Review article

Relationship between Sleep Disorders and Neuropsychiatric Symptoms in Parkinson's Disease: A Narrative Review

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SUMMARY

Aim: The objective of this narrative review was to describe the versatile links between mental status and sleep in patients with Parkinson's disease.
Methods: We searched randomized controlled studies, observational studies, meta-analyses, systematic reviews, and case reports written in English in PubMed during 2015 - 2021. Additionally, to ensure the completeness of the review, a second, more in-depth literature search was performed using the same electronic database with the search inquiries of increased specificity.
Results: The information on pathophysiology, epidemiology, clinical features and risk factors was extracted and formed the basis for this review. Despite how widespread sleep disorders in Parkinson's disease are, there is no systematic information about their association with neuropsychiatric symptoms, such as depression, anxiety, impulse control disorders, apathy, cognitive impairment and psychosis. In this review, we described relationships between these non-motor symptoms of Parkinson's disease, their timeline occurrence, gap in knowledge and perspectives for further research. We suppose that early treatment of sleep disorders in patients with Parkinson's disease can reduce the incidence and extent of neuropsychiatric symptoms.
Conclusion: We have demonstrated multiple, multidirectional relationships between sleep disorders and neuropsychiatric symptoms. However, some of them remain unexplored. The described knowledge can be applied to further study the possibility of influencing neuropsychiatric symptoms through the correction of sleep disorders in patients with different stages of Parkinson's disease.

Keywords: sleep disorders, neuropsychiatric symptoms, Parkinson's disease

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INTRODUCTION

Neuropsychiatric symptoms (NPS) of Parkinson's disease (PD) include depression, anxiety, apathy, psychosis, impulse control and related disorders (ICD), and cognitive impairment (CI). Pathophysiology of neuropsychiatric comorbidities up to now remains vague; the presumptions suggest that it can either be an element of disease process with corresponding neurodegeneration and biochemical changes or psychosocial factors, etc. (1).

Desynchronization of circadian rhythms plays an important role in the pathogenesis of depression and affective disorders in general (2). Daily rhythms are regulated not only by the circadian system, but also by environmental and behavioral reactions, including light, sleep, food and physical activity; at the same time, circadian oscillators play an important role in the regulation of eating behavior, hart rate, sleep-wake cycle etc. These features emphasize complex multidirectional relationships between circadian system and human body (3).

Getting quality sleep is vital to the proper homeostasis and recovery. Additionally, lack thereof leads to the impairment of memory and overall slowdown of neural growth and development. Sleep disorders (SDs) tend to prevail in PD. SDs are situated below the umbrella of "non-motor components" of PD. General research suggests that SDs mainly stretch between 60-98% in PD (4). The aging is characterized by SDs and poor sleep quality. Some authors suggest that sleep problems have become one of the most common diseases in the elderly (5).

Clinically, the manifestation of SDs in PD patients is most often either disturbance in the structure of the sleep or abnormal shift in the sleep pattern. Correspondingly, those usually include insomnia, decreased sleep efficiency and light sleep under the first subgroup, and decrease in the overall sleep time together with lunch drowsiness – under the second (6).

Generally, disturbed sleep in PD is most often linked to the alpha-synuclein pathology within locus coeruleus and raphe nuclei, as well as hypothalamic areas and subcortical/limbic areas such as the amygdala, thalamus, and enterorhinal cortex. The extensive spread of the tau-protein abnormality is also commonly discovered in PD cases with "more sleep problems" (7).

Despite how widespread SDs in PD are, there is no systematic information about their association with NPS. The polymorphism of SDs in patients with PD and various information about the period of the appearance of NPS creates difficulties in understanding their relationships. However, it is necessary to improve treatment and influence on the tactics of choosing drugs or stage of correction of detected disorders.

Since the existing body of knowledge has not been described clearly yet, it is both necessary and rational to dig into the roots of these gaps' existence. Having answered this question, it will be much easier to suggest enhancements to the protocol of care provided to those with PD who have SDs and comorbid NPS. As such, the goal of utter importance was to assess the relationships between SDs and NPS in patients with PD which were based on their pathophysiology and occurring timeline.

