Study Title:
Does Pimavanserin (Nuplazid) improve sleep in patients with Parkinson disease psychosis? A pilot study

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Investigator Initiated Trial Proposal

Study Title:
Does Pimavanserin (Nuplazid) improve sleep in patients with Parkinson disease psychosis? A pilot study

Short Title: Pimavanserin for sleep in PD

Therapeutic area: Parkinson disease (PD)

Key study and administrative contacts:
Daphne Robakis MD (Principal Investigator)
Sofya Glazman (Study coordinator)
Sofya Glazman is a highly experienced research coordinator, having been involved in clinical trial research at SUNY Downstate Health Sciences University since 2004.
Angelika Gruessner (Biostatistician)
Steven Levine (Research advisor)
Dr. Levine is a Distinguished Professor and Vice-Chair of Neurology at SUNY Downstate Health Sciences University, and has extensive experience in clinical research (see CV). He will serve in an advisory role.
Andrew Westwood, MD Sleep Medicine collaborator
Motria Mishko, Pharm.D., R.Ph. is a clinical trials pharmacist at SUNY Downstate Health Sciences University. Dr. Mishko will dispense study drug to the study subjects.

Scientific Basis/Rationale:
Sleep disorders are extremely common in people with Parkinson disease (PD), affecting up to 88% of patients (1). Night-time sleep disruption and daytime sleepiness in PD can have diverse causes, including insomnia, restless legs syndrome (RLS), rapid eye movement (REM) sleep behavior disorder (RBD), medication effects, and treatment-related discomfort such as tremor or dyskinesia (2).

Studies of sleep architecture in PD show increased arousals and sleep fragmentation, and reduced total sleep time and sleep efficiency. Sleep fragmentation, or brief interruptions of sleep, is extremely common in PD and may be related to nocturia, medication effects, or hallucinations and altered dreams. When dreaming occurs without the typical loss of muscle atonia during REM sleep, it leads to REM sleep behavior disorder, which affects almost half of PD patients (3). This disorder causes patients to physically act out their dreams, which are often vivid or violent, and can be dangerous for patients who may injure themselves or their bed partners while dreaming.

The association between psychosis and RBD in PD is well established (4), as both have been correlated with a more widespread distribution of alpha-synuclein in the nervous system (5). In addition, sleep fragmentation, vivid nightmares, and RBD have been associated with the presence of hallucinations (6). It is therefore a common occurrence for PD patients with visual hallucinations and concomitant sleep disturbance to present to the practitioner seeking therapeutic help.

Traditional pharmacologic treatments for RBD are melatonin and clonazepam, which suffer from a lack of good evidence for their use, and are not completely effective in eliminating the symptoms of RBD (7, 8). In addition, clonazepam has risks particularly in elderly patients such as confusion and somnolence, and as a benzodiazepine, may be associated with an increase in cognitive decline and falls (9, 10). Quetiapine, an atypical antipsychotic with sedative properties, is often used in PD patients to treat both visual hallucinations and insomnia, but had no effect on sleep times as measured by PSG in a double blind study (11). Sleep fragmentation is often treated with similarly sedating medications. Even in patients with early stage disease who suffer from sleep problems, these drugs can cause unwanted side effects, particularly over-sedation or daytime sleepiness. Clearly, better treatments are needed for PD patients with sleep disorders.

One potential therapeutic opportunity exists with the relatively new drug pimavanserin. Pimavanserin is an inverse agonist at serotonin 5-HT2A receptors that was approved by the FDA in 2016 for the treatment of psychotic symptoms in patients with PD (12). Limited evidence exists that pimavanserin may have a beneficial effect on sleep. Participants taking pimavanserin as part of the Phase III randomized controlled trial of psychosis in PD reported an improvement in nighttime sleep as detected by the SCOPA-NS sleep scale (13). In addition, pimavanserin has been shown to affect sleep architecture on polysomnography (PSG), particularly to increase slow wave sleep and decrease awakenings in healthy adults (9). Therefore pimavanserin presents an opportunity for a potentially new pharmacologic treatment of sleep disorders in PD patients with psychotic symptoms, and perhaps for all PD patients who suffer from sleep disruptions.

Given the lack of previous research in this area, a pilot study is proposed in order to gather preliminary data regarding the effect of pimavanserin on sleep quality in this patient population. Since sleep is a complex phenomenon, its assessment will integrate quantitative and subjective measures, namely PSG and a series of validated questionnaires.

Hypothesis:
The proposed study is feasible in terms of its design and recruitment, and will provide preliminary data regarding the effect of pimavanserin on sleep parameters in patients with PD psychosis for development of a larger trial.

This is a feasibility study to help generate hypotheses. It is not powered for statistical significance. Our study size is limited by the financial resources available to us.

