Treatment of Sleep Dysfunction in Parkinson's Disease

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Opinion statement

Impaired sleep and alertness affect the majority of Parkinson's disease (PD) patients, negatively impacting safety and quality of life. The etiology of impaired sleep-wake cycle in PD is multifactorial and encompasses medication side effects, nocturnal PD motor symptoms, and presence of co-existent sleep and neuropsychiatric disorders. The primary neurodegenerative process of PD involves brain regions that regulate the sleep-wake cycle, such as brainstem and hypothalamic nuclei. Sleep disorders in PD include insomnia, REM sleep behavior disorder (RBD), sleep disordered breathing (SDB), restless legs syndrome (RLS), and circadian disruption. Despite its high prevalence in the PD population, there is a paucity of clinical studies that have investigated treatment of sleep dysfunction associated with PD. Therefore, we aim to review available evidence and outline treatment strategies for improvement of disorders of sleep and wakefulness in PD patients. Evidence supporting the efficacy of pharmacological and non-pharmacological treatment strategies in PD is limited. There is thus a great need but also opportunity for development of well-designed clinical trials for impaired sleep and alertness in PD. Providing education about sleep hygiene and strategies for its implementation represents the initial step in management. Prompt diagnosis and treatment of co-existent primary sleep and psychiatric disorders are critical, as this may significantly improve sleep and alertness. While the optimal treatment for insomnia in PD has not been established, available strategies include cognitive-behavioral therapy, medications with soporific properties, and light therapy. Safety measures, clonazepam, and melatonin are the mainstay of treatment for RBD. Continuous positive airway pressure is an effective treatment for SDB in PD. The treatment algorithm for RLS associated with PD mirrors that used for idiopathic RLS. Circadian disruption has emerged as an

important etiology of impaired sleep-wake cycles in PD, and circadian-based interventions hold promise for novel treatment approaches.

Introduction

Although Parkinson's disease (PD) is diagnosed by its motor symptoms of bradykinesia, rigidity, rest tremor, and postural instability, non-motor symptoms are also prevalent and are often more disabling than the motor symptoms [1, 2]. Sleep dysfunction is one of the most common of these non-motor symptoms, affecting up to 98% of PD patients [3, 4]. Sleep complaints include sleep fragmentation, insomnia, parasomnias such as rapid eye movement (REM) sleep behavior disorder (RBD), excessive daytime sleepiness (EDS), circadian dysfunction, and restless legs syndrome and periodic limb movements of sleep [5]. Sleep dysfunction adversely affects quality of life (QOL), increases caregiver burden, and, in the case of EDS, can result in inability to safely complete tasks such as driving [6–8].

Sleep dysfunction in PD is multifactorial, influenced by various factors related to the disease and its treatment. The motor symptoms of PD can contribute to sleep fragmentation and insomnia. For example, bradykinesia and rigidity can lead to impaired bed mobility and nocturnal dystonia can cause nocturnal pain and discomfort [9–11]. Additionally, tremor can reemerge during microarousals and sleep stage transitions, contributing to sleep maintenance insomnia [12]. Medications used to treat PD can improve these motor symptoms, but can also contribute to nocturnal sleep problems and EDS [13].

Sleep disorders in PD are also influenced by and interact with other common non-motor symptoms. For example, autonomic dysfunction can cause nocturia, which contributes to worsened subjective and objective sleep in PD [14, 15]. Additionally, mood disorders, including depression and anxiety, are correlated with nocturnal and daytime sleep dysfunction in PD and depression predicts development of insomnia [16–19]. Sleep dysfunction, including RBD, sleep fragmentation, and daytime sleepiness, are also associated with psychosis and hallucinations in PD [5, 20]. Importantly, excessive daytime sleepiness has been demonstrated to be predictive of several neuropsychiatric disorders including depression and psychotic symptoms, and both EDS and RBD are predictive of cognitive decline [21–25]. Further, cognitive dysfunction contributes to sleep disturbances including insomnia and EDS, and is associated with RBD [26–28].