METHODS

This is a narrative review. A sweep through available literature was performed using the database Medline via the PubMed interface for articles written in English. The keywords and MeSH terms "neuropsychiatric symptoms", "Parkinson's disease", and "sleep disturbances" with the use of the Boolean operators "AND" or "OR" helped to distinguish studies and reports necessary for the examination of the connection between SDs and PD. The aforementioned three keywords were chosen exclusively for the primary literature search. Additionally, to ensure the completeness of the review, a second, more in-depth literature search was performed using the same electronic database with the search inquiries of increased specificity. For this purpose, the following terms and their combinations were widely in use: "apathy", "depression", "anxiety", "impulse control disorder", "psychosis", "cognitive impairment" AND "sleep disturbance" OR "sleep disorders" OR "sleep" AND "Parkinson's disease". We included randomized controlled studies, observational studies, meta-analyses, systematic reviews, and case reports published between 2015 and 2021. We reviewed the existing information on the influence of SDs that can be linked with the following syndromes in patients with PD: apathy, depression, anxiety, ICD, psychosis, SDs, and CI. For these relationships, information on pathophysiology, epidemi-

ology, clinical features and risk factors was extracted and formed the basis for this review.

RESULTS

The most common disorders of sleep and wakefulness in PD are rapid eye movement (REM), sleep behavior disorder (RBD), insomnia, restless legs syndrome (RLS), excessive daytime sleepiness (EDS) and circadian rhythm disorders. Though the existing amount of data is constantly enlarging, there are quite a lot of questions waiting to be answered, especially regarding the diagnostic process, epidemiology, etiology and pathophysiology, clinical implications and the prognosis of the underlying disease and its manifestations, and ultimately – evidence-based management (8). We reviewed 62 articles that met the inclusion criteria and contained relevant information for assessing the relationship between SDs and NPS in patients with PD.

Neuropsychiatric symptoms in Parkinson's disease

Depression

Depression is the most common and severe non-motor symptom (NMS) in patients with PD, with a prevalence of around 30 – 50%.

The frequency of the PD with depression is directly proportional to the stage of the illness. Such depression may as well be considered an organic effect of neurodegenerative process, in contrast to the mainly assumed etiological role of psychological distress. Moreover, it is possible for the primary symptom in PD, linked to the rapid decrease in both cognitive and motor abilities, to be depression (9).

A vast array of factors including the reciprocality between the genetic errors, cognitive predisposition, neurobiological impact of the age toll and influence of stress supposedly culminate into depression in PD. The complexity of the issue makes the attempts to pinpoint the specific source of depression in PD unnecessary difficult and impractical, though it is suggested that possible deficiencies in either dopaminergic, serotonergic or cholinergic systems are the roots of PD's depressions pathobiology (10). The accrued Lewy bodies in the mesencephalon harm the dopamine, serotonin and noradrenaline messenger complexes during the PD onset. Considering the fact that these neurotrans-

mitters are essential for the proper regulation of both emotions and cognition, the degenerative process inflicts emotional disturbances per se. As such, depression as a symptom is inherent to the PD, and not an acquired, reactive consequence. The decreased volume of gray matter and the disruption of the structure of white matter in the insula are shown in PD patients with depression. The insula is a part of the cortex of the telencephalon located deep within the lateral sulcus, considered to affect a variety of brain functions including perception, emotion, cognition, etc. (11).

Constant sadness, depressed mood, desensitisation to pleasure as well as belief of own worthlessness and guilt form the main symptoms of depression in PD. Differential diagnosis can often be tricky since some symptoms of depression like slowness, weight loss, SD, or poor emotional expression are not that uncommon, frequently existing even in non-depressed PD patients. According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), patients with PD may present minor, major or persistent depressive disorders. Depression often goes along with the anxiety in PD (12).

Factors connected to the depressive symptoms in patients with PD are hyposmia, quick advancement of the stage of the illness and the use of levodopa. Considering the abnormally high frequency of depressive symptoms in patients with PD, to quickly raise the quality of life and the family environment, an immediate diagnosis as well as treatment are necessary (13). Furthermore, depression presupposes the development of ICD in PD, and the risk is additionally amplified by the dopamine agonists (14). PD victims of depression had considerably worse quality of life (QoL) than do other subject groups, when compared to the PD patients without depression. However, the desired QoL levels were almost identical between the groups, and, therefore, PD patients with depression had the largest disparity between the present QoL and the desired one. This larger disparity makes the decisive contribution to the overall dissatisfaction and lower QoL recorded in this subgroup (15). Depression in PD is closely related to the increased speed of both physical and cognitive deterioration, faster onset of dopaminergic replacement, medication non-adherence, greater prospective fall risk and bigger burden upon the health system (16).

SDs are one of the most consistent symptoms found in patients with pronounced depressive disorder. PD patients who suffer from SDs were found to be at high risk of suffering from neuropsychiatric complications such as depression. Despite the association between poor sleep quality in PD and compromised QoL indices (including physical, social, and psychological functions), interventions that target improving sleep quality are rare. This is because previous studies on PD that reported correlation data and associations between SDs and depression, depression and mental health, and sleep, depression, and quality of life were cross-sectional designs with no therapeutic intervention (17).

