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Treatment of Insomnia in Parkinson's Disease: A Controlled Trial of Eszopiclone and Placebo

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Abstract

Parkinson's disease (PD) is a common neurodegenerative disease affecting up to one million individuals in the US. Sleep disturbances, typically in sleep maintenance, are found in up to 88%

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of these individuals and are associated with a variety of poor outcomes. Despite being common and important, there are few data to guide clinical care.

We conducted a six week, randomized, controlled trial of eszopiclone and placebo in thirty patients with PD and insomnia. Patients with other primary sleep disorders (PSG defined) were excluded. The primary outcome was total sleep time (TST) and secondary measures included wake after sleep onset (WASO), number of awakenings and quality of sleep, among others.

The groups did not significantly differ on TST, but significant differences, favoring eszopiclone, did emerge in number of awakenings ($p=.035$), quality of sleep ($p=.018$) and in physician rated CGI improvement ($p=.035$). There was also a trend towards significance in WASO ($p=.071$). There were no significant differences between groups in measures of daytime functioning. The drug was well tolerated, with 33% of patients on eszopiclone and 27% of patients on placebo reporting adverse events.

Though modest in size, this is the first controlled study of the treatment of insomnia in patients with PD. Eszopiclone did not increase total sleep time significantly but was superior to placebo in improving quality of sleep and some measures of sleep maintenance which is the most common sleep difficulty experienced by patients with PD. Definitive trials of the treatment of sleep disorders in this population are warranted.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease in the US. The physical aspects of the illness, such as tremor, rigidity and postural imbalance, have traditionally been regarded as the most important features of the disease and have understandably received the most attention in both research and clinical practice. Nonetheless, PD affects patients' lives in a broader sense than merely by physical impairment. For example, many of the non-motor aspects of PD, such as sleep disturbance and depression, are common and significantly affect the day-to-day lives of these individuals. Better treatment for these aspects of the illness could produce improved outcomes and an important reduction in suffering.

Disturbances of sleep are highly prevalent in Parkinson's disease (PD), affecting up to 88 percent of community dwelling patients.¹ The most common sleep disturbance in patients with PD is sleep fragmentation, affecting up to 74-88% of patients.^{1, 2} This difficulty with sleep maintenance is accompanied by a decrease in total sleep time and an increase in the number of awakenings and wakefulness after sleep onset.

Furthermore, sleep difficulties are independent, important, and primary determinants of poor quality of life in PD.^{3,4,5 6} Sleep disturbances contribute to excessive daytime sleepiness (EDS) and poor daytime functioning as well as patients' reduced enthusiasm for daily events,⁵ and adverse effects have also been observed in the sleep habits and the quality of life of their spousal caregivers.^{7,8} These findings underscore the significance of sleep problems in PD.

Despite the high prevalence and detrimental impact of sleep problems in PD, there has been, until recently, little research focus on the problem.⁹ While researchers have now begun to describe the phenomenology and epidemiology of sleep in PD, we are aware of no controlled trials of sleep medication in patients with PD. Despite this lack of evidenced-based clinical guidance, community surveys indicate that up to 40% of patients with PD are taking sleeping pills.¹⁰

The most widely used treatment of insomnia in non-PD populations are the nonbenzodiazepine benzodiazepine receptor agonists (also known as nonbenzodiazepine hypnotics), such as eszopiclone, zolpidem and zaleplon. To begin to address the lack of evidence based data to guide clinical care, we conducted a randomized, placebo controlled trial of the efficacy of eszopiclone for insomnia in patients with Parkinson's disease. We chose eszopiclone, because most PD patients have difficulty with sleep maintenance and eszopiclone, unlike zolpidem and zaleplon, is efficacious in sleep maintenance in non-PD populations.

Study Design

This was a five site, double blind, two arm, parallel group, six week, fixed-dose trial of eszopiclone and placebo. Preliminary screening was conducted by telephone. Those individuals appearing appropriate were scheduled for an in-person screening visit and signed an informed consent approved by the institutional IRB at each site. At the screening visit, a detailed sleep, medical and psychiatric history, and a variety of background demographic forms were completed and the inclusion and exclusion criteria listed below were applied.

