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Management of Nonmotor Symptoms in Parkinson Disease

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Abstract

In this review, non-motor of Parkinson's disease is described in the context of the progression of the disease. Also briefly discussed are the major treatment strategies. Parkinson's disease is a slowly progressing neurodegenerative disorder, causing impaired motor function with slow movements, tremor and gait and balance disturbances. A variety of non-motor symptoms are common in Parkinson's disease, they include various neuropsychiatric manifestations including cognitive dysfunction, hallucinations and other psychotic symptoms, anxiety, apathy, and mood disorders such as depression. (Seppi K, Ray Chaudhuri K, Coelho M, Fox SH, Katzenschlager R, Perez Lloret S, Weintraub D & Sampaio C, 2019) Disorders of sleep and wakefulness are common, including insomnia, parasomnias, restless legs syndrome (RLS), and daytime sleepiness. This article describes the different non-motor symptoms and major treatment strategies.

Keywords: Parkinson disease, nonmotor symptoms, management

1. Introduction

Parkinson disease (PD) is a chronic, progressive neurodegenerative disease characterized by bradykinesia (slowness of movement) and hypokinesia (reduced amplitude of movement) combined with rest tremor and/or rigidity. In addition to these typical motor features, patients with PD may experience nonmotor symptoms related to the disease itself or to the medications used to treat it. These include various neuropsychiatric manifestations including cognitive dysfunction, hallucinations and other psychotic symptoms, anxiety, apathy, and mood disorders such as depression. (Seppi K, Ray Chaudhuri K, Coelho M, Fox SH, Katzenschlager R, Perez Lloret S, Weintraub D & Sampaio C, 2019) Disorders of sleep and wakefulness are common, including insomnia, parasomnias, restless legs syndrome (RLS), and daytime sleepiness. Autonomic problems are also prominent, including orthostatic hypotension, sexual dysfunction, and constipation. The management of the nonmotor symptoms described above will be reviewed here.

2. Depression

Depression is the most common psychiatric disturbance seen in PD. Though generally mild to moderate in severity, depressive symptoms in PD are associated with a negative impact on motor disability and decreased quality of life. (Weintraub D, Moberg PJ, Duda JE, Katz IR & Stern MB, 2004; Schrag A, Jahanshahi M & Quinn N., 2000; Ravina B, Camicioli R, Como PG, Marsh L, Jankovic J, Weintraub D & Elm J., 2007) Patients with PD who develop depression usually present with sadness, anhedonia, and decreased interest in activities. Guilt and feelings of worthlessness may occur less frequently in PD-related depression. (Gotham AM, Brown RG & Marsden CD, 1986) Importantly, suicidal ideation and thoughts of death are common in PD. In surveys, such thoughts are present in 20 to 33 percent of patients, (Nazem S, Siderowf AD, Duda JE, Brown GK, Ten Have T, Stern MB & Weintraub D., 2008) and depression is an important risk factor. (Kummer A, Cardoso F & Teixeira AL., 2009; Chen YY, Yu S, Hu YH, Li CY, Artaud F, Carcaillon-Bentata L, Elbaz A & Lee PC., 2021) Though suicide attempts are fortunately uncommon, actively suicidal patients should be hospitalized. (Chen YY,

Yu S, Hu YH, Li CY, Artaud F, Carcaillon-Bentata L, Elbaz A & Lee PC., 2021)

Patients with depression should be offered antidepressant medication, cognitive behavioral therapy (CBT), or both.

Abundant data in the general population, as well as more limited data in patients with PD, indicate that CBT is also an effective treatment for depression in PD. In a pilot randomized trial of CBT versus observation in eight patients with PD, the CBT group had improved depression scores at 10 weeks. (Dobkin RD, Menza M, Allen LA, Gara MA, Mark MH, Tiu J, Bienfait KL & Friedman J., 2011) A larger trial of telephone-based CBT in 72 patients with PD found improvements in depression scores over usual care, which were moderated primarily by a decrease in negative thoughts. (Dobkin RD, Mann SL, Gara MA, Interian A, Rodriguez KM & Menza M., 2020) In the absence of additional evidence specifically in the PD population, data on the treatment of depression in older adults indicate that combining CBT with pharmacotherapy is superior to pharmacotherapy alone for the treatment of depression, and this should be considered in PD.

