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PERSPECTIVE

Pharmacological and non-pharmacological management of sleep disturbances in Parkinson's disease: if when and how

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ABSTRACT

Introduction: Sleep dysfunction occurs in various forms and is a bothersome and intrusive non-motor symptom of Parkinson's disease (PD). Frequently undiagnosed, their poor management can have a great impact on the quality of life of PD patients and their caregivers.

Areas covered: This article covers the safety and efficacy of pharmacological strategies for the management of the most frequent sleep disturbances in Parkinson's disease. Non-pharmacological aspects are also discussed, but these are not the main focus. Literature searches using electronic databases (Medline, Cochrane Library) and systematic checking of references from review articles/other reports were performed.

Expert opinion: Melatonin and clonazepam are the most commonly used therapies for the management of REM sleep behavior disorder (RBD). The most used pharmacological wake-promoting agents in the treatment of excessive daytime sleepiness (EDS) are modafinil and caffeine. Poor nocturnal sleep quality is usually linked to EDS, thus proper sleep hygiene is recommended. As nocturnal motor symptoms are commonly associated with sleep fragmentation and early morning off, optimization of dopaminergic treatment during nighttime is highly recommended for the proper management of insomnia. Further interventions include eszopiclone and melatonin for the management of insomnia. Therapeutic options for restless legs syndrome (RLS) include calcium channel alpha-2-delta ligands and low-dose dopamine agonists (DA). Further confirmatory evidence is needed before the general recommendation of these treatments.

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Parkinson's disease; sleep dysfunction; REM sleep behavior disorder; insomnia; restless legs syndrome; excessive daytime sleepiness

1. Introduction

Sleep dysfunction is frequent in Parkinson's disease (PD), and it includes a wide variety of disturbances such as insomnia, nocturnal motor disturbances (akinesia, restless legs syndrome – RLS, periodic limb movements of sleep), neuropsychiatric/parasomnias (vivid dreams, nightmares, REM sleep behavior disorder – RBD), sleep-related breathing disorders (sleep apnea), urinary difficulties (nocturia), treatment-related motor disturbances (dystonia, dyskinesias, OFF-related tremor/pain), and excessive daytime sleepiness (EDS) [1]. These sleep disturbances have a great impact on the quality of life and safety of PD patients [2], thus their prompt acknowledgment and treatment should be warranted. The aim of this review is to provide comprehensive guidance and expert opinion regarding the management of the most common sleep disturbances in Parkinson's disease.

Chemicals which modulate wakefulness and REM sleep include serotonin, noradrenaline, histamine, acetylcholine, glycine, and hypocretin (orexin) [3].

2. Insomnia

Insomnia is a common and impactful non-motor symptom of PD, resulting from complex interactions between neurodegeneration and treatment effects. It implies significant challenges for patients and clinicians alike, affecting patients' quality of sleep and quality of life [4].

Insomnia is associated with a longer disease duration [5] but is also identified in early PD stages [6], its prevalence varying from 30% to 80% [7]. It can be defined by difficulties to initiate and maintain sleep, early morning awakenings, and non-restorative sleep for minimum 3 days per week, over 3 months [8].

Sleep is an integral part of the Dashboard Vitals of PD [9,10], and improving sleep quality may also contribute to improving patients' quality of life. During sleep (mainly during slow-wave sleep), the glymphatic system (a toxic neural waste clearance pathway dependent on astrocyte aquaporin 4) is activated [11]. Sleep-wake cycle alterations may impair the function of the glymphatic system [11], therefore aiming to obtain a good sleep quality for at least 6–8 h/night may have beneficial effects on overall health. Several non-motor functions in PD are associated with impaired circadian rhythm [12]. Pathophysiological mechanisms are scarcely explored in PD. Neurodegeneration of the hypothalamic suprachiasmatic nucleus (which is the main structure involved in the modulation of the circadian synthesis of melatonin in the pineal

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gland) may be one of the causes of circadian rhythm disorders in PD. Reduced inputs of environmental light, due to neurodegenerative processes affecting the retinal dopaminergic cells may further lead to abnormal function of the suprachiasmatic nucleus. Circadian genes also modulate the synthesis of dopamine, which plays an important role in circadian rhythmicity [12]. According to Bolitho et al., dopaminergic treatment may also influence the synthesis of melatonin and the regulation of the circadian phase [13]. As a result of circadian rhythm dysfunction, daily fluctuations of the motor and non-motor symptoms are commonly observed in PD patients, in addition to sleep disturbances [7].

2.1. Pathophysiology and risk factors

The pathophysiology of insomnia in PD is multifactorial, involving neurodegenerative processes in the central sleep-wake modulating areas of brainstem [1], clock-gene dysfunction, neurotransmitter imbalances, medication side effects, and coexisting conditions [14]. The main factors leading to the appearance of insomnia in PD are shown in Figure 1.

Most patients develop sleep-onset insomnia due to inadequate sleep habits (such as napping during the day, anxiety related to inability to sleep, vigorous exercise before bedtime), or as a result of adverse effects of medications [15]. In this category, pertain antiparkinsonian drugs such as selegiline and amantadine [16], dopamine agonists acetylcholinesterase inhibitors, and selective serotonin reuptake inhibitors [17].

Not only motor symptoms during night (tremor, dyskinesia, hypokinesia) but also non-motor symptoms (nocturia, pain, RBD) can cause sleep fragmentation and, therefore, sleep-maintaining insomnia and awakenings earlier than desired [18]. Additionally, dopaminergic medications and amantadine, while essential for motor symptom management, can disrupt sleep architecture, therefore aggravating insomnia [19]. Insomnia and excessive daytime sleepiness can be associated with fatigue, while PD patients with fatigue present more severe insomnia compared to those without fatigue [20].

2.2. Interventions regarding comorbid disease and concomitant medication

Comprehensive assessment and individualized management strategies are essential to address this symptom effectively.