Subjects meeting all entrance criteria kept sleep-wake diaries for a two-week baseline period. Those who met criteria for insomnia on the sleep diaries received an overnight polysomnographic evaluation (PSG) to screen for primary sleep disorders including REM Sleep Behavior Disorder (RBD), Periodic Limb Movements of Sleep (PLMS), and Sleep Disordered Breathing (SBD). Polysomnographic evaluation was conducted using standard nocturnal polysomnographic procedures. All sleep parameters were collected simultaneously by a computerized acquisition system (REMbrandt, Medcare Diagnostics). Sleep was scored in 30-second epochs according to the standard criteria of Rechtschaffen and Kales.¹¹

Patients who met entrance criteria were equally randomized to eszopiclone or placebo for 6 weeks. Both groups received equal-appearing pills to be taken each night. The dosing in the trial was fixed and stratified by age: those under 65 received 3 mg of eszopiclone or matching placebo at night; those 65 or older received 2 mgs of eszopiclone or placebo at night.

Patients completed the following visits: screening, an interim phone contact to review the sleep diaries, PSG evaluation, baseline and weeks 2, 4, and 6, at which medication was monitored and pill intake, therapeutic response and adverse events were reviewed. All groups recorded sleep-wake diaries during the 2 week screening phase and for the six weeks of the study. Patients were asked, but not required, to provide a care giver who completed questionnaires at the screen visit and the week 6 visit.

Inclusion criteria were as follows: 35 to 85 years old with Parkinson's disease by research criteria; sleep maintenance insomnia (at least 3 of 7 nights of at least 2 awakenings nightly, or a total sleep time of < 6.5 hours) or sleep latency insomnia (at least 3 of 7 nights of sleep latency > 30 minutes), as well as clinically significant daytime distress or impairment (related to insomnia) during the 2 week self assessment prior to baseline. Antidepressant medications, prescribed for depression or anxiety, were allowed if the patient had been on a stable dose for at least one month. Benzodiazepines were permitted if taken during the day prior to 6 PM and if not taken as a sleep aid.

Exclusion criteria were as follows: insomnia that was secondary to depression or anxiety based on the opinion of the investigator; use of psychotropic medication other than benzodiazepines or antidepressants; evidence of dementia, defined as a score of less than 26 on the Mini-Mental State Examination (MMSE);¹² evidence on PSG and symptoms or complaints of significant sleep disordered breathing (central or obstructive apnea), periodic

limb movement disorder (PLMD), or REM sleep behavior disorder (RBD). Significant sleep disordered breathing was defined as an Apnea-Hypopnea Index > 15 events/hr of sleep and/or significant hypoxemia on screening PSG; significant PLMS was defined as a PLM index > 25 events/hr of sleep on screening PSG; RBD was defined based on presence of both clinical symptomatology (demonstrated injury to self or others during sleep) as well as PSG criteria (intermittent loss of REM atonia).

Subjects were instructed to complete the diaries every morning during the monitoring periods and to bring them to each session during treatment. The sleep-wake diaries used were from the National Sleep Foundation's "Sleep Diary" (©2000, National Sleep Foundation, Washington, DC).

Primary Efficacy Measure

The primary outcome was patient reported (diaries done daily and summed over two-week epochs) Total Sleep Time (TST).

Secondary Endpoints

A variety of secondary endpoints were examined, including wake after sleep onset (WASO), number of awakenings and the Sleep Impairment Index (SII)¹³. WASO is calculated by subtracting the total time awake during the night from the total time between falling asleep and waking for the day. The SII is a 7-item patient rated scale that yields a quantitative index of insomnia severity.

Quality of sleep was measured on a ten point Likert scale (1 = extremely poor, 10 = excellent). Quality of life (QoL) was assessed with the Parkinson's Disease Questionnaire short form (PDQ-8)¹⁴. Motor Functioning was measured with the Unified Parkinson's Disease Rating Scale (UPDRS)¹⁵. Overall severity and change were assessed by the raters with the Clinical Global Impression¹⁶ (CGI-severity) and the Clinical Global impression¹⁶ (CGI-improvement). The CGI – Improvement was based on the physician's rating of the global improvement in sleep, not the motor or other aspects of the illness. Daytime functioning measurements included the Ability to Function which was assessed with a 10 point Likert scale (1 = unable to function, 10 = normal functioning). Daytime Alertness was also assessed with a 10 point Likert scale (1 = not at all alert, 10 = extremely alert). Fatigue severity was assessed with the Fatigue Severity Scale (FSS).¹⁷ Caregiver QoL and depression were also assessed, using the Multidimensional Caregiver Burden Inventory (MCBI), and the Center for Epidemiologic Studies Depression Scale (CES-D).¹⁸