Issues arising from the problems of sleep regulation and lack thereof are not secondary to the disease itself; on the contrary, they mostly come prior to the depressive episodes and can endure throughout the remission. Logically, the improvement of sleep quality of the depressed patients is described as a great way to improve outcomes (18). Self-reported short total sleep time may be described as both the predictor and derivative of depression severity in patients with PD and may be more visibly pronounced with depression as PD's comorbidity than among adults without PD (19). RBD plays an important role in the conversion to parkinsonism, with the following rationale: "More development time – higher probability". Rationally, RBD paired with the various non-motor symptoms can act as the predictor of parkinsonism. The olfactory dysfunction as well as constipation are both well pronounced symptoms associated with the conversion of RBD to PD. SDs and depression may appear before the onset of motor symptoms. There is an overlap, co-morbidity and interaction between anxiety, depression, SDs and other NMS, which warrants a multi-disciplinary approach to PD (20). On the one hand, SDs can enhance depression in patients with PD. At the same time, a distinct amount of research proposed that anxiety and depression are also related to poor sleep quality (21). In the multiple linear regression model done with pain, depression, followed by anxiety, was the most pertinent predictor of Parkinson's Disease Sleep Scale-2 (PDSS-2) total score (22). According to a recent study, RLS could increase depressive symptoms in patients with PD (23). Sleep problems, excessive daytime sleepiness, depressive and anxiety symptoms are frequent in PD patients and are significantly associated with each other (24).

Considering that the endogenous rhythm of the suprachiasmatic nucleus differs in its essence from the 24-hour day-night cycle adopted by the society, it has to be entrained by the so called 'zeitgebers' – external cues such as light, physical activity and food intake. Should such a cue be disturbed, the circadian rhythm breaks down as a consequence, which is reflected in the alteration of the patterns of the secretion of cortisol and melatonin. Corresponding damage to the routine circadian rhythm is linked to depressive symptoms and insomnia (25, 26).

Anxiety

Anxiety is one of pre-diagnostic features of PD, predated by another NMS (27). Anxiety is higher in PD patients compared to controls in a large sample of early diagnosed PD subjects (28).

Rodent model of 6-OHDA-induced parkinsonism indicates elevated anxious behaviors that are likely related to the regulative impairment of the neurotransmitter complices in amygdala, prefrontal cortex and striatum – cerebral areas commonly related to the anxiety. In these regions, neurochemical tests revealed a corresponding decline of dopamine and noradrenaline levels. However, serotonin levels were increased in the amygdala, while simultaneously being decreased in the striatum and prefrontal cortex (29). One of the crucial neural structures involved in the anxiety is the locus coeruleus, which is essential for sleep regulation (30).

Anxiety in PD usually manifests in the general inability to relax and constant feelings of excessive concern, tension and restlessness. The presentation may also include somatic symptoms like palpitations, shortness of breath, sweating, digestive upset, etc. Anxiety usually increases the severity of all the parkinsonian symptoms. To make matters worse, the anxiety's implication of deficits of the emotion regulation, irritability, excessive tiredness and – contrarily – difficulties falling asleep are not that rare (31).

Both depression and anxiety pronounce themselves even in the premorbid PD stage, and thus it is rational to suggest that they might be the core aspects of PD. In one of the meta-analyses, depression and anxiety levels were more pronounced in patients with ICD compared to patients without it. ICD itself is suggested to impact negatively on the QoL and consequently make anxiety and depression worse. Additionally, the dysfunction in the mesocortico-

limbic pathways may co-occur as epiphenomena of shared neutral correlates together with the anxiety, depression and ICD (32).

Though comorbidities of anxiety, depression and insomnia are quite frequent in PD patients, there is little to no data regarding the course and interaction. Thankfully, there are different hypotheses regarding the relationship between insomnia and affective disorders, which were products of extensive research in non-PD samples. In the first hypothesis, insomnia is a predecessor to depression and anxiety, ergo can be considered to be a risk factor or a prodromal symptom of affective disorders. Alternatively, affective disorders may cause a disturbance of sleep (33). The anxiety is caused by the reduction of sleep quality, which is in turn caused by RBD. Those who suffer from PD and RBD present with the instabilities in the wake-sleep and non-REM – REM sleep transitions, possibly resulting in a deterioration of sleep quality. Remembering the importance of sleep in the maintenance of the adaptive emotional regulation and reactivity, SD is naturally a risk factor contributing to the arisal of anxiety disorder (34). The PD patients' motor functions, depression, anxiety and sleep/wake behavior are expected to be influenced positively upon by the light therapy, which should act by normalizing circadian disruptions and consequently impact positively on health status (35). Research demonstrates that PD patients with RBD had significantly higher rates of anxiety and depression and a higher mean PDSS-2 score compared to ones without (36). Patients with RLS show more scores of depression and anxiety, lower sleep quality, and more autonomic dysfunctions (37).