As motor fluctuations during night can cause sleep fragmentation, optimization of antiparkinsonian treatment, especially by considering long-acting formula to cover the nighttime [21], may improve sleep-maintaining insomnia. Transdermal rotigotine improves tremor and dystonia during night, reduces latency of sleep onset, improves pain, nocturia, RLS, and overall sleep parameters – as shown by subjective and objective measurements [22–24]. It was shown that rotigotine was effective in improving subjective sleep parameters as an add-on therapy to levodopa/switched from levodopa and another dopamine agonist [25]. Rotigotine is considered 'possible useful' for the treatment of insomnia by the MDS-EBM [26]. Long-acting ropinirole also showed benefits on sleep dysfunctions during night, in adjunction to levodopa [27]. Similarly, sustained-release pramipexole has shown better efficiency on sleep parameters, compared to the immediate-release form [28]. In advanced PD stages, levodopa-carbidopa intestinal gel (LCIG) may be considered, as it showed long-term improvements of insomnia and sleep quality [29,30]. Other novel non-oral continuous drug delivery therapies, such as subcutaneous foslevodopa/foscarbidopa infusion, showed promising results in improving sleep quality and motor symptoms in advanced PD [31]. Deep brain stimulation (DBS) was also an effective device-aided therapy for advanced PD patients in regard to the sleep domain, with improvement in sleep onset and maintenance insomnia, nocturnal restlessness, nocturia, and nocturnal motor symptoms [32].

Nocturia is followed by frequent awakenings during night and significant negative impact on sleep [33,34]. Urinary tract infections and other specific urologic diseases should be ruled out before initiating a specific treatment for nocturia. Reduction of fluid intake prior to bedtime, avoidance of diuretic agents can be initially tried; in resistant cases,

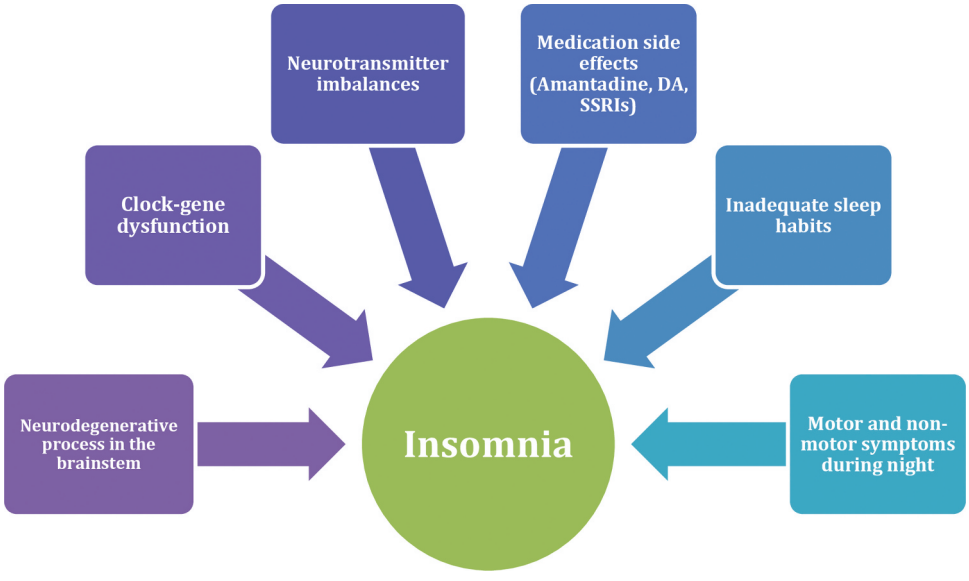

Figure 1. Factors contributing to insomnia in PD patients. DA: dopamine agonists; SSRIs: selective serotonin reuptake inhibitors.

pharmacological treatments or even invasive procedures are needed [35]. Optimization of dopaminergic therapy showed inconclusive data. Rasagiline improved bladder function in early mild PD stages [36]. Solifenacin (a M3 muscarinic inhibitor) is considered by MDS-EBM 'possible useful' in PD, with no significant side effects [26]. Mirabegron (a β3 adrenoreceptor agonist) can be efficient for controlling nocturia in PD [37], although there is insufficient data to support its benefits. Botulinum toxin instillations into the bladder represent an alternative but may induce the risk of urinary retention and infections [38].

Coexisting conditions such as depression and anxiety may further complicate the symptoms of insomnia. Non-pharmacological interventions, such as CBT and physical exercises, described in the next section, may have beneficial effects on insomnia and mood disorders. In refractory cases, antidepressants (such as benzodiazepine) can be recommended, although potential side effects (cognitive decline/dementia) should be considered when recommending long-term therapy [39].

2.3. Non-pharmacologic therapy

2.3.1. Sleep Hygiene

Educating patients about good sleep hygiene practices is essential. This includes adhering to a regular sleep schedule, creating a comfortable sleep environment, avoiding caffeine and alcohol prior to bedtime, avoiding bright light at bedtime (for example with devices such as smartphones and tablets), and engaging in relaxing activities before bedtime [40]. The use of night-light systems may be useful in reducing the risk of falls when getting up at night. Sleep hygiene is recommended to be used in conjunction with other therapies [41].

2.3.2. Cognitive-Behavioral Therapy for Insomnia (CBT-I)

CBT-I encompasses structural programs based on education, behavioral interventions, and cognitive therapy designed to improve insomnia. Studies have shown that insomnia and several sleep parameters were improved following CBT-I in PD population, with sustained results over 3 months [42,43].

2.3.3. Bright light therapy

Exposure to bright light (2500–10000 lux) in burst for 1–2-hours, particularly in the morning, can modulate the circadian rhythm and improve insomnia [44,45].

2.3.4. Exercise

Regular physical activity demonstrated beneficial effects on sleep quality and insomnia. In patients with PD, resisting training exercises [46] and high-intensity exercise training [47] have shown better outcomes on sleep quality and insomnia compared to non-exercised control PD patients.

2.3.5. Alternative treatments and relaxation techniques

Qigong and Tai-Chi, considered 'mind-body' intervention from Traditional Chinese Medicine, showed positive results on sleep quality in PD patients [48,49]. Dance therapies may have beneficial effects [50].