Data Analyses

An intent-to-treat approach, based on data from all randomized participants, was used in all analyses. The primary and secondary endpoints were evaluated at baseline, 2, 4 and 6 weeks using a mixed-model repeated measures analysis of variance.¹⁹ This linear mixed effects model was implemented in the MIXED procedure of SAS Version 9.1, using restricted maximum likelihood estimation. The fixed effects of treatment in this mixed model included study group (placebo, eszopiclone). Random effects were time of assessment (baseline, 2, 4 and 6 weeks), and the study group × time interaction. In modeling covariance structure for all analyses, we chose spatial power as a function of the square root of days from baseline that a given assessment occurred for a given patient (e.g., occasionally the 2 week assessment occurred not on the 14th day but, say the 16th). Covariates comprised patient age, gender and the score at baseline on the motor subscale of the UPDRS. The interaction between treatment group and time in the mixed model was of most interest, since a time effect alone would only indicate improvement over time across both groups, whereas a time

by group interaction indicates differential improvement over time, depending on study (drug) group.

For the secondary outcomes, given that multiple tests capitalize on chance to a considerable degree, the P levels calculated for each outcome were adjusted using the Holm method (PROC MULTTEST; SAS version 9.1).

Results

Forty-five patients signed informed consent. Six patients withdrew consent before finishing the first evaluation. One was excluded because of a MMSE of less than 26 and one was excluded because depression was felt to be the cause of the insomnia. All patients who reported insomnia met insomnia criteria on their diaries. Seven patients were excluded by PSG – 6 for obstructive apnea and 1 for PLMS. A flow diagram can be found in Figure 1.

Thirty patients, 6 females and 24 males, were randomized. The average age was 56; they had been ill with PD an average of 4.5 years and had an average Hoehn-Yahr PD stage of 1.6. Most patients were taking more than one class of Parkinson medication; 6 were taking levodopa alone, and 3 were taking an agonist alone. Overall, 26 patients were taking levodopa, 21 were taking agonists, 8 were taking COMT inhibitors and 7 were taking MAO inhibitors. Eight patients were on an antidepressant (prescribed for depression) and one patient was taking a benzodiazepine during the day for anxiety. Eleven patients (37%) dropped out before the end of the trial, 3 in the eszopiclone arm (2 for lack of efficacy and 1 because of nausea) and 8 in the placebo arm (6 for lack of efficacy, one for increased rigidity and one who left the area).

All patients, by diaries, had maintenance insomnia and 9 also had latency insomnia. The total sleep time on PSG was an average of 5.16 hours (309 minutes) which was significantly correlated with the TST on the diaries (Pearson $r = .44$, $P < .028$). Twenty-three of the 30 subjects had less than 6.5 hours of sleep on the PSG.

The primary and secondary efficacy results are listed in Table 1. Depicted in the Table for each measure are least squared means calculated for baseline and endpoint, the standard deviations, as well as significance levels of the time by group interaction, based on the results of the mixed model repeated measure ANOVA's described earlier. In addition, the significance test for all secondary measures was adjusted for multiple comparisons using the Holm method described above.

While the drug group gained 66.5 minutes of total sleep time compared to 47 minutes in the placebo group, this difference was not significant ($F(3,68) = 2.09$, $p = .1099$). There were, however, significant differences in the number of awakenings ($F(3,68) = 5.16$, $p = .035$), quality of sleep ($F(3,60) = 6.05$; $p = .018$) and CGI – improvement in sleep ($F(1,33) = 10.3$, $p = .035$). There was a trend towards significance in WASO ($F(3,68) = 4.38$, $p = .071$),

There were no differences in the UPDRS motor, ADL, therapeutic complications, mood or Schwab subscales. There were also no significant differences in sleep latency, Fatigue Severity Scale, Sleep Impairment Index, PDQ-8, Ability to Function Scale, the MCBI caregiver burden, the CES-D, or the Daytime Alertness Scale.

