SLEEP AND AUTONOMIC COMPLICATIONS IN PARKINSON'S DISEASE

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Sleep disorders:
Sleep disturbances are very common in PD and in recent years have become of great interest in the movement disorders field with a substantial number of papers published every year. The sleep disorders occur any time in the disease course even premotor, impact motor function and overall quality of life. There are three areas that are particularly troublesome, insomnia, excessive daytime sleepiness, and parasomnias. These will be the focus.

Insomnia: Fragmented sleep
The American Academy of Sleep Medicine defines insomnia as problems involving initiating sleep, maintaining sleep, early awakenings and poor overall sleep quality[1] This is the most common sleep problem in PD, over 60% of cases (compared to 45% in controls) in one study. Risk factors include more severe depressive symptoms, motor fluctuations, higher dopamine agonist doses, sleep medication, female gender, PD duration, and depression/anxiety[1, 2]. The causes of insomnia are varied including nocturnal motor symptoms such as tremor or an inability to move in bed, nocturia (present in >60%), untreated depression, obstructive sleep apnea (OSA) (relationship to PD is unclear), restless leg syndrome and disrupted sleep architecture or primary insomnia (>20%).

Non-pharmacological interventions, if available, are recommended by the American Academy of Sleep medicine including cognitive-behavioral therapy and bright light therapy[3]. Also treatment of OSA including position therapy and devices and exercises.

Pharmacological therapy is available for insomnia (including zolpidem) however, there are few studies specifically in PD subjects. Of those that have been looked at in PD nocturnal doses of carbidopa/ levodopa or dopamine agonists improved motor symptoms that contributed to insomnia[4], but evidence for an improvement in objective sleep parameters or sleep satisfaction have been insufficient. Reduced levels Melatonin in humans are associated with sleep disturbances including changes in slow wave and rapid eye movement sleep and excessive daytime sleepiness. . Hence, melatonin up to 50 mg taken 30-60 min before bedtime is established as effective in improving patients' perception of sleep quality (two Class I studies) but evidence is conflicting regarding objective improvement in sleep quality as measured by polysomnography (PSG)[5, 6]. Melatonin, 3 mg, demonstrated subjective but not objective improvements in sleep in a small double-blind trial[7]. Other drug treatments include eszopiclone, trazodone, quetiapine (average ~30 mg) mirtazapine and doxepin (10mg) have been examined in PD subjects in small groups showing potential[3].

Excessive Daytime Sleepiness (EDS)
The American Academy of Sleep Medicine defines EDS as the inability to maintain wakefulness and alertness during the major waking episodes of the day, with sleep occurring unintentionally or at inappropriate times almost daily for at least three months[8]. It is well known that PD patients suffer from excessive daytime sleepiness (EDS)[9] with spontaneous dozing being significantly more common in PD patients (49%) compared to controls (26%) in one study. It has a significant impact on quality of life. Two types of episodes result from the daytime sleepiness; so called "sleep attacks" occurring without warning and unrelated to somnolence, and "unintended sleep episodes" or "sleep events" which are events with premonitory sleepiness, and the term "sudden onset sleep" includes both groups. Investigations with polysomnography have demonstrated that sleep attacks do occur in both treated and untreated patients which suggest that this is a disease-related and medication-related phenomenon [10]. Several studies have examined the frequency of both types. Meindorfner et al.[11] found that 8% of 5,210 patients experienced at least one episode of sudden onset sleep through a questionnaire; 57% were unintended sleep episodes, 26% had sleep attacks. Sudden onset sleep was often reported in association with change in medications and, in half, was due to the addition of dopamine agonists. A consortium of 18 Canadian trial sites [12] examined 638 cases with a questionnaire. EDS was present in 51% of patients, but sudden onset sleep occurred in 3.8% and actual sleep attacks were reported in 0.7%. They failed to show a relationship with any particular group of drugs. These problems may relate to PD directly but some data suggests an increased risk