Impulse control and related disorders

Impulse control and related disorders (ICD) are a class of psychiatric disorders characterized by impulsivity, inability to fight a temptation, compulsion or impulse that interfere with normal social functioning. Leading ICD in PD include not only pathological gambling, shopping, hyperphagia, hypersexuality and punding, but also compulsive abuse of dopaminergic medicine that in turn leads to dopamine dysregulation syndrome. The disorders mentioned above comprise the extensiveness of ICD's clinical spectrum. Various personal and neuropsychiatric traits contribute to ICD, which

manifests itself as a critical non-motor symptom in PD (38).

ICD commonly have their start as a consequence of the abuse of dopaminergic medications. However, other risk factors like younger age, motor complications, depression, family anamnesis of ICD, alcohol and nicotine abuse and certain personality traits have also been established. The data regarding the prevalence of ICD among people with PD is not consistently supplied. One single site study with a small sample size disclosed an overall ICD prevalence of 39.1% during 21 months of dopaminergic treatment in patients with PD but without prior ICD; the risk factors described were smoking, caffeine abuse, motor complications and higher doses of dopamine agonists. A recent investigation of evidence gathered from 320 early-stage patients with no history of ICD from the Parkinson Progression Markets Initiative database reported the results of 8% (year 1), 18% (year 2), and 25%(year 3) of aggregate post-baseline incidence (39). It is suggested that ICD's pathophysiology is linked to unusual dopaminergic stimulations of the basal regions of the basal ganglia, particularly via negro-mesolimbic pathways (40). As such, the overstimulation of the mesolimbic system by dopaminergic treatment has previously been linked to the episodes of ICD. PD patients suffering from problem gambling have decreased binding potential of a dopaminergic tracer in the ventral striatum. Moreover, a considerable loss of gray matter volume in the frontal lobe accompanies the ICD's progress. Also, decreased baseline dopamine transporter presence have been detected in the areas of right ventral striatum, anterior-dorsal striatum, and posterior putamen among the drug-naïve PD patients with motor symptoms. Additionally, early dysfunction of the mesocorticolimbic circuits has been theorized to have a part in ICD's onset before the start of dopamine therapy in PD patients (41).

As motivational expressions, ICD and apathy are on the opposing ends of a continuous behavioral spectrum concerning hypo- and hyperdopaminergia. Their nature lies in increased or decreased dopamine receptor stimulation, respectively. For example, ICD lies in the hyperdopaminergic end of the behavioral spectrum along with punding and dopamine dysregulation syndrome, all of which are associated with the non-physiological dopaminergic stimulation caused by antiparkinsonian medicine (42).

Frequent dopamine agonists treatment in patients with PD who also suffer from comorbid dementia results in more common ICD and related behaviors, which means that neural substrates associated with PD's dementia intrinsically presuppose the onset of compulsive behaviors (43).

One recent study supports the link between RBD and a higher risk of PD's ICD onset (44). RBD was linked with a relative risk of 1.84 for any ICD or related behaviors symptoms and with a risk of 2.59 for exclusively ICD symptoms. Not only that, PD patients with RBD had more than four-fold risk for pathological gambling appearance (45). Current research regarding the pathophysiology of ICD suggests abnormal signaling of dopaminergic projections into the striatum, orbitofrontal cortex, anterior cingulate, and anterior insula, which are the areas that cannot be pinpointed to the RBD's pathology (46). RLS has also been linked to the more impulsive choices in the overall population no matter the dopaminergic therapy and therefore could be an essential risk factor for PD's impulsive behaviors (47).

Apathy

Like anhedonia, anxiety and depression apathy is one of hypodopaminergic symptoms on the other end of the spectrum. As PD progresses, its key symptom – apathy – correspondingly worsens (48).

Apathy presents in a quarter of PD patients, among those who generally lack motivation and interests and show decreased emotionality. Due to the clinical resemblance, the inexperienced physician may confuse this condition with drug-resistant depression (49).