Yoga [51], meditation [52], and music therapy [53] can help reduce stress and promote relaxation, leading to improved sleep quality in the general population, but the efficacy in PD patients is scarcely explored.

2.4. Pharmacological therapy

Melatonin, a hormone that regulates sleep-wake cycles, may be beneficial for subjective sleep quality in PD patients [54,55]. It is generally well tolerated with minimal side effects, and it may have neuroprotective properties [56]. Although a significant objective improvement in total sleep time was observed in high doses of melatonin (50 mg), this small improvement of 10 min may not be considered clinically relevant [57].

2.4.1. Sedative-hypnotics

Medications such as zolpidem, zaleplon, and eszopiclone may be used for short-term management of insomnia [41]. Eszopiclone was demonstrated to ameliorate insomnia symptoms in a small, randomized trial in PD [58]. However, their use should be limited due to potential side effects, including confusion, dizziness, daytime sedation, and dependence [59]. Eszopiclone and melatonin (3–5 mg) are considered by the MDS EBM as 'possible interventions' for insomnia in PD patients [26].

2.4.2. Antidepressants

Certain antidepressants, such as trazodone, doxepin, and mirtazapine, have sedative effects that can aid in managing insomnia. These medications can be particularly useful in PD patients with comorbid depression [41]. Small doses of doxepin, an H1 histamine receptor blocker, may improve insomnia, posing a relatively safe profile even in elderly population [60]. Agomelatine may be another plausible alternative for the management of sleep disturbances associated with mood disorders [61].

Suvorexant (a dual orexin receptor antagonist) has shown promising results in improving insomnia in elderly people with insomnia, with minimal side effects (EDS) [62]. However, larger randomized clinical trials should be conducted in PD patients in order to prove its efficacy.

Pimavanserin, a novel neuroleptic agent, can be effective in the management of sleep maintenance insomnia in patients with comorbid nocturnal psychotic symptoms [63,64].

3. Rapid eye movement (REM) sleep behavior disorder (RBD)

Rapid eye movement (REM) sleep behavior disorder (RBD) is a sleep disorder characterized by loss of normal muscle atonia during REM sleep with recurrent dream enactment and excessive motor activity [65]. It is a common prodromal feature in patients with Parkinson's disease (PD). Its prevalence increases once PD advances, and thus RBD can be considered as a prognostic factor for PD [66]. The diagnostic criteria for RBD in PD are those provided by the American Academy of Sleep Medicine in the International Classification of Sleep Disorders 3rd edition (ICSD-3) [67] and by the International RBD Study Group (IRBDSG) [68]. For a definite diagnosis of RBD, a video-polysomnography is required, either to document REM-Sleep without atonia (RWA) or the dream enactment events. Polysomnography is also useful to distinguish between RBD and other mimics (such as non-REM

parasomnia). Non-REM parasomnia may differ from isolated RBD, also by the way of morning recalling of dreams – patients with isolated RBD have more aggressive dreams and also more 'white dreams' (having an experience of dreaming, without ability to account for that experience) [69]. Sleepwalking, a typical non-REM parasomnia, can be encountered in PD, especially in late stages [70,71], and if present it helps distinguishing from RBD. However, it must be kept into consideration that several parasomnias can occur simultaneously in PD patients (for example, RBD and sleepwalking) [71,72], therefore a thorough differential diagnosis should be performed in each patient.

Dopaminergic loss, reduced glycine and GABA inhibition, and impairments of the circadian system modulating REM sleep represent some of the proposed mechanisms implicated in the pathogenesis of RBD [73]. Genetic susceptibility also plays a role, as RBD can also be associated with glucocerebrosidase (GBA) mutations in PD patients [74]. Moreover, GBA mutations may accelerate the phenoconversion of idiopathic RBD to parkinsonism or dementia [75].

The frequency of dream enactment episodes can vary from one every few months to more than one episode per night. These episodes can be excessive motor behaviors from minor finger movements to violent body movements, which can be dangerous for the patient and bed partner. The vocalizations can be short noises, laughter, screaming, or small speech fragments. The degree of severity and their frequency is an important decision factor for the beginning of a therapy.

Video-polysomnography is the gold-standard for the assessment and diagnosis of RBD. However, in clinical practice, several validated questionnaires may be used for screening purposes. The REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ) is a validated tool for the screening of RBD [76], but it was shown to be insufficient for identifying RBD in de novo PD patients [77]. RBD can be flagged by items in Non-Motor Symptoms Questionnaire (NMSQ) [78] and can be used in clinical practice as a stepped-care approach [79].

The goals of the therapy for RBD are to reduce the motor behaviors, thus reducing injuries for the patients and their bed partners, improve nightmares associated with RBD, and therefore improve the quality of sleep. To do this, the management includes interventions regarding comorbid disease and concomitant medication and non-pharmacological and pharmacological therapy. In clinical practice, the pharmacological management of RBD attempts to hasten sleep induction or to reduce dream enactment through reducing RWA.

The management of RBD currently depends on the frequency and severity of RBD. Due to the variability and unpredictability of the dream enactment episodes and in many cases the absence of a bed partner to report these episodes, although there are no specific recommendations, the management can be started as soon as RBD is suspected.

3.1. Interventions regarding comorbid disease and concomitant medication

A detailed list of the medication is needed. Polypharmacy is one of the key elements of the vitals that form a dashboard for PD and should be reviewed in each consultation before starting a management plan [9]. Many PD patients suffer from and are treated for depression, mostly with selective serotonergic reuptake inhibitors (SSRIs) or selective noradrenergic and serotonergic reuptake inhibitors (SNRIs). It is known that SSRIs and SNRIs can aggravate or induce RBD. Therefore, this medication should be stopped or changed, when possible, before starting symptomatic treatment for RBD. Physicians should perform a proper assessment of the risks and benefits of stopping the incriminated antidepressant, and patients should be closely monitored for mood disruption after treatment discontinuation. Caution is especially needed when considering discontinuing the SSRIs or SNRIs in patients with long-term treatment with these medications, as the antidepressant discontinuation syndrome may occur [80]. Other medications which can aggravate or induce RBD are tricyclic antidepressants, mirtazapine, monoamine oxidase inhibitors (MAO) (selegiline), and beta-blockers (propranolol, bisoprolol) [81].