with dopaminergic drugs, particularly for unintended sleep episodes[13]. A 2015 report[14] examined, in a prospective manner, the frequency and persistence of EDS in newly diagnosed untreated patients followed 5 years. They found 12% of PD patients vs 4% healthy controls suffered EDS at baseline and in PD that increased to 24% by 5 years of disease. The symptom complex was less persistent in the first year (42%) but became more persistent over time - 79%. Other studies have found similar results[8]. This suggested that PD pathology is related to development of EDS as it is present early and increases with progression but treatment with dopamine agonists represent a potentially reversible enhancer of this problem. However, one study showed different results. The baseline data of the PPMI study demonstrated in 423 PD subjects and 196 healthy controls, using Epworth Sleepiness scale (ESS), 16% PD subjects and 12% healthy controls had ESS score of at least 10 (P = NS) [15].

The risk with EDS is safety related particularly with driving a car. Risk factors for development of EDS include prior history of sleepiness (major driver of this), more severe disease, longer duration of PD, use of drugs that cause tiredness such as benzodiazepines, pain medications, antihypertensive use, and dopamine agonists, dementia, depression, sleep apnea and hallucinations[8]. It is noted that while increasing doses of dopamine agonists worsen sleepiness increasing doses of levodopa lessen it[16]. It should also be noted that while agonists can cause sleepiness they also are associated with nocturnal insomnia. Further, 24 hour preparations (oral or patch) may improve sleep and morning function or make it worse.

Aside from the effect of medications, causes of this problem are probably multifactorial. While it is possible that poor nocturnal sleep may result in EDS it has actually been shown that patients who have the most efficient sleep at night are the sleepiest during the day [3]. Nevertheless, evaluation for such problems as obstructive sleep apnea, poor sleep hygiene is important. Dementia and non-dopaminergic sedating medications also seem to be improtant.

Non-pharmacological approaches to EDS include improving sleep hygiene and exercising. Several pharmacological agents have been tried for EDS in PD. Modafanil has level A evidence for improvement in the symptoms of EDS but there is insufficient evidence that it improves safety [5]. Five placebo-controlled trials have been completed using doses of 200 – 400 mg per day[3]. The results using the ESS were positive but objective measures such as the multiple sleep latency tests were not. There is insufficient evidence for the use of amphetamines and concerns about safety. Studies of memantine and caffeine have been negative. Selegiline, which is metabolized to amphetamine has not be studied adequately but may be helpful as could melatonin.

There is evidence to suggest that sleepiness early in life may predict the development of PD [17] [18] [19]

REM Sleep Behavior Disorder (RBD)

RBD is a parasomnia occurring in ~40% of PD patients and increasing with increased duration of PD [3, 20, 21]. Normal REM sleep is associated with cortical desynchronization, rapid eye movements, cardiorespiratory irregularities, muscle atonia (except respiratory, sphincter, extraocular) and phasic muscle twitches. RBD is defined as REM sleep without the atonia. Patients have a change in dream content so that the dreams are vivid and often violent and patients feel as if they are being chased or attacked. The patients (with eye closed) will punch their bed, pillow or bed partner and may even jump out of bed. There is substantial risk of injury. The first occurrence of RBD is significantly more common in early PD than in healthy controls[22]. Those PD patients more likely to have this disorder include older males with longer duration of disease who experience sleep attacks, orthostatic hypotension, akinetic-rigid disease and more severe parkinsonism [23] [24] [25]. In PD patients, the presence of RBD predicts a non-tremor-predominant subtype, gait freezing, cognitive decline and more progressive clinical course. Interestingly, the symptoms come in clusters and are unpredictable. And they are not permanent in all, one-third of PD patients with RBD at baseline no longer demonstrated the symptoms 4 years later. However, the frequency of RBD in PD populations increases with time. Sleep disordered breathing may be more common in PD patients with RBD than those without[26].