In addition to the constellation of PD-related symptoms and treatments that can contribute to sleep dysfunction, PD patients can also experience primary sleep disorders, such as restless legs syndrome (RLS), periodic limb movements of sleep (PLMS), and sleep apnea [5, 29]. These disorders contribute to worsened subjective sleep quality and objective sleep measures and can be associated with worsened depression and cognition [29–31]. Appropriate

recognition of these primary sleep disorders is important due to their negative influence on QOL in patients with PD [30].

The recognition of the many factors that can contribute to nocturnal and daytime sleep dysfunction in PD is important for optimizing treatment of sleep complaints for individual patients. This review will discuss pharmacologic and non-pharmacologic treatment strategies for improving sleep and alertness in patients with PD. We will explore treatments that act directly on sleep symptoms such as insomnia and daytime sleepiness and also review treatment of motor and non-motor symptoms that indirectly influence sleep and vigilance in PD.

Pharmacologic therapies

Dopaminergic medications

Dopamine plays an essential role in the regulation of the sleep-wake cycle. For example, medications that increase the synaptic availability of dopamine, such as amphetamines, promote alertness. This supports the traditional view of dopamine-related wake-promoting properties. Degeneration of the dopaminergic system therefore may be one mechanism underlying the EDS that is common in PD. Dopamine, however, may also trigger hypersomnolence. While stimulation of D1 receptors results in wake-promoting effects, differential responses may be seen with stimulation of D2 and D3 receptors depending of the dose of the drug [32]. Dopamine also has important connections with the human circadian system [33]. This likely bi-directional relationship is important for sleep-wake homeostasis.

Studies reporting the effects of dopaminergic medications on sleep reveal contradictory findings. While most of these studies evaluate motor function as the primary outcome, some studies also report effects of these medications on sleep. Studies of pramipexole, transdermal rotigotine, and extended-release formulations of levodopa and ropinirole show significant improvements in sleep quality [34–37]. The CLEOPATRA-PD clinical trial, which compared the efficacy of pramipexole and rotigotine, demonstrated significant improvements in sleep as assessed by the Parkinson's Disease Sleep Scale (PDSS) [34]. Extended release ropinirole as adjunctive therapy to levodopa was studied in the EASE-PD clinical trial and revealed favorable effects on sleep quality [36]. In the RECOVER clinical trial, transdermal rotigotine improved sleep as assessed by the PDSS-2 [37]. Observed benefits of dopamine agonists appear to be modulated by improvements in overnight motor PD symptoms, but other mechanisms may be involved as well. For example, dopaminergic medications are useful in the treatment of RLS in other populations, although there are no randomized controlled trials (RCTs) evaluating RLS treatment in PD [5]. Collectively, these studies suggest that extended-release dopamine agonists may have a role in the management of sleep disturbances in PD.

Equally importantly, other studies link levodopa and dopamine agonists with worsened sleep, including the development of insomnia, which may be a dose-dependent phenomenon [38, 39]. Levodopa and dopamine agonists have been also associated with EDS and sudden onset sleep, so-called sleep attacks. Potential risks of dopamine agonist-associated sleepiness, including sleep attacks, should be considered when prescribing dopaminergic

therapies to improve overnight sleep. Other classes of dopaminergic therapies can also influence sleep. For example, selegiline can have stimulant properties that exacerbate insomnia [40].

Non-benzodiazepine sedative hypnotic agents

Non-benzodiazepine sedative hypnotic agents include zolpidem, zaleplon, and eszopiclone. There are limited high-level data on the safety/efficacy of hypnotic agents for treatment of sleep problems in PD. Available studies performed in the PD population have generally had very small sample sizes. In a 6-week study of 30 PD patients with sleep onset insomnia [41], participants were randomized to eszopiclone or placebo. While total sleep time (TST) (the primary outcome) did not improve, number of awakenings, quality of sleep, and the physician-rated clinical global impression scale were all significantly better in the eszopiclone arm. Adverse events were not significantly different between the treatment arms. Based on recommendations in the general older adult population, non-benzodiazepine sedative hypnotic agent use in PD should be limited to brief treatment duration while alternative treatments, including cognitive-behavioral therapy, are being administered [42].