Primary objective: To determine whether there is any evidence that pimavanserin has a beneficial effect on subjective and objective measures of night-time sleep in patients with PD psychosis.

Secondary Objectives
To inform the prospective feasibility of the current study design in terms of recruitment and retention.

Inclusion criteria:

1) Has a diagnosis of idiopathic PD according to UK PD Society Brain Bank diagnostic criteria
2) Has a history of hallucinations or delusions associated with PD
3) Has a history of sleep disturbance
4) Is between the ages of 40 and 85
5) Has been on a stable dose of all PD medications for at least 30 days prior to enrolment

Exclusion criteria

1) Has evidence of an atypical or secondary parkinsonian disorder
2) Has a contraindication to taking pimavanserin
3) Has contraindication to PSG
4) There has been a change to patient's neuropsychiatric medications including dopaminergic medications (Sinemet, dopamine agonists, MAO-B inhibitors), SSRIs, SNRIs, dopamine-blocking agents, anti-epileptics, anticholinergics, or benzodiazepines for at least 30 days prior to enrollment
5) Has traveled through 3 or more time zones within 60 days prior to study screening
6) Patient is a night-shift worker

Primary endpoint:
Evidence of a change pre and post- drug treatment in sleep architecture as seen on PSG in terms of 1) REM Sleep without atonia (RSWA) 2) number of arousals

Secondary endpoints:

1) A change in other PSG parameters pre and post-treatment including:
   a) Sleep latency
   c) wake after sleep onset
   d) total sleep time
   e) sleep efficiency
   f) time in each sleep stage (N1 N2 N3, REM)
2) Change in qualitative sleep and RBD self-assessments (RBDSQ, PDSS-2 and PFS-16).
3) Recruitment and adherence rates

Trial Design check boxes: Other

If other, please specify:
This study uses a self-control design. A similar design was used to study the effect of LCIG on sleep in PD (14).
At baseline/screening and after 6 weeks of treatment with pimavanserin, the following assessments will be completed:
i) Polysomnography (PSG)
ii) Sleep questionnaires:
   a. Parkinson's Disease Sleep Scale, 2nd version (PDSS-2)
   b. Parkinson's disease Fatigue scale (PFS-16)
   c. RBD sleep questionnaire (RBDSQ)
   d. MDS Unified Parkinson's disease rating scale (MDS-UPDRS)
   e. The Montreal Cognitive assessment (MOCA) (administered at baseline/screening only)
At baseline/screening, the following study will be done:
   i) EKG

Study Phase:
If Other, please specify: Pilot study
Number of Sites: 1

Sample size justification/Statistical Analysis:
Estimated number of patients: 10 patients will be enrolled from SUNY Downstate Health Sciences University. As this is a pilot study, there are no formal sample size calculations and power estimates. Estimating a drop-out rate of 10% due to adverse effects as seen in previous studies with pimavanserin (15), we will aim to recruit and enroll a total of 10 patients (our budget therefore assumes a total of 10 patients). If necessary, more participants will be added

to maintain a total of 10 participants with complete data.

Study drug related issues:
The standard dose of Pimavanserin (Nuplazid) 34mg capsules oral daily will be used in this study. Patients will be treated for 6 weeks in keeping with prior studies to ensure adequate treatment duration (12). Using the above estimate for number of patients to be enrolled: 1 tablet per day x 10 patients x 42 days = 420 capsules will be requested.

Estimated Duration of study:
Year 1
Months 1-3: Administrative set-up, IRB submission and approval, set up screening protocols, role out study awareness within the recruiting hospitals, subject recruitment
Months 4-12: Subject enrollment and ongoing recruitment
Goal 50% enrollment by end of year 1
Year 2
Months 1-6: Subject enrollment
Months 7-9: Complete all study visits and subject follow-up; clean, edit, and lock study database
Months 10-12: Data analyses, manuscript preparation and submission

Study visits procedures:

Visit 1 – Screening/Baseline

1) Informed Consent
2) Screening for inclusion/exclusion criteria
   Vital Signs (blood pressure, pulse, height and weight)
   medical history, personal information (date of birth, gender, race/ethnicity) and medications taken (including over-the-counter)
3) Clinical Evaluation
   a. Parkinson's Disease Sleep Scale, 2nd version (PDSS-2)
   b. Parkinson's disease Fatigue scale (PFS-16)
   c. RBD sleep questionnaire (RBDSQ)
   d. MDS Unified Parkinson's disease rating scale (MDS-UPDRS)
   e. The Montreal Cognitive assessment (MOCA) (administered at baseline only)
   f. EKG
4) Dispense study drug if a patient is eligible for the study
5) A subject will be scheduled for Polysomnography (PSG), sleep study, at United Sleep Diagnostics, Inc.
   PSG records the changes that occur during sleep, e.g., number of arousals, sleep latency, wake after sleep onset, total sleep time, sleep efficiency, time in each sleep stage.

