	X			
Medical assessment	X			
Actigraphy assessment		X		X
MRI scan		X		X
Questionnaires		X	X	X
Cognition and memory tests		X		X
Blood collection		X		X
Pulse wave velocity and analysis		X		X
24-hour central blood pressure monitoring		X		X
Adverse event collection			X	X
Melatonin dispensing		X	X	

Data storage

All data will be stored at the HBA Clinic in written and electronic formats. Participants' information will reside on a secure server that is regularly backed up. Data will be entered manually by keyboard into the electronic data capture system (REDCap), which has range checks for data values where appropriate. All participants will have unique screening and randomisation numbers. Participant personal details (name, date of birth and so on) will be de-identified in each record but are linkable via the allocated screening number. Only the investigator team will have access to the final trial data set. Any other persons would require approval from the investigator team. All data will be stored securely for at least 15 years as per local guidelines.[52] Storage of the data collected will adhere to the University of Sydney regulations and the Australian Code for the Responsible Conduct of Research.

Confidentiality

Participant data will be identified by a code number that will be allocated after the participant gives consent to participate in the study. The key linking the participant's identity to the relevant code will be stored in a password-encrypted file. In any publication and/or presentation, information will be provided in such a way that participants cannot be identified, except with their written, informed permission. Any information obtained for the purpose of this research that could identify participants will be treated as confidential and securely stored.

Adverse events

From the time the participant receives the study medication, all AEs (including SAEs), regardless of relatedness to the study drug, will be recorded. Relevant diagnosis, signs and symptoms associated with significant laboratory changes will be recorded as an AE. Surgical interventions which are planned prior to study enrolment will not be considered as AEs. In the event of an SAE, both PIs will be informed, and local regulatory authorities will be notified within 24 hours of the investigators becoming aware of the SAE. Study medical officers will ensure that follow-up of the participant is appropriate to the nature of the event, and that it continues until resolution.

Any change in terms of diagnosis, intensity, seriousness, measures taken, causality or outcome regarding an AE already reported will be recorded. If the AE has not resolved at the participant's final visit in the study, the participant will be followed up suitably and any information on the outcome of the event will be noted. The information will be collected at a follow-up visit. If the follow-up of the participant is not done directly by the investigator (hospitalisation, followed by a specialist or the participant's general practitioner), the investigator will make all reasonable attempts to establish/maintain contact with the person/department in charge of follow-up of the participant.

Monitoring

All AEs and SAEs will be monitored by the investigating team and discussed at weekly meetings. These discussions will be undertaken blinded to treatment allocation. The participants will be called the week after commencing treatment and asked open-ended questions about any symptoms they are experiencing. The Leeds Sleep Evaluation Questionnaire[53] will also be administered at the 6-week and 12-week visits to assist with AE collection. Participants will be permitted to withdraw from the trial on their request, or if recommended by the medical PI. Participants will still be asked for data to use in an intention-to-treat analysis.

There are no planned interim analyses. The final decision to terminate the trial lies with the PIs. Stopping decisions will be based on (1) safety data and (2) ongoing trial funding. The investigators will conduct a blinded six monthly reviews of all SAEs; and if after discussion the rate of SAEs is deemed unacceptable by the PIs, then the study will be stopped, and the Human Research Ethics Committee will be advised of the decision.

Sample size

The current protocol is intended as a feasibility study to demonstrate that this population would be willing and able to complete the study requirements. A power analysis was not conducted due to the exploratory nature of this study. A sample size of 20 participants in each group (40 total) was decided to be adequate to provide accurate information on the feasibility, tolerability and acceptability.

Data analysis

Data will be analysed using SPSS (IBM, V.25.0). Primary outcome data will be analysed by assessing the proportion of people who were eligible to join the study, agreed to be randomised and adhered to the trial medication. The minimum feasibility will be 80% for the three measures.

Secondary outcome data will be analysed using linear mixed-model analysis of variance due to expected inter-patient variability and repeated measures. Participants will be random factors. Treatment and time (0, 6 and 12 weeks where appropriate) will be fixed factors. The treatment x time interaction will be examined to see the specific difference between treatments at the 12-week time point with repeated measures. Analysis will be by intention-to-treat whereby all available data will be used in the final analyses, regardless of adherence to protocol or termination of study involvement. Per-protocol analyses will be performed in completed participants as well as participants who are adherent to medication (taken on a specified proportion of nights). Correlations between outcomes of interest will be examined using Pearson's correlation or Spearman's correlations where appropriate. Qualitative, subjective feedback from participants and referrers will also be collected to determine barriers to feasibility.

Patient and public involvement

This study was developed by the investigators based on existing literature, and patients were not consulted in terms of study design and the development of the protocol. However, as feasibility is the primary outcome, completed participants and consumer representatives will be invited to be involved in the development and design of larger scale trials.

ETHICS AND DISSEMINATION

This protocol has been approved by the Sydney Local Health District Ethics Committee (X18-0077). This RCT will be conducted in compliance with the protocol published in the registry, the International Conference for Harmonisation on Good Clinical Practice and all other applicable regulatory requirements. The findings of the trial will be disseminated via conferences, publications and media, as applicable. Participants will be informed of results of the study at the conclusion of the trial. Eligible authors will include investigators who are involved in the conception and design of the study, the conduct of the trial, the analysis of the results, and reporting and presentation of study findings.

DISCUSSION

The current study aims to provide evidence for the feasibility, acceptability and tolerability of 25 mg of melatonin in MCI. Evidence of the use of melatonin in populations 'at risk' for dementia is extremely limited. This pilot will inform the powering and design of a larger definitive RCT to understand the effects of melatonin on modifiable dementia risk factors as well as on cognition and brain functioning. This trial protocol may be of interest to others aiming to trial early interventions in MCI, which is a unique population with great potential for impacting progression to dementia.

Trial status

Recruitment began in October 2019 and is estimated to last for 2 years.

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