Benzodiazepines

Benzodiazepines used for sleep include short-acting benzodiazepines such as triazolam, temazepam, flurazepam, and lorazepam as well as longer-acting benzodiazepines such as clonazepam. Given the risks associated with benzodiazepine use, including increased risk of falls and cognitive impairment, their use in older adults, including PD, should generally be avoided [42].

Unfortunately, therapies for RBD are limited, and clonazepam remains the mainstay of treatment for RBD (along with melatonin; see below) [43]. Data supporting the efficacy of clonazepam for RBD in PD is limited. Studies in the so-called idiopathic RBD population (individuals with RBD without a diagnosed neurodegenerative disorder) are also limited, with no large RCTs available. However, retrospective studies and large case series suggest that clonazepam reduces dream enactment and thus risk of injury [43].

Data supporting the use of benzodiazepines for other sleep disorders in PD are limited. In the appropriate clinical context, they may be considered for nocturnal anxiety, panic attacks, periodic limb movement disorder, and even sleep fragmentation insomnia, but only in cases where potential benefits outweigh potential risks. For example, in a PD patient with REM sleep behavior disorder, sleep onset and sleep maintenance insomnia, and PLMD, the potential benefits of clonazepam may outweigh the medication-related risks, as well as the risks of polypharmacy should each sleep problem be targeted with differing pharmacotherapy.

Psychotropic medication

In treating neuropsychiatric symptoms in PD patients with co-morbid sleep disorders, several principles of rational pharmacotherapy warrant consideration. First, when possible, psychotropic medications that can be used to treat both the neuropsychiatric symptoms as well as the co-morbid sleep disorder should be selected. Second, potential worsening of co-

morbid sleep problems as an adverse effect of a given psychotropic should always be considered. For example, many anti-depressants can worsen RBD and RLS, as discussed further below. There are limited high-level data on the safety/efficacy of psychotropic medications for sleep problems in PD, but data from a few studies in PD and from several studies in the general older adult population provide for some guidance in this regard. See Table 1 for more information.

Anti-psychotics—The majority of anti-psychotics are recommended against in PD as they can significantly worsen Parkinsonism [49]. However, there are some exceptions namely quetiapine, clozapine, and pimavanesrin.

Quetiapine is widely used in PD [50] despite lack of evidence for its efficacy [51] and increased risk of various adverse effects including increased mortality [52, 53]. However, given limited treatment options for psychosis in PD, its use in PD may be justified in select cases. For example, in patients with significant nocturnal psychotic symptoms, it may be considered when other pharmacologic and non-pharmacologic measures have not been successful. While the use of quetiapine as a primary treatment for insomnia should be avoided [54•], its sedating properties can be leveraged in the latter situation. A small study in PD suggests a beneficial effect on nocturnal visual hallucinations without a significant effect on most sleep measures [55]. However, non-significant improvements in several objective sleep measures were noted including increased TST and reduced wake time after sleep onset [55].

Of all the anti-psychotics, clozapine has the highest level of evidence supporting its efficacy for PD psychosis. Unfortunately, risk of agranulocytosis, as well as the impracticality of the required frequent blood monitoring, limits its use. There are some data to suggest clozapine improves sleep in PD. Large retrospective studies indicate it may improve sleep fragmentation, insomnia, sundowning, vivid dreams, and nocturnal akathesia [46]. Importantly, EDS is a common adverse event, occurring in nearly half of treated patients [46]. These data suggest that while sleep disturbance in and of itself is not an appropriate indication for clozapine therapy, in patients with PD psychosis and significant nocturnal disturbances, consideration for clozapine should be given, but with the understanding that up to one half of treated patients will experience EDS.

Pimavanserin is a 5-HT2A inverse agonist with anti-psychotic efficacy in PD, as demonstrated in an RCT [47•]. In that trial, a secondary outcome included subjective sleep, as assessed with the Scales for Outcomes in Parkinson's Disease (SCOPA-SLEEP). Pimavanserin significantly improved SCOPA-SLEEP compared to placebo. Interestingly, there was no correlation between improvements in sleep and psychosis, which, combined with results from studies on effects of pimavanesrin on sleep in adults without PD [48], suggests that the sleep improvements due to pimavanserin may be independent of its anti-psychotic effect. Additional studies are required to confirm this. However, this preliminary data does suggest that in the appropriate context, such as in PD patients with sleep disrupted by nocturnal psychotic symptoms (such as hallucinations or paranoia), pimavanserin may be considered.