In the absence of a clear first choice for treating depression associated with PD, drug selection should be based on potential advantages versus potential side effects. (Seppi K, Ray Chaudhuri K, Coelho M, Fox SH, Katzenschlager R, Perez Lloret S, Weintraub D & Sampaio C, 2019; Okun MS & Watts RL., 2002) It is reasonable to start with a selective serotonin-norepinephrine reuptake inhibitor (SNRI) or a selective serotonin reuptake inhibitor (SSRI) in most patients with PD, as the likelihood of adverse events is lower with these agents than with tricyclic medications (such as amitriptyline, lesser extent nortriptyline). (Seppi K, Ray Chaudhuri K, Coelho M, Fox SH, Katzenschlager R, Perez Lloret S, Weintraub D & Sampaio C, 2019) The anticholinergic side effects of tricyclic medications, which can include cognitive impairment and orthostatic hypotension with an increased risk of falls, may be particularly troublesome in the setting of PD. However, for patients who do not improve with SNRI or SSRI treatment, a tricyclic antidepressant is a reasonable option, particularly when tremor is a dominant symptom, and the potential benefit is thought to outweigh the risk of anticholinergic side effects. Evidence from other randomized controlled trials suggests that dopamine agonists may improve depressive symptoms in patients with PD. (Seppi K, Ray Chaudhuri K, Coelho M, Fox SH, Katzenschlager R, Perez Lloret S, Weintraub D & Sampaio C, 2019; Pahwa R, Stacy MA, Factor SA, Lyons KE, Stocchi F, Hersh BP, Elmer LW, Truong DD & Earl NL, 2007; Barone P, Poewe W, Albrecht S, Debieuvre C, Massey D, Rascol O, Tolosa E & Weintraub D., 2010; Seppi K, Weintraub D, Coelho M, Perez-Lloret S, Fox SH, Katzenschlager R, Hametner EM, Poewe W, Rascol O, Goetz CG, et al., 2011)

A practice parameter from the American Academy of Neurology (AAN) reviewed six small and randomized controlled trials of pharmacologic treatment for depression in patients with PD. (Miyasaki JM, Shannon K, Voon V, Ravina B, Kleiner-Fisman G, Anderson K, Shulman LM, Gronseth G & Weiner WJ, 2006) In one of these trials, amitriptyline (but not fluoxetine) treatment was associated with significant improvement. (Serrano-Duenas M., 2002)

Since the AAN report, a number of randomized placebo-controlled trials have reported the following observations regarding the treatment of depression in patients with PD:

● Desipramine and citalopram were equally effective. (Devos D, Dujardin K, Poirot I, Moreau C, Cottencin O, Thomas P, Destee A, Bordet R & Defebvre L., 2008)

● Nortriptyline was efficacious while paroxetine controlled release was not. (Menza M, Dobkin RD, Marin H, Mark MH, Gara M, Buyske S, Bienfait K & Dicke A., 2009)

● Atomoxetine was not beneficial. (Weintraub D, Mavandadi S, Mamikonyan E, Siderowf AD, Duda JE, Hurtig HI, Colcher A, Horn SS, Nazem S, Ten Have TR, et al., 2010)

● Paroxetine and venlafaxine improved depression and did not worsen motor function. (Richard IH, McDermott MP, Kurlan R, Lyness JM, Como PG, Pearson N, Factor SA, Juncos J, Serrano Ramos C, Brodsky M, et al., 2012)

SSRIs and SNRIs are generally safe in patients with PD. However, they can cause QT prolongation, and monitoring for this is essential where indicated, for example, when patients are known to be on other medications that cause QT prolongation and/or in patients with underlying heart disease.

3. Apathy

Apathy and abulia can be seen in patients with PD both in the context of depression and in the absence of other signs of clinical depression. Patients with PD who have apathy as a feature of depression should be treated with antidepressant medications and/or psychotherapy.