Adverse Events

Both drug and placebo were well tolerated. Overall, 30% of patients reported adverse events; 5 (33%) patients on drug and 4 (27%) patients on placebo had adverse events. Two of 15 patients (13%) in the eszopiclone arm had adverse events that were assessed as related

or possibly related to the study drug. Both of these patients had sedation during the day and one of them also had dizziness which resolved on its own. Four of 15 patients (27%) of patients in the placebo arm had adverse events that were rated as related or possibly related to the study; three of these had increased daytime fatigue and one had an increase in PD rigidity. No patients dropped out because of adverse events. Other adverse events that were assessed as unrelated were pain (2 on eszopiclone), weight gain (1 on placebo), infection (1 on placebo and 1 on eszopiclone).

Discussion

We did not find a statistically significant difference between groups on total sleep time, our primary outcome, but we did find significant improvements, favoring the eszopiclone group, in the number of awakenings, quality of sleep and in physician rated CGI improvement. WASO, a common measure of sleep maintenance, showed a trend towards significance. Among other sleep measures, there were no significant differences between groups in sleep latency or the Sleep Impairment Index. Our findings suggest that eszopiclone improved the quality of sleep and some measures of sleep maintenance, compared to placebo, in patients with PD and that it was well tolerated. These results need to be viewed cautiously as the study was small and may have capitalized on chance findings.

We did not find evidence for improvements in next day functioning related to drug group. The improvements in sleep that we saw also were not accompanied by any change in their PD motor symptoms.

The improvement we found in the number of awakenings is consistent with the literature showing significant problems with sleep maintenance in patients with PD. For instance, community-based surveys have consistently found a greater prevalence of sleep problems in patients with PD compared to healthy controls, matched for age and gender and compared to patients with other medical disorders like diabetes^{10, 20, 21} with up to 88% of patients describing sleep fragmentation.¹

Insomniacs have been shown to have lower quality of life than good sleepers within both healthy and chronically ill populations.^{22,23} Treatment trials of insomnia in non-PD populations suggest that improvements in sleep measures are associated with improvements in QoL and daytime functioning^{24, 25} but we did not find any difference between groups in the PD quality of life scale or in measures of daytime functioning. This may be related to low power or could indicate that patients with PD have other impairments that overwhelm QoL daytime functioning measurements. In the end, these measures are what really matter to patients, so future trials should emphasize measures of daytime alertness and function.

Poor sleep in patients with PD has also been associated with depression and burden in caregivers^{7,8} but we did not find any improvements in either caregiver burden or depression that were associated with drug group. Again, this may be related to low power or could indicate that patients with PD have other impairments that these measurements.

Patients in this study tolerated eszopiclone and placebo well. Only 13% of patients had an adverse event assessed as related to study drug, (sedation and dizziness) and these were mild. Unpleasant taste, sedation and dizziness are the most common side effects of eszopiclone seen in clinical practice but in this study only two patients had sedation, one had dizziness and none had an unpleasant taste in their mouth.

To our knowledge, this is the first randomized controlled study of a sleep medication for insomnia in patients with PD. It was, however, small by clinical trial standards, and many of our positive findings could capitalize on chance. Likewise, many of our negative findings

could be related to poor power to detect differences in these variables. Furthermore, the group was relatively young (56 years old) with relatively mild disease and the results may not generalize to an older more ill population. The drop out rate was also high which was largely due to lack of efficacy. Patients generally understood that if they hadn't gotten benefit in the first few weeks of the trial they were not likely to improve and so they dropped out and sought active treatment. Nonetheless, we believe that the trial is important as up to 40% of community dwelling patients with PD are using sleeping pills,²⁶ and there are no other controlled data available.

The outcome measures in this study were subjectively rated sleep diaries. While there is often a divergence in subjective and objective (PSG) sleep measures,²⁷ they are usually correlated²⁸ and we did find a significant correlation between baseline TST on the diaries and on the PSG. The study may suggest, however, that TST may not be the best choice of a sleep measure for PD patients and that future trials should focus on measures of sleep maintenance and sleep quality.