Consistently, dopaminergic depletion, specifically in the nigrostriatal system constitutes a major part in the apathy's progression. Ventral striatum is crucial for the modulation of emotional behaviors by the frontal cortex, thus its dopamine depletion is the main cause of the apathy. Additionally, apathy has also been linked to the precuneus and right medial temporal lobe in PD patients. The precuneus itself has been linked to the vast array of psychological ailments, including depression and ICD. When assessed by magnetoencephalography, precuneus modulated with the unpleasant stimuli in subjects without signs of pathology was linked to the distribution of attention among the emotional faces. Im-

plicit processing of recognized objects is done by the right medial temporal lobe which is also linked to CI. Apathy without comorbid depression and dementia is called pure apathy, which is also identified as a decrease in goal-directed behavior with the evident absence of motivations, feelings, interest and emotions. Such apathy is linked to the severe impairment of routine functions, decrease of QoL and increased load upon the caregivers (50). Despite the frequent coexistence of apathy with other neuropsychiatric dysfunctions like depression and CI, it is more and more often acknowledged as a specific syndrome with various features that are not consistent. Since patients suffering from apathy are still capable of enjoying the activities, apathy is not identical to anhedonia. This syndrome has unfortunately never been formally researched in the prodromal period of the PD, despite the fact that it often occurs retrospectively prior to the outbreak of motor symptoms (51).

There is an apparent connection between cognition and apathy. Despite not being able to conclude future status of cognitive abilities, ongoing apathy is a behavioral indicator of CI, with more severe apathy resulting in poorer cognition.

Since apathy and depression split into a number of symptoms (e.g. anhedonia), they may be related to each other, indicating shared etiology and consequently shared therapeutic principles (52).

In the initial research aiming to assess the scope of apathy in RBD, the conclusion was that this dysfunction is common yet not acknowledged enough. The incidence of patients with apathy among the RBD cohort was about half, which was comparable to the incidence seen in established PD. The apathy in RBD was not related to excessive daytime sleepiness, poor sleep quality or sedatives. All the subdomains of apathy (minus emotional responses) were compromised in RBD, implying that issues with motivation for action, intellectual curiosity and self-awareness are more prevailing in victims of RBD rather than affect (53).

Group of PD patients with RLS showed more severe apathy, which was indicated by the significant increase of MAES scale scores. RLS was also empirically linked to the impaired DA system. Therefore, there have been a speculation that RLS and apathy could have coinciding neurochemical nature in PD patients (54).

Cognitive impairment

CI in PD has high variance regarding its severity, pace of development, and concerned cognitive domains. It fluctuates between the slight cognitive shifts to overall deficits, between mild cognitive impairment (MCI) and dementia. MCI in PD positively influences the chance of dementia's onset, however longitudinal studies provided data about some patients remaining stable with MCI, and others – going back to healthy cognition. Some patients with PD-associated CI might have memory deficits more impactful compared to the non-amnestic dysfunction (55).

A greatly increased overall risk of dementia in people with PD compared to the general population has been reported consistently by the research since the 1990s, with the point prevalence being reported at 25 - 30% mark by systematic reviews. Additionally, surviving more than 10 years after the PD's diagnosis is a major indicator for dementia's onset, as have been shown by several long-term longitudinal studies (56). It has also been recently suggested that RBD could be an independent risk factor for CI in PD, and those with RBD are more prone to having MCI (57). Overall, only cognition was a clear variable distinguishing dementia and parkinsonism. It is not yet known if the switch to dementia vs PD applies to either different "top-down" synuclein spread upwards to cortex before the substantia nigra or to outcomes of comorbidity, i.e. if a person with RBD has comorbid amyloid cortical pathology, even slight cortical deposition of synuclein could provoke the rapid cortical neurodegeneration resulting in a dementia-first phenotype (58). Considerably, Braak hypothesis of caudal-rostral spread of pathology can be countered by the discovery of cognitive deficiencies early in the prediagnostic course (this depends, indeed, on the anatomical evidence of the complaints) (59). Consistent with the other symptoms, CI in PD is likely associated with dopaminergic, noradrenergic and serotonergic issues. The following pathophysiological mechanism likely leads to CI: degeneration of dopaminergic neurons in substantia nigra causes dwindled levels of dopamine in the striatum, impairment of the cortical-subcortical dopamine loop between basal ganglia and frontal lobe, and depletion of dopamine in the frontal lobe (60).

Behavioral symptoms (like apathy, depressed or anxious mood, hallucinations, delusions or excessive daytime sleepiness) support the diagnosis of PD

though their absence does not reject the diagnosis altogether (61).