There are no standardized treatments for apathy or abulia in the absence of depression or for persistent apathy despite treatment of depression. Based on results of a small trial, the cholinesterase inhibitor rivastigmine may be considered, (Seppi K, Ray Chaudhuri K, Coelho M, Fox SH, Katzenschlager R, Perez Lloret S, Weintraub D

& Sampaio C, 2019) even in those without depression or cognitive dysfunction. (Devos D, Dujardin K, Poirot I, Moreau C, Cottencin O, Thomas P, Destee A, Bordet R & Defebvre L., 2008) However, the clinical relevance and reproducibility of the changes observed in the trial are uncertain, and further studies are needed.

4. Anxiety

Anxiety is common in patents with PD, occurring in over a third of patients. It may occur alone, or it may be comorbid with depression.

Importantly, anxiety may be a symptom of wearing off of dopaminergic medication in patients who experience motor and nonmotor fluctuations. (Van der Velden RMJ, Broen MPG, Kuijf ML & Leentjens AFG., 2018) In such cases, A variety of strategies can help mitigate “wearing off” phenomena and require individualized trial-and-error approach. Among them, the most important measure is to adjust the amount of levodopa.

Selective serotonin reuptake inhibitors (SSRIs) (such as citalopram and sertraline), serotonin-norepinephrine reuptake inhibitors (SNRIs) (such as venlafaxine and mirtazapine), and serotonin-selective agents (such as buspirone) may all be considered.

Therapeutic use of cannabinoids is of interest in patients with PD and nonmotor symptoms, especially anxiety and sleep disturbances. A small pilot trial of synthetic nabilone (not available in the United States) found potential benefits on anxiety, sleep, and pain symptoms, with similar adverse effects compared with placebo. (Peball M, Krismer F, Knaus HG, Djamshidian A, Werkmann M, Carbone F, Ellmerer P, Heim B, Marini K, Valent D, et al., 2020) In addition, a small randomized, placebo-controlled crossover study showed that a single dose of cannabidiol decreased anxiety symptoms including anxiety-related tremor in patients with PD. (de Faria SM, de Morais Fabricio D, Tumas V, Castro PC, Ponti MA, Hallak JE, Zuardi AW, Crippa JAS & Chagas MHN., 2020) Beneficial effects on anxiety have also been observed in adults without PD. (Black N, Stockings E, Campbell G, Tran LT, Zagic D, Hall WD, Farrell M & Degenhardt L., 2019) These preliminary findings are promising but require confirmation in larger studies before cannabinoids can be recommended for treatment of nonmotor symptoms in PD.

5. Cognitive Impairment

While PD can coexist with other common causes of dementia, such as Alzheimer disease and vascular dementia, cognitive impairment and dementia are increasingly recognized as a common feature of PD itself. Cognitive impairment in PD has a heterogeneous cognitive profile that is different from that of Alzheimer disease (AD) (Svenningsson P, Westman E, Ballard C & Aarsland D., 2012) The general pattern is one of executive dysfunction and impaired visuospatial function, with less prominent memory deficits and relatively preserved language function. (Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, Broe GA, Cummings J, Dickson DW, Gauthier S, et al., 2007) Executive dysfunction is often present early in the disease course and is manifested by deficiencies in set shifting, attention, and planning.

We initiate treatment trials of cholinesterase inhibitors and/or memantine in a stepwise fashion in patients with PDD, monitoring for side effects and tapering if no improvement or side effects develop.