While no specific trials have examined the treatment of insomnia in patients with PD, both pharmacologic and non-pharmacologic measures have been shown to be beneficial in the treatment of insomnia in the general population and in the elderly with pharmacotherapy being the most widely used treatment for insomnia in clinical practice.²⁹ The results of this trial are generally consistent with previous studies of eszopiclone in non-PD patients with insomnia which have found improvements the number of awakenings, WASO, total sleep time and associated quality of life.^{30, 31,32,33}

The interactions between PD and sleep are complicated. While we excluded patients with other primary sleep disorders, many PD patients with insomnia in clinical practice will also have co-occurring sleep disorders such as RBD, PLMS and Sleep Disordered Breathing. Furthermore, sleep disturbances may be related to factors such as nocturia, pain, dystonia, akinesia, difficulty turning in bed and vivid dreaming.³⁴ Therefore all patients with sleep difficulties need careful evaluation before proceeding to treatment.

A variety of medications are available for use in patients with insomnia, including benzodiazepines, the nonbenzodiazepine hypnotics, melatonin, antihistamines and sedating antidepressants. While the nonbenzodiazepine hypnotics are widely used and generally cause less confusion and morning sedation than the benzodiazepines, caution is still advised in using these agents as they have been associated with an increase in daytime sedation, abnormal sleep behaviors and falls.³⁵

Psychosocial treatments for insomnia are supported by controlled trials in patients without PD but appear to be rarely used in PD. There are advantages to these treatments, including that they are generally benign and free of adverse side effects and may engender more lasting changes following treatment cessation.³⁶ However, treatment can be costly and it may be difficult to find clinicians to administer it. Other new treatments that target the movements of PD may also have positive effects on sleep. For instance, deep brain stimulation (DBS), an effective therapeutic option for the treatment of advanced Parkinson's disease, has been shown to improve sleep in PD.³⁷

In summary, we did not find, in this small controlled trial, significant differences between groups in our primary outcome of TST or in measures of daytime QoL and functioning. We did, however, find that eszopiclone outperformed placebo on the number of awakenings and the quality sleep quality in these relatively young patients with early PD. We also found the drug to be well tolerated. Considering the importance of sleep disturbances in PD, treatment should be addressed in larger more definitive studies that specifically focus on improvements in daytime functioning that accompany changes in sleep.

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References

- Factor SA, McAlarney T, Sanchez-Ramos JR, Weiner WJ. Sleep disorders and sleep effect in Parkinson's disease. *Mov Disord.* 1990; 5:280–285. [PubMed: 2259351]
- Oerlemans WG, de Weerd AW. The prevalence of sleep disorders in patients with Parkinson's disease: A self-reported, community-based survey. *Sleep Med.* 2002; 3:147–149. [PubMed: 14592234]
- Scaravelli T, et al. Health related quality of life and sleep disorders in Parkinson's disease. *Neurol Sciences.* Oct; 2003 24(3):209–210.
- Karlsen KH, Tanberg E, Arslan D, Larsen JP. Health related quality of life in P Parkinson's disease: A prospective longitudinal study. *J Neurol Neurosurg Psychiatry.* Nov.2000 69:584–589. [PubMed: 11032608]
- Pal PK, et al. Nocturnal sleep disturbances and daytime dysfunction in patients with Parkinson's disease and in their caregivers. *Parkinsonism Relat Disord.* Mar; 2004 10(3):157–168. [PubMed: 15036171]
- Karlsen KH, Tanberg E, Arslan D, Larsen JP. Health related quality of life in Parkinson's disease: A prospective longitudinal study. *J Neurol Neurosurg Psychiatry.* Nov.2000 69:584–589. [PubMed: 11032608]
- Pal PK, et al. Nocturnal sleep disturbances and daytime dysfunction in patients with Parkinson's disease and in their caregivers. *Parkinsonism Relat Disord.* Mar; 2004 10(3):157–168. [PubMed: 15036171]
- Smith MC, Ellgring H, Oertel WH. Sleep disturbances in Parkinson's disease patients and spouses. *J AM Geriatr Soc.* 1997; 45:194–199. [PubMed: 9033518]
- Garcia-Borreguero D, Larrosa O, Bravo M. Parkinson's disease and sleep. *Sleep Med Rev.* 2003; 7:115–129. [PubMed: 12628213]
- Tandberg E, Larsen JP, Karlsen K. A community-based study of sleep disorders in patients with Parkinson's disease. *Mov Disord.* 1998; 13(6):895–899. [PubMed: 9827612]
- Rechtschaffen, A.; Kales, A. Manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Brain Information Service/Brain Research Institute; Los Angeles: 1968.
- Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975; 12:189–198. [PubMed: 1202204]
- Bastien CH, Vallieres A, Morin CM. Validation of Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Medicine.* 2001; 2:297–307. [PubMed: 11438246]
- Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The PDQ-8: development and validation of a short-form Parkinson's disease questionnaire. *Psychol Health.* 1997; 12:805–14.
- Fahn, S.; Elton, RL.; Members of the UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. In: Fahn, S.; Marsden, CD.; Calne, DB.; Goldstein, M., editors. Recent developments in Parkinson's disease. Vol. 2. Macmillan Health Care Information; Florham Park (NJ): 1987. p. 153-64.
- Guy, W. ECDEU assessment manual for psychopharmacology. Washington, D.C.: U.S. Department of Health, Education, and Welfare; 1976.
- Krupp LB, LaRocca NC, Mait-Nash J, et al. The fatigue severity scale applied to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol.* 1989; 46:1121–1123. [PubMed: 2803071]
- Radloff LS. The CES-D scale: A self report depression scale for research in the general population. *Applied Psychological Measurement.* 1977; 1:385–401.