The patients with cognitive dysfunction suffered a higher percentage of SD. Overall, those with NMS (depressive symptoms, anxiety symptoms, urinary tract symptoms, hallucinations/delusions) also suffered from comparably poor sleep quality and often had insomnia. Better cognition is associated with better sleep quality, and may as well predict it. NMS hallucinations/delusions score was the most crucial determinant condition for sleep disorders in the patients with CI; among those without CI, NMS such as anxiety and medication were associated with sleep disorders (62). One meta-analysis showed a big influence of sleep (or, rather, lack thereof) on global cognitive function, long-term verbal recall, long-term verbal recognition, shifting, updating and fluent reasoning. Furthermore, a precise link was described between sleep disorders and memory and executive functions deficits in PD specifically. On the other hand, this conclusion should be taken with a grain of salt and reviewed thoroughly, considering the small number of studies and plentiful methodological issues within them (63). CI is more severe in patients with RBD. A strong link was additionally described between the global cognitive performance and wake time after sleep onset and the number of state changes during sleep, which was measured in the polysomnography of PD patients (64). According to the big set of conclusions, the PD patients with RBD are way more likely to have CI than patients without it. The pedunculopontine nucleus is crucial to the mechanism mediating RBD, and it produces the lion's share of the cholinergic input to the thalamus and nucleus basalis magnocellularis. PD patients with RBD achieve bad results in attention/executive and visuospatial tasks in the majority of studies. Furthermore, poor cognition is linked to the lessened intermissions between the beginning of RBD and the following PD onset, yet the root of this process is to be cleared up (65). Recent research carried out during the last two decades has evidenced the link between feeding behavior/nutritional habits and cognitive processes, and has highlighted the impact of circadian sleep disorders on cognitive deterioration (66).

RLS in PD may be linked to cognitive deficits, with the sleep quality being the intermediate. Bigger losses in both the sleep quality and cognitive function were more prevalent in individuals with RLS

and PD than those without RLS; nonetheless, cognitive dysfunction in patients with PD and RLS in that sample was not evaluated through with the sleep quality (67).

Psychosis

Psychosis is a status of mentality formally construed as a loss of contact with reality. Psychotic symptoms in PD (like delusions or hallucinations) are risk factors for dementia and robust predictors of poor prognosis, mortality and nursing home. Specifically speaking about psychosis in PD patients, it is described as the arousal of either hallucinations, delusions, or both, with most of such symptoms being of visual nature, though the potentiality of other sensory modalities to be also engaged exists. A partition of hallucinations into minor and non-minor ones exist, and minor can additionally be split into three forms – illusions (real objects are subjectively transformed into other entities), passage hallucinations (hallucinated entities or dots of light appearing in the peripheral vision) and presence hallucinations (the sense of some other living entity's presence) (68).

PD psychosis is not only carrying clinical implications, but also rising as a crucial biomarker of disease progression and cognitive outcome. Despite the lion's share of PD patients developing hallucinations as the condition advances (after 12 years, 60% are estimated to be suffering from psychosis), a distinction should be made between those developing psychotic symptoms early as disease onsets and those developing them in the later stages. Visual hallucinations are linked to the decreased gray matter volume in the visual system, hippocampus, frontal regions (especially lateral frontal cortex) and cerebellum, which is coherent to the common neuropsychological findings. Additionally, some research described visual hallucinations as a robust predictor of later dementia or greater decline of cognition. Although the fundamental mechanism of this link is yet to be revealed, cross-sectional studies have reported that PD patients with visual hallucinations are having higher visual function deficits in domains of object and visuospatial perception and cognitive declines in domains of attention, memory and executive function than patients without hallucinations (69).

When managing the psychosis of patients with PD, it is first and foremost important to assess the possible existence of delirium and link between psychosis and antiparkinsonian drugs. Therefore, if the delirium is not present and psychosis can probably be tracked to the use of antiparkinsonian drugs, the therapeutic effort should be aimed at cutting these drugs (70).

A common neural substrate for psychosis, affective symptoms and sleep-wakefulness disorders in PD can be suggested by the relevant findings in non-demented patients, specifically at that point of the disease where the pathology is located in the brainstem, midbrain, basal forebrain and dorsal striatum. Mild cognitive deficits are comparably often found in early PD, and are linked to the striatal dysfunction, midbrain cholinergic deficits, and, likely, brainstem noradrenergic deficits, while overlapping with the implied neural substrate of psychosis (71).