The PSG monitors brain activity (EEG - electroencephalography), eye movements (EOG - electrooculography), muscle activity (EMG - electromyography), and heart rhythm (ECG - electrocardiography)
A subject will report to the United Sleep Diagnostics located at 808 8th Ave, Brooklyn NY 11215 at 8 pm on the scheduled date for the sleep study and stay overnight.
A sleep technician will attach the electrodes (metal discs) to a subject's skin and monitor a subject during the study.
The report will be sent to the study doctor for analysis.

Visit 2 - Baseline PSG (same day as Screening/Baseline)

1) Polysomnography will be done at United Sleep Diagnostics clinic
2) Start study drug Day 1

Visit 3 - Phone Call Week 2

1) Phone visit with Study coordinator to evaluate how a study participant tolerates the study drug and how it is affecting his/her Parkinson's symptoms; review of current medications

Visit 4 - Follow-up PSG Week 6

1) Polysomnography

Visit 5 -Week 6 (same day as PSG)/Early Withdrawal

1) Clinical Evaluation
    a. Parkinson's Disease Sleep Scale, 2nd version (PDSS-2)
    b. Parkinson's disease Fatigue scale (PFS-16)
    c. RBD sleep questionnaire (RBDSQ)
    d. MDS Unified Parkinson's disease rating scale (MDS-UPDRS)

2) Return of empty study drug bottle and unused study drug

A study participant will be reimbursed after Visit 2 Baseline PSG of $200 ($50 for Visit 1 Screening/Baseline; $150 for Visit 2 Baseline PSG). Then a study participant will be reimbursed after Visit 5 6 weeks/Early Withdrawal of $350 ($150 for Visit 4 Follow-up PSG 6 weeks; $200 for Visit 5 6 weeks/Early Withdrawal).
A check will be mailed to a study participant.
If a study participant leaves the study early, he/she will be reimbursed only for visits that he/she completes**.**

A plan to monitor conduct of the study at the site

Because this is Investigator-Initiated study, the PI/sponsor-investigator, Daphne Robakis, MD understands her responsibility for
oversight of the study, and takes responsibility for any unanticipated problems or serious or continuing non-compliance;
attends a study "kickoff" meeting;
will be responsible for reporting any reportable events that occur;
conducts site initiation visit with all study staff to provide any needed training on study protocol;
is responsible to address any issues that arise;
will conduct conference calls with all study staff; agenda and minutes will be recorded and filed;
will assess all SAEs.

Investigator comments:

Dr. Robakis and her study team have extensive experience in academic clinical research. Dr. Robakis completed her fellowship at Columbia University under the tutelage of Stanley Fahn. During her fellowship she also received instruction in clinical trials research from Dr. Cheryl Waters. Her first academic faculty position was at Yale University where she was mentored by Dr. Elan Louis, who has an extensive publication record in the field of movement disorders. Currently, she works closely with Dr. Steven Levine, the Vice-Chair of Neurology at SUNY Downstate Health Sciences University and a nationally recognized researcher. Dr. Robakis is currently involved in clinical research at SUNY Downstate Health Sciences University, including a translational research project funded by the Michael J. Fox Foundation, and a multi-site clinical drug trial for PD. In addition, her scholarship encompasses mentoring resident physician research and forging collaborations with faculty. To further strengthen the study team, two additional academic neurologists in the field of movement disorders and sleep medicine with proven track records in clinical research will be consulted to help guide the study set-up and manuscript publication.

Please note that the clinical portion of this study will take place at SUNY Downstate Health Sciences University Neurology Department. The sleep study will be performed at the United Sleep Diagnostics lab.

The study will be advertised on the e-screens around the SUNY Downstate Health Sciences University campus.

There is no intent to seek a new indication for the drug.

AE / SAE Reporting:	*To Report all adverse events directly to the FDA in accordance with applicable law and Study protocol.* *All serious adverse events (SAE) must be reported to Acadia Call Center at 1-844-4-Acadia (1-844-422-2342) within 24 hours of such SAE.* *A copy of any reports to the FDA (e.g. SUSAR) will be sent to Acadia at the time of submission to the FDA.* *All complaints (product complaints or product grievances), regardless of origin, must be reported to the Acadia Call Center at 1-844-4-Acadia (1-844-422-2342).*

Describe support:
None

Planned Publications: Does pimavanserin improve sleep in patients with Parkinson disease psychosis? A pilot study

SUPPORT:
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