19. Verbeke, G.; Molenberghs, G. *Linear Mixed Models for Longitudinal Data*. Springer; New York: 2000.
20. Nausieda PA, Weiner WJ, Kaplan LR, Weber S, Klawans HL. Sleep disruption in the course of chronic levodopa therapy: an early feature of the levodopa psychosis. *Clin Neuropharmacol*. 1982; 5(2):183–194. [PubMed: 7139632]
21. Oerlemans WG, de Weerd AW. The prevalence of sleep disorders in patients with Parkinson's disease: A self-reported, community-based survey. *Sleep Med*. 2002; 3:147–149. [PubMed: 14592234]
22. Leger D, Scheuermaier K, Philip P, Paillard M, Guilleminault C. SF-36: Evaluation of quality of life in severe and mild insomniacs compared with good sleepers. *Psychosom Med*. 2001; 63(1): 49–55. [PubMed: 11211064]
23. Zammit GK, Weiner J, Damato N, Sillup GP, McMillan CA. Quality of life in people with insomnia. *Sleep*. 1999; 22:S379–S385. [PubMed: 10394611]
24. Walsh JK, Krystal AD, Amato DA, Rubens R, Caron J, Wessel TC, Schaefer K, Roach J, Wallenstein G, Roth T. Nightly treatment of primary insomnia with eszopiclone for six months: effect on sleep, quality of life, and work limitations. *Sleep*. Aug 1; 2007 30(8):959–68. [PubMed: 17702264]
25. Krystal AD. Treating the health, quality of life, and functional impairments in insomnia. *J Clin Sleep Med*. Feb 15; 2007 3(1):63–72. [PubMed: 17557457]
26. Tandberg E, Larsen JP, Karlsen K. A community-based study of sleep disorders in patients with Parkinson's disease. *Mov Disord*. 1998; 13(6):895–899. [PubMed: 9827612]
27. Kryger MH, Steljes D, Pouliot Z, Neufeld H, Odynski T. Subjective versus objective evaluation of hypnotic efficacy: Experience with zolpidem. *Sleep*. 1991; 14(5):399–407. [PubMed: 1759092]
28. Unruh ML, Redline S, An MW, Buysse DJ, Nieto FJ, Yeh JL, Newman AB. Subjective and Objective Sleep Quality and Aging in the Sleep Heart Health Study. *J Sleep Res*. 2009; 3(3):152–158.
29. Kupfer DJ, Reynolds CF. Management of insomnia. *N Engl J Med*. 1997; 336:341–346. [PubMed: 9011788]
30. Walsh JK, Krystal AD, Amato DA, Rubens R, Caron J, Wessel TC, Schaefer K, Roach J, Wallenstein G, Roth T. Nightly treatment of primary insomnia with eszopiclone for six months: effect on sleep, quality of life, and work limitations. *Sleep*. Aug 1; 2007 30(8):959–68. [PubMed: 17702264]
31. McCall WV, Erman M, Krystal AD, Rosenberg R, Scharf M, Zammit GK, Wessel T. A polysomnography study of eszopiclone in elderly patients with insomnia. *Curr Med Res Opin*. Sep; 2006 22(9):1633–42. [PubMed: 16968566]
32. Roth T, Walsh JK, Krystal A, Wessel T, Roehrs TA. An evaluation of the efficacy and safety of eszopiclone over 12 months in patients with chronic primary insomnia. *Sleep Med*. Nov; 2005 6(6):487–95. [PubMed: 16230048]
33. Krystal AD, Walsh JK, Laska E, Caron J, Amato DA, Wessel TC, Roth T. Sustained efficacy of eszopiclone over 6 months of nightly treatment: results of a randomized, double-blind, placebo-controlled study in adults with chronic insomnia. *Sleep*. Nov 1; 2003 26(7):793–9. [PubMed: 14655910]
34. Lowe AD. Sleep in Parkinson's disease. *J Psychosom Res*. 1998; 44(6):613–617. [PubMed: 9678736]
35. Terzano MG, Rossi M, Palomba V, Smerieri A, Parrino L. New drugs for insomnia: comparative tolerability of zopiclone, zolpidem and zaleplon. *Drug Saf*. 2003; 26(4):261–82. [PubMed: 12608888]
36. Morin CM, Colecchi C, Stone J, Sood R, Brink D. Behavioral and pharmacological therapies for late-life insomnia: A randomized controlled trial. *JAMA*. 1999; 281(11):991–999. [PubMed: 10086433]
37. Cicolin A, Lopiano L, Zibetti M, Torre E, Tavella A, Guastamacchia G, Terreni A, Makrydakis G, Fattori E, Lanotte MM, Bergamasco B, Mutani R. Effects of deep brain stimulation of the subthalamic nucleus on sleep architecture in parkinsonian patients. *Sleep Med*. Mar; 2004 5(2): 207–10. [PubMed: 15033145]