Sleep apnea (OSA) should always be treated when present. The movements occurring at the end of respiratory events can resemble those from RBD, making a clinical differential diagnosis difficult [82]. RBD can also occur concomitantly with OSA. Untreated OSA can pose a problem when initiating treatment with benzodiazepines [83].

3.2. Non-pharmacologic therapy

Since motor behaviors can be violent, securing the sleep environment is of utmost importance. This can be done using mattresses on the floor, a mechanical barrier between the bed partners, bed rails, removing blunt objects and weapons or padding sharp corners [84]. In a pilot study, a Posey bed alarm system was shown to reduce the RBD sleep-related injuries with the use of pressurized bed alarms with calming messages [85]. When the bed partner is very distressed due to the dream enactments of the patient, sleeping in separate beds or rooms could be a solution.

3.3. Pharmacological therapy

The recommendations for medical therapy are based on RBD management guidelines [86] and on only a few randomized controlled studies (RCT) and case series for the treatment of RBD in general. The treatment recommendations for RBD in PD are also based on these, as well.

The most used agents in clinical practice are melatonin and clonazepam.

Melatonin seems to suppress the dream enactment by suppressing REM-sleep without atonia [87]. One controlled randomized study (RCT) using a chronobiotic protocol of 3 mg melatonin taken at the same time in the evening showed an improvement in the clinical global impression scale in the melatonin group vs placebo [88]. A case series showed the efficacy of low dose immediate-release melatonin [89]. Two others recent RCTs did not show any benefit of melatonin extended release (circadin) over placebo [90,91]. Melatonin is mostly well tolerated. The treatment is started with 2–3 mg immediate-release melatonin before going to bed and is titrated up to 12 mg. The side effects are dose dependent

and include headache, nausea, and sleepiness [91]. However, the efficacy of melatonin is controversial, and the current evidence regarding its benefits in PD is insufficient [92,93].

Clonazepam reduces motor activity in REM Sleep. The mechanism for that is still not completely understood. It binds to the benzodiazepine alfa-receptors, promoting GABAergic inhibition, thus reducing phasic activity in REM sleep. Nonetheless, RWA can still be observed in vPSGs of patients taking this drug [94]. It has a good outcome at doses from 0,25 mg to 1 mg, especially in patients without cognitive impairment or sleep apnea. Although rare, worsening untreated sleep apnea was noted in patients treated with clonazepam, therefore melatonin is a better alternative in these cases [95]. One RCT failed to show an efficacy at 0,5 mg in PD patients with RBD maybe due to subthreshold dosage [96]. Hypotension, daytime sleepiness, postural instability, and cognitive dysfunction are among the side effects of clonazepam. Therefore, caution is needed especially in elderly patients.

RBD is a core feature of the noradrenergic (NA) subtype of PD [97]; therefore, rivastigmine, an acetylcholinesterase inhibitor, may be considered as a possible therapeutical alternative [98]. One treatment option for RBD in PD with cognitive dysfunction is *rivastigmine transdermal patch*. Two RCTs proved the efficacy of 4,6 mg rivastigmine on the nocturnal episodes reported by the bed partners [99,100]. Other formulations of rivastigmine did not show any effect on RBD. For memantine and donepezil, the data are very scarce [101,102].

The dopamine agonist *pramipexole* in daily dosage of 0,2 mg has been shown to have a positive effect on RBD in an open-label study [103]. The side effects for pramipexole include impulse control disorders, orthostatic hypotension, and hallucinations.

Other medications such as memantine, safinamide, and sodium oxybate have been used for the treatment of RBD; however, their effectiveness was not demonstrated in PD patients. Memantine may reduce the total REM sleep duration and frequency of dream enactment in PD patients [104] and can be useful in PD patients with cognitive decline. Sodium oxybate has been used in refractory cases of RBD, with contradictory results in patients with and without PD [105–107]. A randomized longitudinal pilot study suggested that safinamide improved RBD symptoms in PD patients with a reduction in RBD-related motor behaviors and a significant increase in total sleep time on video polysomnography [108] evaluation of the treatment efficacy is complicated. The subjective measures should include the reports of the bed partner, when available, since the patient rarely has a recollection of the events. The RBD Symptom Severity Scale (RBDSSS) was developed by the International RBD Study Group (IRBDSS) for clinical or research use [109]. The scale has a version for patients and one for the bedpartner. It has recently been validated in North America [94].

Even with the objective measure of video polysomnography, one cannot completely assess the treatment effect, given the high night-to-night variability of the RBD events. The RBD severity scale (RBDSS) evaluates the motor behavior and vocalizations during vPSG monitoring in PD patients [110]. Motor events are quantified from 0 until 3 as follows: '0' – no visible motor activity presence of RWA, '1' – small movements or jerks, '2' – proximal movements including violent behavior and '3' – axial movements including bed falls. Vocalizations are rated as: "0" (absent) or "1" (any sleep associated sound, other than respiratory noises) [96]. The IRBDSG has presented scoring rules with different weights for the motor events (1, 5 or 10), with a total overnight score and an average score for 10 min of REM Sleep [68].

4. Excessive daytime sleepiness

Excessive daytime sleepiness (EDS) is a prevalent non-motor symptom in Parkinson's disease, characterized by an overwhelming somnolence or drowsiness during daytime [111]. In certain cases, EDS may be associated with episodes of sudden onset of sleep ('sleep attacks' term in the past), defined as sudden and unpredictable episodes of sleep that occur often at inappropriate or passive situations, with or without warning signs [112].

The Park-Sleep subtype is a non-motor subtype of PD characterized by EDS, sometimes in association with sudden onset of sleep, and other sleep disturbances, especially insomnia and RBD [113].

The prevalence of EDS in PD patients varies significantly across studies, from 11.8% to 67% [114]. This variability may be attributed to differences in diagnostic criteria, evaluation tools, and demographic characteristics [114]. EDS is acknowledged as a non-motor symptom with a significant negative impact on patients' quality of life [115], leading to impairment of activity of daily living [116], and an increased risk of accidents [117].