Psychosis in PD is also associated with SDs. Sleep troubles like insomnia or excessive daytime sleepiness are frequent in PD. The so-called "continuum hypothesis" of psychosis argues that SDs in PD causes altered dream phenomena, which in turn presupposes frank daytime hallucinations and delusions. Undoubtedly, such early phenomena are frequent to happen in PD. Research suggests that as much as half (48%) of PD patients had some altered dream phenomena like vivid dreams, nightmares and reports expressive of REM disorder or night terrors. One retrospective manuscript disclosed that almost one third (30.7%) of subjects had vivid dreams. It is widely considered that the association between SDs and PD psychosis features a disruption in REM sleep. Furthermore, a link between visual hallucinations and short, splintered REM sleep was found by the polysomnographic investigation of PD patients. To be more particular, those who had hallucinations also had lower sleep efficiency and decreased overall REM sleep time and percentage when contrasted against those without. Also, visual hallucinations in PD may be a kind of representation of a narcolepsy-like phenomena associated with the interference of REM dream imagery with and into the waking state. Such an interference may be linked to the decrease in acetylcholine levels, which prompts the disinhibition of the dream images and their discharge into the wakefulness (72).

DISCUSSION AND FUTURE DIRECTIONS

This narrative brief literature review demonstrated the presence of multiple relationships between NPS in PD and influence of SDs that may occur even in the preclinical stage of the disease. Table 1 demonstrates the state of knowledge of the problem of the association between SDs and NPS in patients with PD.

Table 1. *The relationship between SDs and NPS in patients with PD*

Sleep disorders	Neuropsychiatric symptoms					
	Depression	Anxiety	Apathy	ICD	CI	Psychosis
RBD	Present; bidirectional	Present; bidirectional	Present	Present; indirec	Present; bidirectional	Present
RLS	Present	Present	Present	Present; indirec	Present	Unknown
EDS	Present	Present	Unknown	Unknown	Present; bidirectional	Unknown
Insomnia	Present; bidirectional	Present; bidirectional	Absent	Unknown	Present	Present
Circadian rhythm disorder	Present	Present	Unknown	Unknown	Present	Unknown
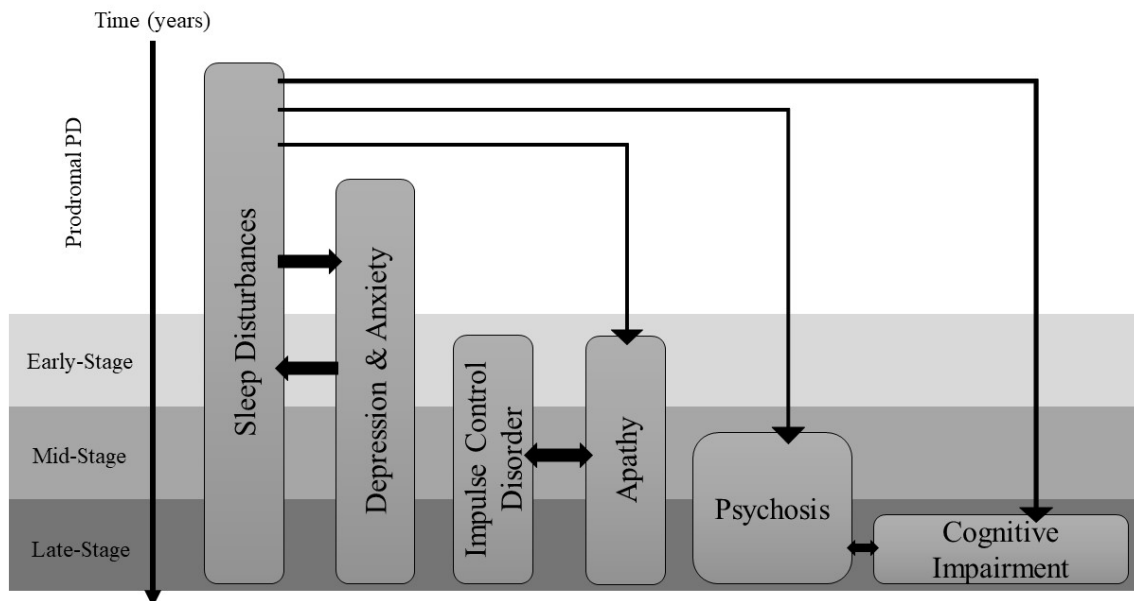
Figure 1. *Timeline and relationship between SDs and NPS in the progression of PD*

It is worth noting that the most studied are the relationships of neuropsychiatric symptoms with RBD. It was revealed how RBD can enhance the manifestations of anxiety, depression and cognitive impairment, and vice versa. The effect of RBD on ICD is considered indirect. RLS is associated with higher level of almost all NPS. EDS can occur with cognitive impairment and vice versa, while also associated with manifestations of depression and anxiety. CI and psychosis in patients with PD are associated with the quality of sleep and the presence of insomnia. The comorbidity of insomnia, depression and anxiety indicates their bidirectional relationships. The absence of the effect of apathy on the detection of insomnia in patients with PD was estab-

lished. Circadian rhythm disorders show comorbidity with depression, anxiety and CI.