Figure 1.
Flow diagram

TABLE 1

Primary and secondary efficacy measures

	Eszopiclone		Placebo		Significance
	Baseline	Endpoint	Baseline	Endpoint	
Primary Outcome					
TST (hours)	4.5 (1.28)	5.7 (1.16)	5.3 (1.28)	6.0 (1.16)	NS
Secondary Outcomes					
WASO (minutes)	54 (57)	17 (50)	49 (51)	46 (45)	.071
Number of awakenings	2.0 (1.5)	1.0 (1.4)	1.7 (1.4)	1.8 (1.2)	.035
Quality of sleep	3.4 (2.1)	5.0 (2.1)	3.8 (1.9)	5.3 (2.2)	.018
Sleep latency (minutes)	18 (17)	11 (15)	23 (15)	20 (14)	NS
CGI (improvement) Low = improved		2.3 (1.2)		3.2 (1.5)	.035
UPDRS (total)	32.5 (8.8)	32.4 (9.8)	28.3 (9.1)	27.4 (8.5)	NS
UPDRS motor	19.8 (7.7)	16.7 (7.0)	15.2 (5.3)	12.7 (6.4)	NS
UPDRS ADL	11.2 (3.3)	11.0 (3.3)	7.9 (4.7)	6.2 (3.5)	NS
Fatigue Severity Scale	37 (17)	32 (15)	36 (15)	33 (15)	NS
PDQ-8	17.3 (6.0)	16.0 (5.6)	14.2 (5.5)	13.9 (5.6)	NS
Ability to function	6.3	5.9	7.6	7.9	NS
Caregiver burden -MCBI	13.6 (30)	16.7 (28)	15.8 (26)	11.6 (20)	NS
Caregiver depress- CESD	28 (11)	30 (9.8)	28 (9.7)	26 (10.6)	NS
Daytime alertness	6.8 (1.7)	6.9 (2.0)	5.7 (1.6)	5.9 (1.6)	NS
Sleep Impairment Index	4.3 (2.9)	4.0 (2.7)	4.3 (2.6)	4.0 (2.4)	NS

P values for the secondary outcomes are adjusted for multiple comparisons