4.1. Pathophysiology

The pathophysiology of EDS in PD is multifactorial, involving neurodegenerative process, treatment-related factors, and genetic susceptibility [111]. Research studies have observed dysfunctions of the neural activity in the left angular gyrus [118], dopaminergic deficits in the caudate nucleus [119] or low monoamine modulation of the thalamus [120] in patients with PD and EDS [97]. Moreover, dysfunctions of the adenosine-dopaminergic axis, serotonin, cholinergic, and orexin pathways can also be involved in the pathogenesis of EDS [121,122]. Circadian dysfunction may also be a potential culprit of EDS in PD [123].

The unawareness of naps in association with EDS in PD [124] resembles the clinical features of narcolepsy, and the loss of hypocretin neurons in patients with both PD and narcolepsy (even if in PD patients, the loss of hypocretin neurons is not as pronounced as in narcolepsy type I) might support a common underlying pathogenesis for these two entities [125].

The co-existence of other sleep disorders such as sleep apnea, RLS or RBD, and the discomfort induced by the motor symptoms may lead to sleep fragmentation and subsequent daytime sleepiness [126,127]. Antiparkinsonian drugs, especially dopamine agonists (DA) were demonstrated to exacerbate EDS, due to selective activation of the D2/D3 dopamine receptors [128,129]; however, some studies observed an association with LEDD, rather than a specific DA [130,131]. Furthermore, the presence of non-motor symptoms (pain,

depression, nocturia, dysautonomia) can also lead to sleep fragmentation and EDS [132].

4.2. Interventions regarding comorbid disease and concomitant medication

Comorbidity and polypharmacy take part of the Parkinson's vitals that should always be checked in PD patients [9]. Research demonstrated associations between EDS and anxiety and depression [133], therefore special attention should be given to comorbid mood disturbances when planning a management algorithm.

As EDS may be the consequence of non-restorative sleep caused by other primary sleep disorders, motor or non-motor symptoms, it is important to identify and treat accordingly these possible associated factors. The therapeutical options for RLS and RBD are described in the corresponding sections of this chapter. However, caution should be given when recommending clonazepam for the treatment of RBD, as it can induce somnolence as a side effect [134] and also worsen sleep apnea [95].

Optimization of antiparkinsonian treatment is necessary for patients experiencing EDS but can be challenging in certain cases. Disturbing motor symptoms during nighttime (tremor, dyskinesia, akinesia) may contribute to unrefreshing sleep and EDS, therefore long-acting formulations of levodopa or dopamine agonists taken at night may help reduce nighttime awakenings and improve daytime alertness [113]. However, DA may cause EDS, especially D3 agonists such as pramipexole and ropinirole [113], therefore low doses of DA may be tried or switching to other DA or antiparkinsonian drug. Selegiline (a monoamine oxidase type B inhibitor) may be considered as an add-on treatment, as it was shown to increase alertness in PD patients [135]. In advanced PD patients, levodopa/carbidopa intestinal gel may be recommended, as it may also improve EDS [136].

A well-conducted pharmacological treatment of the non-motor symptoms that can impair sleep (for instance pain, nocturia, hallucinations) may also be effective on EDS. Last but not least, the concomitant medication that can induce sleepiness as a side effect (benzodiazepines, antipsychotics, antidepressants, etc.) should be avoided. The main associations of EDS that should be addressed when developing a management plan are listed in Figure 2.

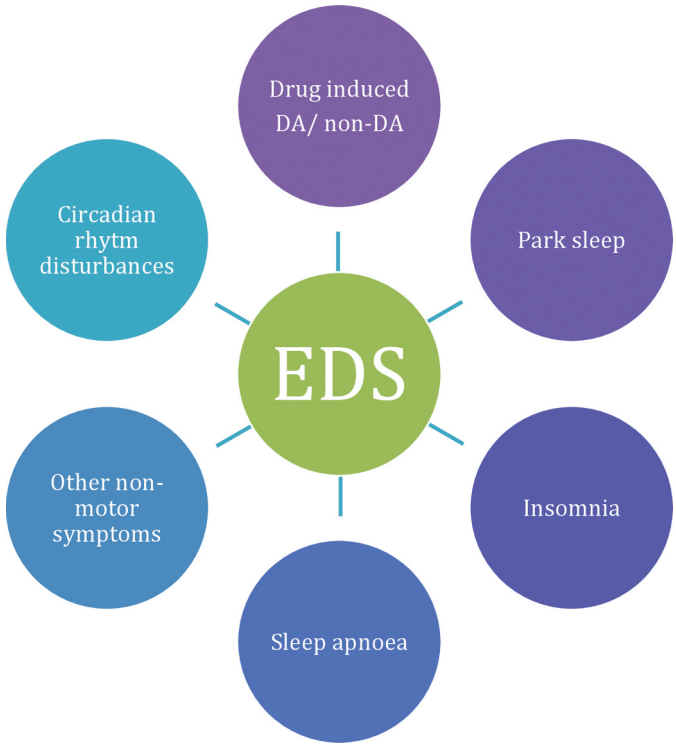

Figure 2. Main associations of excessive daytime sleepiness (EDS) in PD. DA – dopaminergic.

4.3. Non-pharmacologic therapy

4.3.1. Cognitive-Behavioral Therapy for Insomnia (CBT-I)

CBT-I is based on structured programs designed to address behavioral and psychological factors that contribute to sleep disturbances. CBT-I can improve insomnia and sleep quality [42], but the effects on EDS are still scarcely explored.

4.3.2. Sleep hygiene

PD patients with EDS should be informed regarding sleep hygiene rules, including regular sleep schedule, physical activity during daytime but avoidance of intense physical activity 3–4 h before bedtime, creating a comfortable sleep environment and avoiding stimulants such as caffeine or nicotine close to bedtime [137]. These changes in lifestyle can improve insomnia and sleep quality [137] and may reduce somnolence during daytime.