However, the links between psychosis, ICD and apathy with circadian rhythms disorders and EDS, between psychosis and RLS, between insomnia and ICD remain unexplored. A study of the epidemiological and pathophysiological aspects of the occurrence of NPS and SDs in patients with PD made it possible to compare their timeline and relationships with the progression of the underlying disease presented in Figure 1.

It was shown that first SD occurs at the prodromal stage of PD and may influence NPS in the following stages. There are many common points in the pathogenesis of SDs and NPS in PD, such as inflammation, oxidative stress, and others (73, 74). Therefore, it is necessary to study whether treatment aimed at reducing SDs affects the manifestation of NPS. It was shown that NPS are associated with different motor subtypes of PD, which may predict association between SDs and motor symptoms (75). Although there are recommendations in this systematic review, currently, there is also scarcity of the evidence regarding the therapy of SDs in PD patients; as such, further studies should be done (76). Recently, a lot of work has been done analyzing the neural circuitry fundamental to the arousal state change and genetic factors in both health and disease. Hopefully, these breakthroughs will finally inspire innovative therapy for sleep-wake and circadian disruption and linked comorbidities (77).

It was shown by the longitudinal studies that the overall incidence of most psychiatric and cognitive complications exceeds the earlier estimates reported by cross-sectional studies, and the outcomes reported herein expand many of these findings to early PD. Speaking from a research point of view, it is an indication that NPS has a potential to be an outcome for clinical trials which assess PD progression and treatment. Currently, there is under-recognition of NPS and meager management options for most NPS. Considering the common, accumulating and frequent comorbidities of numerous NPS, it is imperative to enhance their recognition and therapy. It is important to remember that PD is a neuropsychiatric disease as well – and always has been – and should be treated as such (78). At the same time, we should consider ageing changes, such as pineal calcification, cerebrovascular pathology, etc. (79). We suggest that early treatment of SDs in patients with PD can reduce the incidence and extent of NPS. As a result, we can expect an improvement in their QoL and general health.

CONCLUSIONS

Patients with PD demonstrate multiple, multidirectional relationships between SDs and NPS. However, some of them remain unexplored. The described knowledge can be applied to further study the possibility of influencing NPS through the correction of SD in patients with different stages of PD.

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Odnos između poremećaja sna i neuropsihijatrijskih simptoma kod bolesnika sa Parkinsonovom bolešću: narativni pregled

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SAŽETAK

Cilj. Cilj ovog narativnog pregleda bilo je opisivanje promenljivih odnosa između mentalnog statusa i sna kod bolesnika sa Parkinsonovom bolešću.

Metode. Ispitivane su randomizovane kontrolne studije, opservacione studije, metaanalize, sistematski pregledi i prikazi slučajeva napisani na engleskom jeziku i objavljeni na *PubMed*-u u periodu od 2015. do 2021. godine. Pored toga, kako bi se postigla celovitost pregleda, izvršena je druga, detaljnija pretraga literature, korišćenjem iste elektronske baze podataka sa upitima za pretragu povećane specifičnosti.

Rezultati. Izvučeni su podaci o patofiziologiji, epidemiologiji, kliničkim karakteristikama i faktorima rizika, koji su činili osnovu ovog preglednog rada. Uprkos tome, koliko su poremećaji spavanja kod bolesnika sa Parkinsonovom bolešću rasprostranjeni, ne postoje sistematske informacije o njihovoj povezanosti sa neuropsihijatrijskim simptomima, poput depresije, anksioznosti, poremećaja kontrole impulsa, apatije, kognitivnog poremećaja i psihoze. U ovom preglednom radu opisan je odnos između ovih nemotornih simptoma Parkinsonove bolesti, njihovog trenutka javljanja, jaza u znanju i predstavljena je perspektiva za dalja istraživanja. Verujemo da rano lečenje poremećaja sna kod bolesnika sa Parkinsonovom bočešću može da smanji incidenciju i opseg neuropsihijatrijskih simptoma.

Zaključak. Pokazali smo višestruke, višesmerne odnose između poremećaja spavanja i neuropsihijatrijskih simptoma Parkinsonove bolesti. Međutim, neki od njih ostali su nerazjašnjeni. Opisano znanje može se primeniti na dalja ispitivanja mogućnosti uticaja na neuropsihijatrijske simptome kroz korekciju poremećaja spavanja kod bolesnika sa različitim stadijumima Parkinsonove bolesti.

Ključne reči: poremećaji spavanja, neuropsihijatrijski simptomi, Parkinsonova bolest