Research Protocol

Lemborexant for insomnia in a patient with dementia: An N-of-1 trial

Version 2.1
January 17, 2024

Principal Investigator:
Shanna C Trenaman, BScH, BScPharm, MAHSR, ACPR, PhD
College of Pharmacy, Dalhousie University
5968 College Street
Halifax, NS B3H 4R2

Qualified Investigator:
Kenneth Rockwood, MD, FRCP, FRCPC
Division of Geriatric Medicine
5955 Veterans Memorial Lane
Halifax, NS B3H 2E1

Background & Rationale

Insomnia is a highly common, chronic disorder for older adults (1) that can also affect those living with dementia (2). Insomnia can be distressful for people living with dementia, but also introduces challenges for caregivers and can give rise to a heavy burden on the healthcare and caregiver team (3,4). Sleeping aids like benzodiazepines and other sedatives (e.g., zolpidem, zopiclone) have been widely used to help treat insomnia. However, sleeping aids are also known to cause adverse drug reactions such as drowsiness and dizziness, that increases the risk of falls, driving impairment, visual impairment, cognitive impairment, and upon discontinuation may cause paradoxical rebound insomnia, delirium, and nightmares all of which exacerbate the initial insomnia (5). The negative aspects of sleeping aid use are exaggerated for older, frail adults and are more severe for adults living with dementia.

Some patients experience an early (young-age) onset dementia with a substantial component of insomnia. Due to the many risks associated with traditional sleeping aids they are often inappropriate in adults living with cognitive impairment and/or frailty (6). Lemborexant comes from a new class of medications for insomnia. Lemborexant is a dual orexin receptor antagonist that blocks the binding of wake-promoting neuropeptides orexin A and orexin B to their receptors OX1R and OX2R, which is thought to suppress wake drive. Unlike other traditional sleeping aids, 1emborexant has not shown to be significantly associated with driving impairment, rebound insomnia, or dependence/withdrawal symptoms (7). Also, in clinical trials it only rarely causes the types of adverse events associated with benzodiazepines and other traditional sedatives and is less often associated with discontinuations due to adverse events.

While 1emborexant is available on the Canadian market it is unclear how this medication will be tolerated by patients living with an early onset dementia. Understanding the effectiveness, tolerability, and safety of 1emborexant will be helpful in an N of 1 trial to understand the details of effect and tolerability in individuals living with dementia and insomnia.

Hypothesis

We hypothesize that lemborexant will be effective and safe in the treatment of insomnia in adults living with both early onset dementia and concomitant sleep difficulty.

Objective

The objective of this study is to evaluate lemborexant for efficacy and safety as a sedative medication for insomnia in adults living with both early onset dementia and insomnia.

Methods

Design:

This is an investigator led, 8-week, N of 1 trial for adults with early onset dementia and insomnia, where treatment with lemborexant is altered with a placebo in an "ABBABAAB" format. N of 1 study methodology allows us to present data from one case in isolation and re-deploy the study when a new patient meets the eligibility criteria (find supplemental inclusion/exclusion criteria).

Participant Selection:

Participants will be recruited from Dr. Rockwood's Geriatric Ambulatory Care Clinic located in the Camp Hill Veterans Memorial Building in the Central Zone of the Nova Scotia Health Authority. While this trial is designed for a particular patient case (i.e. recruitment of 1 participant), we anticipate that there may be opportunities in the future for this N-of-1 trial to be redeployed to other adults living with early onset dementia and insomnia with a maximum enrollment of 3 patients over the following 5 years.

Inclusion/Exclusion Criteria:

Inclusion criteria are a referral to investigator 1's memory clinic, early onset dementia (any type) as defined by age at less than 65 years at diagnosis, symptoms of insomnia or reduced sleep that is distressing to the patient or their caregiver.

A patient must have all inclusion criteria and none of the exclusion criteria to be eligible to participate in the study.