4.3.3. Bright light therapy

Exposure to bright light (up to 10 000 lux) can help improve the circadian rhythm and promote alertness during daytime in patients with PD, with good tolerance. One proposed mechanism of action of light therapy on the sleep-wake cycle is by activating the suprachiasmatic nucleus [44].

Caloric vestibular stimulation (CVS) improved daytime sleepiness in a double-blind, placebo-controlled, randomized study that included 33 PD patients [138]. Further RCT studies are needed to confirm the benefits of CVS on EDS in PD.

4.4. Pharmacological therapy

Modafinil is a non-amphetamine wake-promoting agent that has shown efficacy in reducing EDS in PD patients [112]. According to a meta-analysis, modafinil has significant beneficial effects on EDS in PD, as evaluated with the Epworth Sleepiness Scale [139]. Starting dose should be 100 mg/day, which can be slowly increased up to 200–400 mg/day [112]. Modafinil was overall well-tolerated, with mild, dose-dependent side effects that include headache, nausea, xerostomia, and anorexia. According to the same study, the cardiovascular side effects (elevated blood pressure and increased heart rate) are infrequent [140]. The exact mechanism of action of modafinil is still unknown, however it may reduce EDS by

activating the wake-promoting neurons in the tuberomammillary nucleus and by inducing inhibitory effects on the sleep-promoting neurons in the ventrolateral preoptic area [141]. Modafinil is considered by the Movement Disorders Society Evidence-Based Medicine Committee (MDS-EBM) as a 'possibly useful' therapeutic options for EDS [26]. Although not specifically studied for PD patients, *armodafinil*, another wake-promoting agent, was shown to reduce hypersomnia in patients with Dementia with Lewy Bodies, with acceptable safety and tolerability [142].

Methylphenidate, a derivate of amphetamine, has also been used to manage EDS in PD by enhancing the release of dopamine and norepinephrine. Devos et al. found that methylphenidate effectively reduced the ESS score in PD. Mild side effects were noted (dry mouth, anorexia, weight loss, headaches) [143].

Caffeine, a nonselective adenosine antagonist known to improve daytime somnolence in general population, was scarcely explored in PD. A 6-week randomized controlled trial in which up to 200 mg caffeine was administered twice daily failed to prove the beneficial effects on EDS in PD [144]. No differences were found regarding side effects between the caffeine and placebo arms [144].

According to one trial, *sodium oxybate* (a depressor of the central nervous system recommended as first-line treatment in narcolepsy type-1) may be a promising therapeutic option for EDS and nocturnal sleep disturbances in PD. This study provides class I evidence for the efficacy of this drug. Although all patients enrolled in the trial experienced adverse effects, those ones were mild or moderate and were remitted once the dose was adjusted [145]. It should also be administered with caution in patients with sleep apnea due to its depressant respiratory effects [146]. Further studies are needed in order to assess the safety profile of sodium oxybate in PD patients with EDS.

Istradefylline, is a selective adenosine A2A receptor antagonist which showed significant beneficial effects on EDS in PD patients in a single-center, open-label trial. The administered doses were 20–40 mg/day [147]. However, there is insufficient data to support its use in clinical practice.

Solriamfetol, a dopamine/norepinephrine reuptake inhibitor, has reached phase II of the randomized, double-blind, placebo-controlled trial regarding EDS in PD [148]. No significant differences were noted between ESS scores in the active and placebo arms, although Maintenance of Wakefulness Test may be suggestive for some improvements in EDS with solriamfetol. The most common side effects were nausea, dizziness, dry mouth, headache; solriamfetol should not be administered together with monoamine oxidase inhibitors [148]. Further studies are warranted to determine the efficacy of solriamfetol on EDS and its safety profile.

Pitolisant, a histamine-3 receptor inverse agonist, was shown to improve EDS in PD patients with concomitant narcolepsy in a double-case report. Further studies are needed to observe the long-time effects of pitolisant, as it may promote neurodegeneration by stimulating the histamine release in substantia nigra [149].

Atomoxetine, a selective norepinephrine reuptake inhibitor, failed to improve depressive symptoms in PD patients, but may improve EDS (at target dose of 80 mg/day) [150].

5. Restless legs syndrome (RLS; Willis Ekbom disease)

Restless legs syndrome (RLS, Willis-Ekbom disease) is characterized by uncomfortable dysesthesias leading to an uncomfortable urge to move the affected extremity occurring at rest, most frequently during nighttime. RLS is a prevalent non-motor symptom among Parkinson's disease patients. Diagnosis of RLS is based on 5 essential diagnostic criteria that were proposed by the International Restless Legs Syndrome Study Group (IRLSSG), a positive diagnosis requiring all five criteria to be met [151]. Particular to PD, nocturnal symptoms such as wearing-off, dystonia and akathisia may mimic RLS symptoms, thus making the diagnosis of RLS more difficult in case of PD patients [152].

The estimated prevalence of RLS in PD is variable but can be as high as over 15% [152–155]. The pathophysiology of RLS in PD is unclear. Several theories postulated RLS to be in relation to the presence of dopaminergic dysfunction in PD (as dopaminergic drugs help alleviate RLS symptoms), abnormal iron metabolism or RLS and dopaminergic dysfunction in PD can represent two separate entities entirely [156].

5.1. Interventions regarding comorbid disease and concomitant medication

Effective management of RLS requires a thorough history regarding the patients' comorbidities and medications. For example, anxiety and depression are frequent non-motor symptoms and comorbidities in PD patients. The use of serotoninergic antidepressants might aggravate RLS symptoms, thus the need for this medication should be thoroughly evaluated and changed whenever possible [157]. Other drugs that may induce or aggravate RLS include antihistamines, neuroleptics, and dopamine-blocking agents (such as metoclopramide, a dopamine-blocking antiemetic) [158].

5.2. Non-pharmacologic therapy

An initial approach to RLS management should include non-pharmacologic strategies such as abstinence from alcohol and caffeine, physical activity, hot or cold baths, massage of the affected limbs and mental exercises [159].