Anti-depressants—As mentioned above, depression and sleep disturbances are commonly comorbid in PD. There are some, though limited, data to support the beneficial effect of anti-depressants on sleep. The mechanism of efficacy is not known but could result from the sedating properties of the agent, improvement in mood/anxiety, or both. In RCTs that included subjective sleep measures as a secondary outcome, both venlafaxine [44] and nortriptyline were associated with improved subjective sleep compared to placebo [45]. Mirtazapine, an anti-depressant with sedating properties, is useful in older adults with co-morbid insomnia and depression, but data on its use in PD is limited [42].

Several anti-depressants have sedating properties at doses lower than what would typically be administered for an anti-depressant effect. These include trazodone and doxepin. Data to support their use and safety in PD is limited, but one small pilot study reported a benefit in PD patients treated with doxepin [56•]. Data from the non-PD older adult population suggest efficacy for treatment of sleep maintenance insomnia with good tolerability [42]. Duloxetine is an NSRI that is efficacious for several etiologies of pain including fibromyalgia and neuropathic pain. It may be an appropriate consideration in PD patients with significant nocturnal pain, though trials supporting its use in PD have not been reported.

All selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) have the risk of worsening RLS and RBD. In such instances, lowering the dose may be sufficient to mitigate the worsening, but in many cases, discontinuation and identification of another agent to treat the depression and other sleep disturbances may be required.

Wake-promoting agents

Medications used to promote wakefulness in primary disorders of hypersomnolence, such as narcolepsy, include stimulants such as dextroamphetamine, methylphenidate, modafinil, and armodafinil. Some of these medications have been tested in patients with PD. For example, methylphenidate improved subjective sleepiness as a secondary outcome in a placebo-controlled trial testing the effects of this medication on gait dysfunction in PD patients after deep brain stimulation [57]. The most common adverse effects of methylphenidate in this study were elevation of heart rate and weight loss [57]. Modafinil has been tested in three small RCTs with varying results. Two studies demonstrated improvement in subjective sleepiness with modafinil, while another showed no significant improvement compared to placebo [58–60]. Modafinil did not alter objective measures of sleepiness [58, 60]. A recent meta-analysis of these three trials demonstrated evidence for improvement in subjective EDS due to modafinil in PD [61•]. Caffeine has also been studied in a placebo-controlled manner for EDS in PD, but showed only a trend toward reduction in scores on the Epworth Sleepiness Scale. In an open-label study, orally disintegrating selegiline was shown to significantly reduce EDS, but the trial included concurrent reduction of dopamine agonist, making it difficult to determine direct impact of selegiline on sleepiness [40]. A placebo-controlled trial of atomoxetine for treatment of depression in PD did not show any improvement in depression, but did improve cognition and reduce EDS as secondary outcomes [62]. Though efficacy data is limited for these therapies, these medications are

generally well tolerated, and it is reasonable to consider their use for EDS in PD, particularly if there is a safety risk related to the EDS.

Melatonin

Melatonin is a hormone produced by the pineal gland. Its soporific properties and synchronizing effects on the circadian system provide the basis for its therapeutic use in sleep medicine. In PD, melatonin has been primarily used for the management of insomnia and RBD. It is generally well tolerated although morning sleepiness and headaches have been reported. Despite its relatively common use in the PD population, RCTs of melatonin in PD are scarce. Long-term data on the efficacy of melatonin in treating sleep disorders in PD are not available, though short-term studies are promising.

In an RCT of 18 PD patients, treatment with melatonin (3 mg) resulted in significant improvements in sleep quality as assessed by the Pittsburgh Sleep Quality Index (PSQI) [63, 64]. PSG-derived sleep metrics, however, did not differ between placebo and melatonin groups. Treatment with melatonin was well tolerated without impact on motor performance.