Diagnostic criteria include a history of potentially harmful behaviors in sleep or documented behaviors in REM sleep during polysomnography (PSG), as well as the presence of abnormal muscle tone measured by EMG during REM sleep in PSG. Additional clinical clues include: [1]behaviors occur in the later third of the night (when REM sleep is concentrated), [2]a lack of behavior during the first hour of sleep (when REM sleep is not expected to occur), [3] a tendency for the eyes to be closed during the event, [4] a typical lack of getting out of bed to walk, [5] a change in the semiology of events based on dream content (as opposed to the stereotyped behaviors seen in nocturnal epilepsy) [27]. Actigraphy can be very helpful in making the diagnosis [28]. The neuroanatomic substrate

of RBD in PD is unclear but had been thought to relate to brainstem, pedunculopontine nucleus degeneration. A recent MRI imaging study, however, suggested that decreased grey matter volume in the left posterior cingulate and hippocampus[29]. DAT-PET study suggests more severe nigro-caudate degeneration than PD without RBD [30]. Ictal single photon emission tomography displayed the activation in the bilateral premotor areas, the interhemispheric cleft, the periaqueductal area, the dorsal and ventral pons and the anterior lobe of the cerebellum, bypassing the basal ganglia. A pathological study found higher density of synuclein pathology in 10 areas examined [31] Genetic studies have found an association of the PD genes SCARB2 rs6812193 (OR = 0.67, 95 % CI = 0.51-0.88, p = 0.004) and the MAPT rs12185268 (OR-0.43, 95 % CI-0.26-0.72, p = 0.001) with RBD [32].

Perhaps the most interesting finding relating to RBD is its use as a predictive marker for synucleinopathies, particularly Parkinson's disease and Lewy body dementia[33]. One single center study estimated the 5-year risk of neurodegenerative disease to be 18%, the 10-year risk was 41%, and the 12-year risk was 52%[34]. One other found even higher conversion rate, with the risk of a defined neurodegenerative syndrome from the time of idiopathic RBD diagnosis being 33% at five years, 75.7% at ten years, and 90.9% at 14 years. The median conversion time in this cohort was 7.5 years[35]. A multicenter, prospective trial with follow-up to 6 years demonstrated the risk of developing neurodegenerative disease was 41% in 5 years. Approximately 42% had PD, 50% dementia and 8% MSA[36]. Risk factors typically reported for developing PD and DLB were not the same for those with RBD who converted to develop these disorders after 5 years. The similarity of RBD features between those who converted to those who did not with respect to these risk factors suggests that RBD is a relatively homogeneous disorder. Homozygous carriers of the USP25 rs2823357 SNP had converted to synucleinopathies faster [32] Screening procedures for prodromal PD based on RBD are being examined [37]

RBD is a treatable syndrome although there is insufficient evidence for any one treatment[5]. Treatment is recommended when there is risk of injury to the patient or partner and when there is sleep disruption. One non-pharmacological approach is to make the room safe with padding on the corners of furniture and even bedrails. Often the partner will sleep in another room. Clonazepam, 0.5 to 2 mg per day, is generally the treatment of choice based on case series[38]. Melatonin, 3-12 mg, has been shown in a small double-blind, crossover trial, to be effective[39]. One survey study suggested that clonazepam showed a trend to being superior but with more adverse events compared to melatonin. Finally, a small double blind study of rivastigmine patch, 4.6 mg/24 hrs, demonstrated a decrease in RBD episodes compared to placebo[40]. Other drugs that have been utilized include memantine, pramipexole, levodopa, and zopiclone.

Autonomic Disorders:

Autonomic symptoms are common in PD, more common than often recognized, but the exact figure is unknown. However, a commonly quoted estimate is that at least 50% of patients have some autonomic features[41]. The most common symptoms reported are constipation, urinary issues and orthostatic hypotension. There is no clear correlation with duration or severity of disease. The occurrence may be of central or peripheral nervous system origin. Patients with significant autonomic changes are often misdiagnosed as having Multiple System Atrophy.