5.2.1. Peroneal nerve stimulation

Noninvasive bilateral electrical stimulation of the common peroneal nerve (NPNS) has been proposed as an alternative treatment for RLS. Studies showed a positive outcome of NPNS with a reduction in RLS symptoms and an improvement in sleep-onset [160,161]. Adverse effects can include uncomfortable sensations in the limbs, muscle fatigue, and skin irritation.

5.2.2. Cognitive behavioral therapy

Cognitive-behavioral therapy for insomnia (CBT-I) has been proposed as a non-pharmacological treatment for RLS since RLS symptoms may induce or exacerbate insomnia. Two studies, one longitudinal and one randomized, that were investigating the effects of CBT-I in RLS showed improvements in quality of life

and self-reported sleeping variables, such as total sleep time and latency to sleep onset in the CBT-I group [162,163].

5.2.3. Near-infrared light therapy

One randomized control study (RCT) evaluated the efficacy of monochromatic near-infrared light in RLS patients. The results showed a significant improvement in RLS symptoms over the period of treatment that was still significant posttreatment [164].

These above-mentioned therapies have not been studied specifically for PD patients. Further work is needed in order to deem these therapeutic options feasible.

5.2.4. Subthalamic deep brain stimulation (STN-DBS)

The effect of STN-DBS on PD patients with RLS showed conflicting results across studies, with both development and improvement of RLS symptoms [165–167].

5.3. Pharmacologic therapy

The most commonly used agents for the pharmacological treatment of RLS in clinical practice are non-ergot dopamine agonists, levodopa, alpha-2-delta calcium channel ligands and opioids. The majority of RCT studies regarding the pharmacological treatment of RLS are based on non-PD and RLS populations, thus recommendations are mostly derived from these data.

5.3.1. Iron supplementation

As an abnormal brain iron metabolism is thought to be involved in RLS pathophysiology, current consensus guidelines by the IRLSSG task force propose iron supplementation in RLS patients with decreased iron levels [168]. Ferric carboxymaltose (1000 mg) was deemed effective for treating moderate-to-severe RLS in those with serum ferritin <100 µg/l and transferrin saturation <45% and could be used as a first-line treatment for RLS in adults [168]. However, caution is recommended, as all intravenous iron products have the potential to cause hypersensitivity reactions (infusion reactions, hypotension, and, in rare cases, anaphylaxis) and hypophosphatemia [169]. Furthermore, oral iron (ferrous sulfate 325 mg twice a day with vitamin C) was deemed possibly effective for treating RLS in those with serum ferritin under 75 µg/lbut ineffective in adults with serum ferritin over 75 µg/l [168]. However, iron supplementation has not been studied specifically for PD patients.

5.3.2. Alpha-2-delta calcium channel ligands

The alpha-2-delta calcium channel ligands, gabapentin, gabapentin enacarbil, and pregabalin, are currently the first-line of therapy recommended for initial RLS treatment due to their low risk of augmentation [170]. RCTs showed that gabapentin enacarbil (a prodrug and controlled-release form of gabapentin) was effective in reducing RLS symptom severity when compared to placebo [171–173]. A large RCT that compared pregabalin with pramipexole in RLS patients showed no differences in efficacy between the two but a decreased risk of augmentation with pregabalin [174]. These should also be considered as first-line therapy in PD patients with RLS and comorbidities, such as anxiety, insomnia, or pain [175].

5.3.3. Dopamine agonists and levodopa

The non-ergot dopamine agonists rotigotine, pramipexole, and ropinirole were deemed effective for the short-term treatment of RLS based on multiple RCTs [176–180]. Furthermore, a double-blind RCT found that treatment with 2–3 mg rotigotine patch daily lowered Restless Leg Syndrome Rating Scale (IRLS) scores after 6 months of treatment when compared to placebo, thus deeming rotigotine effective also in the long-term treatment of RLS [179]. Side effects of dopamine agonists include the risk of augmentation (rare in PD) and the risk of impulse control disorders (ICDs). In the general population, the risk of augmentation is higher for the short-acting dopamine agonists ropinirole and pramipexole (40–70% of patients developing augmentation during a 10-year period) compared to rotigotine which poses a lower risk [181,182]. Moreover, switching from oral dopamine agonists to rotigotine may be efficient in improving augmentation symptoms [183]. However, the protocols to prevent augmentation in the general RLS population cannot be applied in PD patients with RLS, since PD patients need the dopaminergic treatment to manage their motor symptoms. A supplementary dose of levodopa during evening/nighttime may alleviate RLS symptoms and reduce the risk of RLS rebounds during morning [184]. Keeping the lowest efficient dose of dopamine agonists/levodopa is advisable to prevent augmentation, ICDs, and motor fluctuations as possible side effects [184]. Levodopa-carbidopa intestinal gel [185] and nocturnal subcutaneous apomorphine infusion may be efficient alternatives in treating RLS in advanced PD patients [186].

5.3.4. Opioids

Low-dose opioids were suggested to be effective in RLS management as they decrease RLS severity, improve sleep and quality of life [187,188]. However, given the risk of daytime drowsiness, cognitive dysfunction, respiratory depression, and substance abuse, they should be reserved as a means of treatment for RLS refractory to other medications [175]. Further studies are needed to explore the efficiency of opioids in the management of RLS in PD patients.

5.3.5. Augmentation

Augmentation, albeit rare in PD, represents the worsening of RLS symptoms severity manifested by earlier onset of symptoms (compared to before starting treatment), increased intensity of symptoms, spread of symptoms to other body parts, and a shorter duration of the effect of medications [170]. Moreover, patients with long-term treatment with dopamine agonists may benefit less from other therapeutic choices, such as gabapentin enacarbil [189]. Although augmentation is rarely possible in PD patients, once it is identified, switching the initial treatment with levodopa to a low dose of dopamine agonist or switching the initial oral rdopamine agonist to rotigotine patch may be tried. In resistant cases, switching the dopamine agonist to an alpha-2-delta calcium channel ligand or opioid may be effective [190].