In another double-blind, placebo-controlled, cross-over clinical trial, 40 PD patients were treated with either melatonin 5 or 50 mg, or placebo [63, 64]. Nocturnal sleep was assessed by actigraphy and sleep diaries, whereas daytime sleepiness and function were assessed with questionnaires. A statistically significant improvement in total nighttime sleep time by 10 min was observed during the 50 mg melatonin treatment compared to 5 mg or placebo, but this is of unclear clinical significance. Significant improvement in subjective sleep disturbance, sleep quantity, and daytime sleepiness were seen during the 5 mg melatonin treatment compared to placebo.

Supraphysiological doses of melatonin in patients with RBD reduce abnormal motor and vocal behaviors and restore muscle atonia in REM sleep [65]. The mechanism of action of melatonin in RBD remains unknown. Several case series documented beneficial effects of melatonin for RBD with daily doses up to 12 mg [66–68]. A double-blind, placebo-controlled, cross-over trial of melatonin in 8 male patients with mild RBD revealed complete resolution of dream enactment behaviors in 4/8 patients, partial resolution in 3/8, and no change in 1 patient [69]. Higher doses of melatonin at bedtime (6–15 mg) restore REM atonia in association with disappearance of RBD symptoms [69]. An open-label clinical trial of the melatonin receptor agonist, ramelteon, demonstrated improvements of RBD in a cohort of 35 PD patients with co-existent sleep disturbances [70].

Miscellaneous

Suvorexant is an orexin antagonist. Studies of suvorexant for treatment of insomnia in the general older adult population are limited but suggest it can be efficacious and well tolerated in this patient population [71]. It has not been studied in PD.

Gabapentin is an anti-convulsant that has demonstrated efficacy for neuropathic pain as well as restless leg syndrome in the general population, with a fair amount of data available on its efficacy and safety in older adults [72, 73]. While data on its utility in PD are limited, in PD patients with RLS and/or neuropathic pain, gabapentin may be considered.

Agomelatine is melatonin MT1/MT2 receptor agonist and $5HT_{2c}$ receptor antagonist that improved sleep quality and daytime sleepiness and reduced nocturnal awakenings in an open-label trial in patients with PD [74]. Randomized, controlled trials in PD are not yet available for this medication.

Sodium oxybate is a medication used to treat cataplexy and EDS in narcolepsy and has been tested in PD patients in an open-label study [75]. The 27 participants who completed the study had significant improvements in subjective sleepiness, sleep quality, and fatigue as well as a significant objective improvement in slow wave sleep by polysomnography, but also showed an increase in the apnea hypopnea index [75].

Rivastigmine is a cholinesterase inhibitor that is indicated for treatment of dementia in PD and Alzheimer's disease. One small ($n = 12$), double-blind, placebo-controlled, cross-over study investigated rivastigmine in patients with PD who had RBD [76]. Rivastigmine treatment was associated with reduced frequency of RBD episodes.

Non-pharmacologic therapies

Because medication therapies have the potential for detrimental side effects, non-pharmacologic therapies offer a promising alternative for treatment of sleep disorders in PD. However, similar to studies on pharmacologic therapies for sleep-related therapy in PD, there are few RCTs investigating the efficacy of non-pharmacologic treatments. In this section, we will discuss available evidence for use of exercise, light therapy, and cognitive-behavioral therapy for disorders of sleep and wakefulness in PD.

Exercise

In healthy older adults, exercise improves both sleep quality and objective sleep outcomes, as measured by polysomnography. A meta-analysis investigating the impact of exercise on sleep showed that regular exercise in older adults improves sleep quality, reduces sleep latency, and increases TST and sleep efficiency [77]. In PD, there are limited data evaluating the impact of exercise on sleep. The only RCT demonstrated that a multimodal exercise intervention over 6 months improved subjective sleep quality and instrumental activities of daily living in patients with PD in the exercise group ($n = 23$) compared to those in the control group ($n = 19$) [78•]. There are no published studies on the effects of exercise on objective sleep outcomes in PD, nor its effects on circadian rhythm. Pilot studies suggest that group therapy exercise [79] and Qigong (a traditional Chinese meditative exercise) [80] may improve sleep in PD.