Autonomic testing labs are not ubiquitous so diagnosis is usually clinical. Testing in such labs usually involves cardiovascular tests (tilt table, cardiac response to deep breathing and response to Valsalva) and sudomotor sympathetic function [42].

Constipation

Gastrointestinal symptoms are present at multiple levels of the nervous system including weight loss, drooling, dysphagia, nausea, delayed gastric emptying, constipation and defecatory dysfunction[43]. Constipation is most common. It is defined by the Rome III criteria as including 2 or more of the following for at least 25% of defecations: straining, lumpy or hard stools; sensation of incomplete evacuation; sensation of anorectal obstruction/blockage; use of manual maneuvers to facilitate evacuation; fewer than 3 defecations per week. Other sets of criteria have also been developed but these are most commonly used. Subjective complaints of constipation are present in 20-60% of PD cases[44, 45]. It appears to relate to slow colonic transit of fecal material (or colonic inertia) or anorectal dysfunction[46]. There seems to be low correlation between subjective symptoms and objective measures because asymptomatic objective findings are common. While present early in the course of disease constipation worsens with disease progression. It is worsened also by medications particularly anticholinergics and levodopa. Pathologically, α-synuclein overexpression is seen in the enteric and CNS and autonomic nerves[47, 48]. The relevance and specificity of this finding in relation to symptoms requires further validation in human studies and in control and PD patients with and without constipation.

Constipation can also be a premotor feature. Several studies have now suggested that fewer bowel movements earlier in life may be a predictor of developing PD[49, 50]. A meta-analysis demonstrated an increased risk of 2.27 overall[50]. In a study of incident cases of PD it was reported that even constipation beginning over 20 years before motor onset was associated with an increased risk of PD diagnosis.

Constipation due to anorectal dysfunction is particularly characterized by excessive straining and pain and a sense of incomplete evacuation. This appears to be more prevalent in PD than slowed transit time, seen in approximately 67% of PD patients[51]. Because of incomplete emptying, which could lead to multiple evacuations in close proximity, using the number of bowel movements per day is not an appropriate outcome measure for clinical trials. Anorectal dysfunction appears early in the course of disease and is due to pelvic floor dyssynergia. Paradoxical hypercontractile response of the external anal sphincter and puborectalis muscles where relaxation is expected leads to outlet obstruction [52]. This has been considered to be a focal dystonia. It is diagnosed via anorectal manometry, EMG, and defeccography.

The treatment for constipation of the slowed transit type includes behavioral therapies such as drinking adequate fluids (2 L of fluid per day), increased dietary fiber (15 g psyllium), regular exercise and regular bowel habits. Medical approaches include polyethylene glycol which is shown to be safe and effective in 1 class II study[53], a Level C recommendation[5]. Other over the counter options include stool softeners such as bisacodyl, senna products, fiber supplements, and magnesium based products. Prescription options include osmotic laxatives such as lactulose and lubiprostone (Amitiza) where there is a 4 week RCT with 54 PD participants demonstrating improvement[54]. It has been suggested that polyethylene glycol and lubiprostone are treatments of first choice[55]. A recent class I study demonstrated the efficacy of fermented milk containing multiple probiotic strains and prebiotic fiber[56]. The clinical trial of the Ghrelin receptor agonist RM-131 (Relamorelin) (The MOVE-PD study) had inadequate enrolment so the effectiveness of this class of agents remains unknown[43].

For anorectal dysfunction dopaminergic medications seem to be helpful, particularly apomorphine[57]. Botulinum toxin injected via transrectal ultrasonographic guidance improved symptoms for 2-3 months[58] although recommendations are level U due to insufficient data. Other options include stool softeners and behavioral therapy – biofeedback.

Lower Urological Issues

Bladder dysfunction is another common autonomic feature of PD with an overall frequency of 27-70%[59].