6. Conclusion

A wide variety of interventions, both pharmacological and non-pharmacological, are available for the proper management of sleep disturbances in Parkinson's disease. However, the complexity

of these disorders, alongside the existence of other non-motor symptoms and comorbidities, may limit the use of some of these therapies, thus making their management challenging. More PD-targeted studies are needed in order to fully understand the potential benefits and drawbacks of these therapies.

7. Expert opinion

RBD is considered an early manifestation of neurodegenerative diseases, mostly alpha-synucleinopathies. Until now, there is no evidence that the treatment of RBD, even in the isolated form of RBD, induces neuroprotection. Nonetheless, the recognition of RBD in the early, preferable preclinical phases of PD is important with regard to future possible neuroprotective medication. One of the main limitations of initiating treatment for RBD is the recognition and timely diagnosis of the disease, especially in people without a bed partner. Future modalities including home polysomnography recordings or video cameras could represent a solution for this unmet need. A big challenge is to find the balance between treatment efficacy and side effects, especially in elderly PD patients with other comorbid conditions. The final question to be answered is for how long do we need to treat RBD? Will it recur once the therapy is stopped? More prospective studies are needed to clarify the aspects mentioned above.

Treatment of EDS in PD is challenging. Effective management requires a tailored approach, considering the patients' complaints, comorbidities, and treatment regimen. All the associated treatments that may have EDS as a side effect should be revised and avoided before starting a management plan. It is necessary to promote sleep hygiene and to identify and treat accordingly the symptoms that may impair sleep during night (both motor and non-motor symptoms), aiming to improve sleep quality and therefore to reduce sleepiness during daytime. Low doses of long-acting DA can be recommended to improve the nocturnal motor status of patients, with careful observation of EDS as a possible side effect. For patients undertaking DA, the risk of daytime somnolence and sudden onset of sleep should be assessed, and the advice regarding safety of driving should be individualized. Modafinil, methylphenidate, and caffeine may be efficient pharmacological agents for the management of EDS; novel pharmacological interventions are still under investigation.

Considering the multifactorial causes of insomnia in PD, effective management requires a comprehensive approach, incorporating both pharmacological and non-pharmacological strategies. History taking plays a decisive role in this regard, and the following important steps should be included: main complaints and clinical evaluation; pre-sleep habits, medication side effects, and pre-sleep symptoms assessment; identification of symptoms during sleep (motor symptoms, non-motor symptoms and other comorbid sleep disorders), and assessment of daytime consequences. Sleep hygiene and correction of bad habits before bedtime represents the first steps in conducting a personalized treatment plan for insomnia. Common associated factors, such as anxiety, depression, and nocturia, should be properly assessed and treated, when identified. Other motor and non-motor features that can contribute to sleep fragmentation and/or sleep-onset insomnia should be included in the therapeutic plan, starting with non-pharmacological strategies (education on sleep hygiene, CBT-I, bright light therapy exposure, exercise, relaxation, and alternative techniques). In cases when these methods are inefficient, pharmacological treatment should be tried. Good control of motor symptoms during nighttime may contribute to reducing insomnia, and the antiparkinsonian treatment regimen should be revised in this regard. Antidepressants should be used with caution as long-term therapeutic options, especially in the elderly population; when indicated, the minimum efficient doses should be maintained. Eszopiclone, doxepin, and suvorexant can represent alternatives with a relatively good safe profile, while melatonin may be indicated in relation to circadian rhythm dysfunction; however, the data obtained from clinical trials conducted specifically for PD patients are limited.

Pharmacologic therapy of RLS in PD can also be challenging. Medications such as antihistaminic drugs, anticholinergics, and antidepressants are known exacerbators of RLS symptoms and must be avoided if possible. Secondary causes of RLS such as iron, vitamin B12 and folate deficiency or renal failure must be excluded or treated if present for a proper personalized care. Dopamine agonists (prolonged release) or levodopa before bedtime in the smallest efficient doses may be recommended for controlling both RLS and motor symptoms. If these options are not efficient or not tolerated, alpha-2-delta ligands and opioids should be tried. In resistant cases, DBS or apomorphine/continuous intrajejunal levodopa administration should be considered. In patients with augmentation, treatment options include the use of calcium alpha-2-delta calcium channel ligands such as pregabalin or low-dose opioids. Gabapentin can be used as an alternative treatment, especially in PD patients with RLS and pain.

A proposed algorithm for a personalized management of sleep disorders in PD is shown in Figure 3.

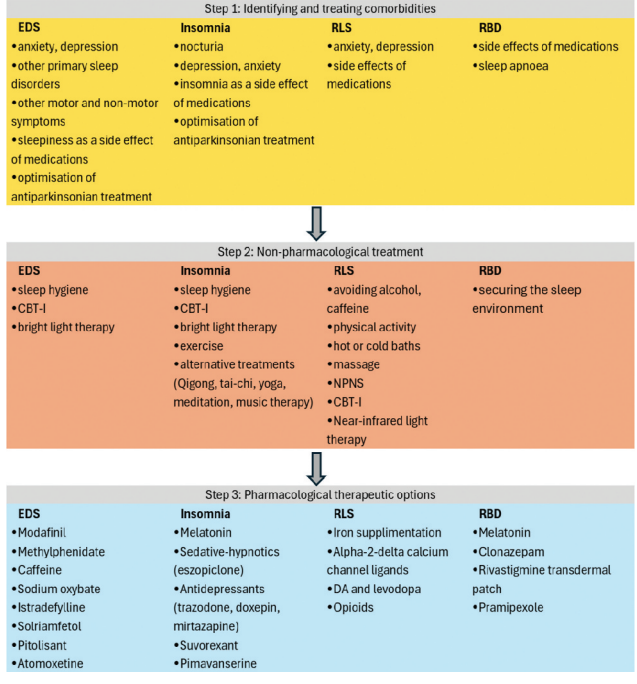

Figure 3. A proposed flowchart for the management of sleep disorders in PD. CBT-I: cognitive-behavioral therapy for Insomnia; DA: dopamine agonists; EDS: excessive daytime sleepiness; NPNS: noninvasive bilateral electrical stimulation of the common peroneal nerve; RBD: REM sleep behavior disorder; RLS: restless legs syndrome.

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