Circadian-based interventions

Circadian disruption has been demonstrated in several animal models of parkinsonism as well as in patients with early and advanced PD; this may relate to the integral role dopamine plays in regulation of circadian rhythmicity. Low circadian amplitude has been linked with EDS associated with PD. There is thus a strong rationale for the exploration of circadian-based interventions for impaired sleep and alertness in PD.

Applications of light therapy, melatonin, and physical exercise are common circadian-based treatment interventions used for treatment of primary sleep and psychiatric disorders in the non-PD population. In PD, melatonin has mainly been primarily used in the treatment of insomnia and RBD (above). Circadian properties of melatonin have not yet been explored as a treatment strategy for improving sleep-wake cycles in PD.

Supplementary exposure to bright light (light therapy, LT) has shown beneficial effects on sleep quality and daytime vigilance in healthy elderly as well as patients with dementia [81–86]. Reported effect sizes of LT are equivalent or superior to psychopharmacological treatments [87]. Activation of the SCN has been hypothesized as one of the mechanisms of bright environmental light effects on mood, sleep, and circadian rhythms [88, 89]. To date, several studies have been published on LT in PD [90–92]. In a series of 12 PD patients with insomnia and/or depressive symptoms, bright LT of 1000–1500 lx administered for 60–90 min prior to the habitual bedtime over a 2-week period resulted in improved sleep onset latency, sleep continuity, and mood [90]. In an open-label study, 120 PD patients were prescribed bright LT at the dose of 4000 to 6000 lx for 60 min prior to the habitual bedtime and were followed from a few months to 8 years [91]. Patients with good compliance achieved improvements in mood, anxiety, and tests of motor function. In another controlled LT study, 36 PD patients were randomized to receive bright LT with 7500 lx or placebo LT of 950 lx for 30 min in the morning during a 2-week period [92]. Bright LT was associated with significantly improved Unified Parkinson Disease Rating Scale (UPDRS) part I and II scores, and modest improvements in mood and daytime sleepiness.

In the most recent clinical trial of LT in PD, 31 patients receiving stable dopaminergic therapy with co-existent EDS and without cognitive impairment or primary sleep disorder were randomized 1:1 to receive bright LT or dim-red LT (control condition) twice daily in 1-h intervals for 14 days [93•]. Bright LT resulted in significant improvements in EDS as assessed by the ESS. Both bright LT and dim-red LT were associated with improvements in sleep quality as captured by the PSQI and the PDSS. Bright LT improved several self-reported sleep metrics, including sleep fragmentation, sleep quality, and ease of falling asleep. Light therapy was associated with increased daily physical activity as assessed by actigraphy. Of interest are also improvements in UPDRS part I, II, and III scores after the LT intervention.

In summary, these studies demonstrate beneficial effects of bright LT on sleep, mood, and non-motor function in PD. LT, already widely used in sleep medicine, holds a promise as a non-pharmacological treatment intervention for disruptions of sleep and alertness in PD.

Cognitive-behavioral therapy

Another non-pharmacologic intervention that has been used successfully to treat insomnia in non-PD populations is cognitive-behavioral therapy for insomnia (CBT-I). The American Academy of Sleep Medicine recommends this intervention as treatment for insomnia [94]. CBT-I teaches patients to change dysfunctional behaviors and thinking patterns that contribute to their sleep impairment and employs methods such as stimulus control, cognitive therapy for dysfunctional thinking, sleep relaxation, sleep hygiene instruction, and sleep restriction [94]. In healthy adults with insomnia, a meta-analysis demonstrated that

CBT-I reduces sleep latency and wake after sleep onset and increases sleep efficiency [95]. Additionally, in patients with insomnia and another comorbid condition, including psychiatric disease, COPD, kidney disease, cancer, chronic pain, and osteoarthritis, another meta-analysis showed that CBT-I is effective for insomnia in the setting of other psychiatric and medical diagnoses [96]. We are aware of only one small study that evaluated CBT-I in PD. This randomized, controlled study evaluated three groups of six patients: CBT-I in combination with light therapy, doxepin, and control. The CBT-I/light therapy group showed improvement in the Insomnia Severity Index, PDSS, and examiner-reported clinical global impression of change, but showed a worsening of quality of life [56•]. The success of CBT-I in other populations suggests that further study is warranted to evaluate its effects on PD patients with insomnia.