Singer et al reported that 46% of patients complain of urgency and 42% of sensation of incomplete bladder emptying[60]. Urinary symptoms may be an initial complaint in only 4% of patients [61] but, more typically they follow onset of motor symptoms by 6 years[62]. This is confirmed by the work of Araki et al who found that they correlate with severity of disease[63]. Sakakibara et al[64] examined the frequencies by gender as summarized in the table below.

Symptom	Women	Men
Urgency	42%	54%
Daytime frequency	28%	16%
Nocturnal frequency	53%	63%
Urge incontinence	25%	28%
Slowed initiation		44%

Types of urinary symptoms are be categorized as irritative or obstructive [65]. The irritative symptoms include urinary frequency, urgency, and urge incontinence. These are the more common complaints, ~75% of patients, and they tend to occur more in the off time. The obstructive type includes urinary hesitancy with a weak stream and incomplete bladder emptying. The later features are more common in multiple system atrophy.

Irritative symptoms are generally the result of a hyperactive bladder. Cystometric studies demonstrate detrusor hyperreflexia whereby the patients have accentuated involuntary contractions in response to even a small amount of bladder filling that cannot be inhibited. 25% of PD patients who are asymptomatic have detrusor hyperreflexia. Furthermore, some patients with apparent obstructive symptoms will also have detrusor overactivity. Obstructive symptoms, however, are more likely the result of detrusor areflexia which is characterized by decreased sensation when filling. In such cases the bladder can fill with 600 ml or more. The diagnosis can be easily made

with non-invasive ultrasound done in the clinic to examine for voiding residuals. This scenario is rare in PD and when present is often the result of anticholinergic therapy. This scenario increases risk for repeated urinary tract infections. If present without anticholinergic therapy then the physician should consider a diagnosis of multiple system atrophy.

Urinary symptoms may also be the result of pelvic floor and sphincteric dysfunction. This has not been well studied and the role for specific symptoms is unclear but they are more likely obstructive. Uroflow studies and urethral pressure profile for obstruction can provide diagnostic support. Similar to the bowel, poor dyssynergia of the pelvic floor relaxation may play a role representing a form of dystonia or if delayed relaxation is present this may represent sphincter bradykinesia[66].

Treatment is multifactorial as with bowel issues[67]. In general, trials in PD of many of the treatments are lacking. First line involves life style changes with fluid, caffeine and alcohol restriction, especially at night, control of constipation, treatment of ankle edema, avoidance of nocturnal hypertension, appropriate sleep hygiene and exercise. Pelvic floor muscle exercise (Kegels's) for urge suppression has been demonstrated to be effective[68]. Also the use of continence products such as pads, briefs, and external collection system can be very helpful. Finally, scheduled prompted voiding: especially in those with cognitive impairment would be useful.

Medical therapies include antimuscarinics[69]. These are commonly used but there is no data specifically in PD with one exception, solifenacin[70]. It should be remembered that they may impact cognition, cause signs of outlet obstruction and other typical anticholinergic side effects. The cognitive effects vary depending on the agent. For example, trospium and darifenasin have less penetration into the brain hence fewer cognitive effects while oxybutynin and tolterodine have more penetrance. Other agents include alpha-1 blockers such as tamsulosin and silodosin and the more recently approved beta-3-agonist mirabegron 25-100mg per day which can cause increased blood pressure but no cognitive problems[71]. For dosing see reference by Batla et al 2016[67]. Dopaminergic drugs improve voiding efficiency, decreased outflow resistance and relaxation of the pelvic floor. It is unknown what the effect is on detrusor hyperreflexia. Apomorphine use is supported by a Class III study. Subthalamic deep brain stimulation may impact on urinary issues as supported by several class IV studies[5]. Data for the treatment of urinary incontinence with apomorphine or DBS are insufficient. Botulinum toxin therapy with 200 units injected into the bladder has also demonstrated effectiveness that lasted 5 months[72]. For obstructive symptoms regular self-catheterization may be required.