Inclusion Criteria

A diagnosis of early onset dementia (dementia before age 65)
Experiencing insomnia that is distressful to the patient or the patient's care givers
Have a caregiver to support completing the sleeping response log

Exclusion Criteria

Hypersensitivity or intolerance to the drug or any ingredient in the formulation
Intolerance of lactose
Diagnosis of the hereditary diseases of galactose intolerance
Severe hepatic impairment
Severe COPD
Pregnancy
Breastfeeding
Use of medications that moderate or strong inhibitors of CYP 3A
A history of distressing sleep paralysis

Study Procedures:

1. Patients identified to have early onset dementia and insomnia by the Qualified Investigator (Geriatrician) during routine patient care will be approached to determine their interest in the N of 1 trial.
2. Principal investigator (Pharmacist and Researcher) will meet the potential patient, review of the project details and study objectives. There will be a discussion of risks and benefits and the consent form will be reviewed. There will be an invitation for the patient to provide informed consent. Given that the study will include people living with dementia and cognitive impairment we will ensure that a caregiver or substitute decision maker will participate in these discussions as well.
3. If the patient provides informed consent the patient will be considered enrolled in the study and will be provided with (1) Study medication and (2) Study reporting tool.
   (1) Study medication will be provided for an 8-week period. Medications will be dispensed in an $AB_iBABAAB$ sequence where each letter represents 7 days of treatment, A represents placebo, B_i represents lemborexant 5mg and B represents lemborexant 10 mg. This doubly counterbalanced design defends against both linear secular trends and nonlinear trends. Medication will be provided in 7-day packs (plastic or cardboard dosettes) marked to correspond to the assigned treatment week and assigned as follows.

   Week 1 = placebo

   Week 2 = lemborexant 5 mg

Week 3 = lemborexant 10 mg

Week 4 = placebo

Week 5 = lemborexant 10 mg

Week 6 = placebo

Week 7 = placebo

Week 8 = lemborexant 10 mg

Medications will be placed inside an opaque capsule to minimize the difference in appearance for the active and inactive treatments. Dispensing details of the 3 treatments will be provided with each of the 8 weeklong medication supplies. Please note that there will be no washout time between treatment periods (for practical purposes, washout periods may not be necessary when treatment effects (e.g., therapeutic half-lives) are short relative to the length of the treatment periods. Since treatment half-lives are not well characterized and vary among individuals, the safest course is to choose the weeklong treatment length and to take frequent (e.g., daily) outcome measurements.

(2) The patient will also be provided with a Study reporting tool (Appendix 1) where they can record details of drug response and any other noticed events/effects.

4. The participant/caregiver will receive weekly follow up phone calls from the Principal Investigator to report the efficacy and harms that the participant experienced in the last 7 days for the 8-week duration and ensure that the treatment is being tolerated. These details will be recorded for consideration and assessment when determining patient response.
5. Efficacy outcome that will be measured in the Study Reporting tool will include:

i) Whether at the medication was taken

ii) total sleep time,

iii) sleep onset latency (SOL),

iv) wake time after sleep onset (WASO),

v) number of night awakenings to be measured nightly based on patient and caregiver estimate,

Risk outcome that will be measured will include:

i) presence & severity of adverse drug reactions (ADRs); this may include somnolence, headache, sleep paralysis, etc.),

ii) patient's willingness to drop-out due to ADRs.

And will be assessed at the telephone call check-ins that occur every week over the 8-week study.

Furthermore, provision of follow-up care will be ensured by the Qualified Investigator.

Statistical Analysis

We will calculate basic descriptive statistics (means, standard deviations, medians, and ranges) for each outcome variable (total sleep time, sleep onset latency (SOL), wake time after sleep onset (WASO), and number of night awakenings) across each week of treatment/placebo. The assumption will be that each week is an independent event and will allow us to compare response over time (by week). We will generate time series plots to visualize trends over time with marking to identify periods of active treatment and placebo. Examination of these time dependent graphs for each outcome will be visually inspected for patterns, trends, and potential relationships between variables. We will utilize the R statistical computing language for the statistical analysis.