Summary

Impaired sleep and alertness are common in the PD population. Its causes are multifactorial, which adds to the complexity of the treatment. Despite the wide range of sleep disturbance in PD and its major clinical impact, almost no systematic treatment studies have been performed. This emphasizes the need to focus efforts on development and execution of clinical trials that will lead to optimization of existing treatments as well as development of novel treatment modalities for various aspects of sleep, wakefulness, and circadian disturbances in PD.

Acknowledgements

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Table 1.

Evidence and considerations for use of psychotropic medications to treat sleep disturbances in PD

	Medication	Therapeutic target	Potential effects of sleep	Adverse event considerations
Anti-depressants	Venlafaxine	Depression	Compared to placebo, improved subjective sleep [Pittsburgh Sleep Quality Index (PSQI), secondary outcome] in randomized controlled trial [44]	May worsen RBD and RLS. May cause weight gain
	Nortriptyline	Depression	Compared to placebo, improved subjective sleep (PSQI, secondary outcome) in randomized controlled trial [45]	May worsen RBD and RLS. May cause weight gain. May have anti-cholinergic and alpha-blocking side effects at higher doses
	Mirtazapine	Depression	Limited evidence for efficacy	May worsen RBD. May cause weight gain
	Trazodone	Depression	Limited evidence for efficacy	May worsen RBD and RLS. Doses required for anti-depressant effect may be associated with severe side effects in PD (anti-cholinergic, alpha-blocking side effects) [42]
	Doxepin	Depression	Limited evidence for efficacy	May worsen RBD. Doses required for anti-depressant effect may be associated with severe side effects in PD (anti-cholinergic, alpha-blocking side effects) [42]
	Duloxetine	Depression, pain	Limited evidence for efficacy	May worsen RBD and RLS
Anti-psychotics	Quetiapine	Psychosis	Limited evidence for efficacy	May prolong QT interval
	Clozapine	Psychosis	Based on retrospective studies, may improve sleep onset and maintenance insomnia, vivid dreams, and nocturnal restlessness [46]	May lead to significant daytime sleepiness [46]
	Pimavanserin	Psychosis	Improved subjective sleep (secondary outcome) in randomized placebo-controlled trial [47•, 48]	May prolong QT interval
Anti-depressants	Venlafaxine	Insufficient evidence	Acceptable risk without specialized monitoring	Possibly useful. May be considered in PD patients with co-morbid depression and nocturnal sleep disturbance
	Nortriptyline	Insufficient evidence	Acceptable risk without specialized monitoring	Possibly useful. May be considered in PD patients with co-morbid depression and nocturnal sleep disturbance
	Mirtazapine		Acceptable risk without specialized monitoring	Possibly useful. May be considered in PD patients with co-morbid depression and nocturnal sleep disturbance. Lower doses are more sedating than higher doses [42]
	Trazodone	Insufficient evidence	Acceptable risk without specialized monitoring	Possibly useful. May be considered to treat sleep disturbance with or without co-morbid depression (anti-depressant doses are typically higher than doses required to treat insomnia)
	Doxepin	Insufficient evidence	Acceptable risk without specialized monitoring	Possibly useful. May be considered to treat sleep disturbance with or without co-morbid depression (anti-depressant doses are typically higher than doses required to treat insomnia)
	Duloxetine	Insufficient evidence	Acceptable risk without specialized monitoring	Possibly useful. May be considered in PD patients with sleep onset/maintenance insomnia with co-morbid neuropathic pain
Anti-psychotics	Quetiapine	Insufficient evidence	Acceptable risk without specialized monitoring	Possibly useful. May be considered in PD patients with psychosis and sleep disturbances

Medication	Therapeutic target	Potential effects of sleep	Adverse event considerations
Clozapine	Insufficient evidence	Acceptable risk with Specialized monitoring	Possibly useful. May be considered in PD patients with psychosis and sleep disturbances, but to be used in caution in those with baseline EDS
Pimavanserin	Insufficient evidence	Acceptable risk without Specialized monitoring	Possibly useful. May be considered in PD patients with psychosis and sleep disturbances