Orthostatic hypotension

Blood pressure is influenced by sympathetic and parasympathetic components on the baroreceptor reflex. Failure of the sympathetic system is what leads to orthostatic hypotension[73] in PD. Orthostatic hypotension is defined by a fall in systolic blood pressure of at least 20 mmHg and or in diastolic of at least 10 mmHg on either standing or 60 degree head up tilt on a tilt table test[74]. The resultant hypoperfusion to the brain leads to several clinical features including dizziness, visual disturbance, clouded thinking and cognitive change[75], fatigue, neck and shoulder pain (coat-hanger syndrome) upon standing, and contributes to falls or syncopal episodes when going from lying down to sitting or sitting or squatting to standing. Seizure like episodes can occasionally occur from cerebral hypoxia and dyspnea from lung hypoxia (platypnea). It is not always recognized by patients and in this scenario, and if no action is taken, like sitting or squatting, syncope will occur. Some patients have abnormal nocturnal BP regulation (supine hypertension) and in the morning have high measures[76]. Orthostatic hypotension is a risk factor for motor decline, mortality and a cause of falls[77].

PD patients should be routinely screened. Assessments include orthostatic pressures at bedside (5 minutes lying or sitting and 1-3 minutes of standing) and the tilt table test. One should examine for delayed orthostatic drops. Variation in BP may relate to several factors in PD including age, stage of disease, concomitant medications and other associated disorders. Further evaluations should include home BP monitoring, medication review, cardiac evaluation then specialty testing[74]. The prevalence of OH in PD varies from 30-60% [78, 79 80]. It is present in 15% of newly diagnosed patients. Most of these patients are asymptomatic[78]. The prevalence rises with age, disease severity and disease duration.

In PD, ganglionic and postganglionic sympathetic pathology (synuclein pathology) is a key finding and differentiates it from MSA. MIBG scans and skin biopsies can be diagnostically helpful. As a result there are subnormal levels of basal plasma noradrenaline and impaired response to head up challenge. This explains responsiveness or lack thereof to various treatments that require an intact peripheral system.

The goal of treatment is to reduce falls, prolong standing time, improve tolerance to physical activity, and restore independence. When to treat is, especially in patients who have asymptomatic drop in BP. It has been suggested that a mean BP after standing of 75 mmHg is a level when symptoms begin[81]. Initial management includes eliminating medications that lower BP including dopamine agonists, tamsulosin and similar agents, tricyclic antidepressants and antihypertensive agents. Non-pharmacologic measures include increasing water and salt intake (cold glass of water upon awakening or when symptomatic). The recommended daily intake of water is 2.0-3.0 L/day and of sodium chloride is 6–10 g[74, 82]. Behavioral steps include avoiding standing quickly, avoiding large meals, alcohol, hot baths or showers, using support stockings and keeping the head of the bed propped up[82]. For medications, it has been shown that the definition of a diagnosis of OH does not define when to initiate therapy and there are no guidelines. Only a portion of patients with OH have symptoms. Palma et al demonstrated recently that most patients who are symptomatic have a mean standing BP below 75 mmHg and that appears to be a more useful target when deciding whether the benefits of initiating pharmacological treatment outweigh the risks of exacerbating supine hypertension[81]. Data are insufficient to make a recommendation on the use of indomethacin, fludrocortisone, pyridostigmine, or domperidone in treating OH in PD. Nevertheless fludrocortisone (0.1-0.2 mg/day); midodrine (its metabolite desglymidodrine is a α-adenoreceptor agonist; up to 10 mg TID) and droxidopa (noradrenaline precursor; 100-300 mg TID – approved in 2014[83, 84]) can be helpful [74, 82]. Their use should be avoided in the late afternoon or evening to prevent supine hypertension which is more of a concern with midodrine. Other possible medication choices include ephedrine, pyridostigmine, indomethacin or ibuprofen.

Other less common autonomic issues to be discussed are sexual dysfunction and hyperhidrosis.

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