Equity, Diversity, and Inclusion Considerations

The study investigators will invite a very specific patient type for the N of 1 trial without consideration of sex, gender, ethnicity, or sexual orientation.

Feasibility, Challenges, and Mitigation Strategies

This is an intensive evaluation for the patent and caregiver due to tracking sleep (own outcome recording) but we will attempt to manage this with two check-ins by the co-investigator that will help inform adverse events and any tolerability concerns.

4.1 Confidentiality

Information collected for purposes of this study will be handled confidentially.

Participants' name, contact information, age, height, and weight measurements may be used in the study records but no identifying information will leave the Nova Scotia Health Authority. All study information will be stored in a separate research database on a password protected drive, in which all patients will be identified with a unique number. A separate file will link patients to their study identification numbers and will also be password protected. The only hardcopy documentation will be the signed consent forms (stored separately from other hard copy data) which will be kept in a locked drawer, in a locked room. No identifying information will be publicly available; patients will be identified only by their study identification numbers. Access to any file relevant to this study will be limited to the study personnel at NSHA, the NSHA Research Ethics Board (NSHA-REB) and auditors, upon request.

Results from this study may be presented at scientific meetings or published in a peer-reviewed journal. The population studied will be described in general terms. No identifying data will be disclosed when presenting study results.

4.2 Harms

The potential harms associated with the proposed study are minimal. Participants risk an adverse drug reaction which may manifest as headache, drowsiness, or other symptom. It is possible that the medication will not help with sleep or may worsen the insomnia. Serious adverse reactions that could occur include a drug-related delirium or an episode of sleep paralysis.

4.3 Benefits

While there are no direct benefits to participants over standard care as a result of participating in this study, this research works towards identifying a method to support sleep in someone living with dementia and insomnia.

4.4 Disclosure of any Financial Compensation

Participants will receive no monetary compensation. There will be no direct expenses incurred by participants, and therefore there will be no reimbursement for such costs.

References

1. Brewster GS, Riegel B, Gehrman PR. Insomnia in the Older Adult. Sleep Med Clin. 2022 Jun;17(2):233–9.

2. Lee S, Nelson ME, Hamada F, Wallace ML, Andel R, Buxton OM, et al. Sleep Disorders and Cognitive Aging among Cognitively Impaired vs. Unimpaired Older Adults. The Gerontologist. 2023 Nov 7;gnad152.

3. Benca R, Herring WJ, Khandker R, Qureshi ZP. Burden of Insomnia and Sleep Disturbances and the Impact of Sleep Treatments in Patients with Probable or Possible Alzheimer's Disease: A Structured Literature Review. J Alzheimers Dis JAD. 2022;86(1):83–109.

4. Brewster GS, Wang D, McPhillips MV, Epps F, Yang I. Correlates of Sleep Disturbance Experienced by Informal Caregivers of Persons Living with Dementia: A Systematic Review. Clin Gerontol. 2022 Oct 31;1–28.

5. Dell'osso B, Lader M. Do benzodiazepines still deserve a major role in the treatment of psychiatric disorders? A critical reappraisal. Eur Psychiatry J Assoc Eur Psychiatr. 2013 Jan;28(1):7–20.

6. Picton JD, Marino AB, Nealy KL. Benzodiazepine use and cognitive decline in the elderly. Am J Health-Syst Pharm AJHP Off J Am Soc Health-Syst Pharm. 2018 Jan 1;75(1):e6–12.

7. Pan B, Ge L, Lai H, Hou L, Tian C, Wang Q, et al. The Comparative Effectiveness and Safety of Insomnia Drugs: A Systematic Review and Network Meta-Analysis of 153 Randomized Trials. Drugs. 2023 May;83(7):587–619.