Cholinesterase inhibitors—We suggest the use of cholinesterase inhibitors in patients with PDD. Most (but not all) studies of cholinesterase inhibitors in PDD have noted a mild to moderate benefit but an increased risk of side effects, including worsened tremor and nausea:

Rivastigmine was evaluated in a 24-week, double-blind, placebo-controlled study of 501 patients with mild to moderate PDD and was found to result in moderate improvement in dementia, mean improvement of 2.1 points on the Alzheimer Disease Assessment Scale-Cognitive Subscale (ADAS-cog) score compared with 0.7-point decline in the placebo-treated group. (Sun C & Armstrong MJ., 2021) Clinically meaningful improvements were seen in 20 and 14.5 percent in the treatment and placebo groups, respectively, while clinically meaningful worsening was observed in 13 and 23 percent. This suggests that 15 percent of patients benefited from treatment. (Szeto JY & Lewis SJ., 2016)

Memantine—Memantine has reported efficacy in moderate to severe Alzheimer disease (AD) and in vascular dementia. One 24-week randomized controlled study of 72 patients with either dementia with Lewy bodies (DLB) or PDD found that patients treated with memantine performed better on the primary outcome assessment measure, the clinical global impression of change, but not on other secondary outcome measures. (Aarsland D, Ballard C, Walker Z, Bostrom F, Alves G, Kossakowski K, Leroi I, Pozo-Rodriguez F, Minthon L & Londos E., 2009) In a more recent, 24-week randomized controlled study, DLB patients, but not PDD patients, were improved on the same outcome measure. (Emre M, Tsolaki M, Bonuccelli U, Destee A, Tolosa E, Kutzelnigg A, Ceballos-Baumann A, Zdravkovic S, Bladstrom A, Jones R, et al., 2010) Memantine was well tolerated in these trials and in another shorter study of patients with PDD. (Leroi I, Overshott R, Byrne EJ, Daniel E & Burns A., 2009) However, hallucinations and worsened neuropsychiatric symptoms have occasionally been reported with

the use of memantine, suggesting some caution with its use in PDD. (Friedman JH., 2017)

6. Psychosis

Psychosis is a frequent complication of PD. It is characterized mainly by visual hallucinations and delusions, which are often paranoid in content. (Forsaa EB, Larsen JP, Wentzel-Larsen T, Goetz CG, Stebbins GT, Aarsland D & Alves G., 2010) Hallucinations are the most common manifestation, and they affect up to 40 percent of patients with PD, particularly those at an advanced stage of illness. Delusions can also be a prominent feature of psychosis in PD and are usually paranoid in nature. Many patients with PD who have psychotic symptoms nevertheless retain the insight that their hallucinations are not real. However, patients with PD can also have delirium or dementia and manifest psychosis as a result. The patients in this latter category tend to be less responsive to treatment.

Commonly reported risk factors for psychosis in PD include the use of high doses of antiparkinson drugs, the presence of dementia, advancing age, impaired vision, depression, presence of sleep disorders, high comorbid disease burden, and longer disease duration. (Aarsland D, Larsen JP, Cummins JL & Laake K., 1999; Manni R & Mazzarello P., 2001; Biglan KM, Holloway RG, Jr., McDermott MP, Richard IH & Parkinson Study Group C-PDI, 2007) Psychosis can be triggered by systemic conditions such as symptomatic or occult infection (e.g., pneumonia or urinary tract infection), so this possibility should be investigated and treated if present. (Friedman JH., 2013; Connolly B & Fox SH., 2014) Anticholinergics can contribute to confusion and exacerbate psychosis in PD. Psychoactive medications (including sedatives, anxiolytics, and antidepressants) are potential culprits and should be reduced or stopped if possible.

● Antiparkinson medication adjustments—Stopping all potentially offending antiparkinson drugs is usually not an option, although dose reduction can frequently be accomplished with amelioration of hallucinations and little loss of drug-related benefit.

Antiparkinsonian drugs may be reduced or stopped in an order that balances their potency as antiparkinson agents and their likelihood of exacerbating disabling hallucinations. Decisions regarding which drug to stop in this setting should also take into account which one drug might have triggered the psychosis.

If a temporal relationship is not clear, the suggested sequence of discontinuation begins with anticholinergic drugs, followed by amantadine, dopamine agonists, monoamine oxidase type B (MAO B) inhibitors, and COMT inhibitors. (Figure 1) Levodopa should be the last of a drug combination to be reduced, since it is the most effective antiparkinson agent and least likely to cause psychosis. However, if given in unusually high doses, it too might need to be reduced.

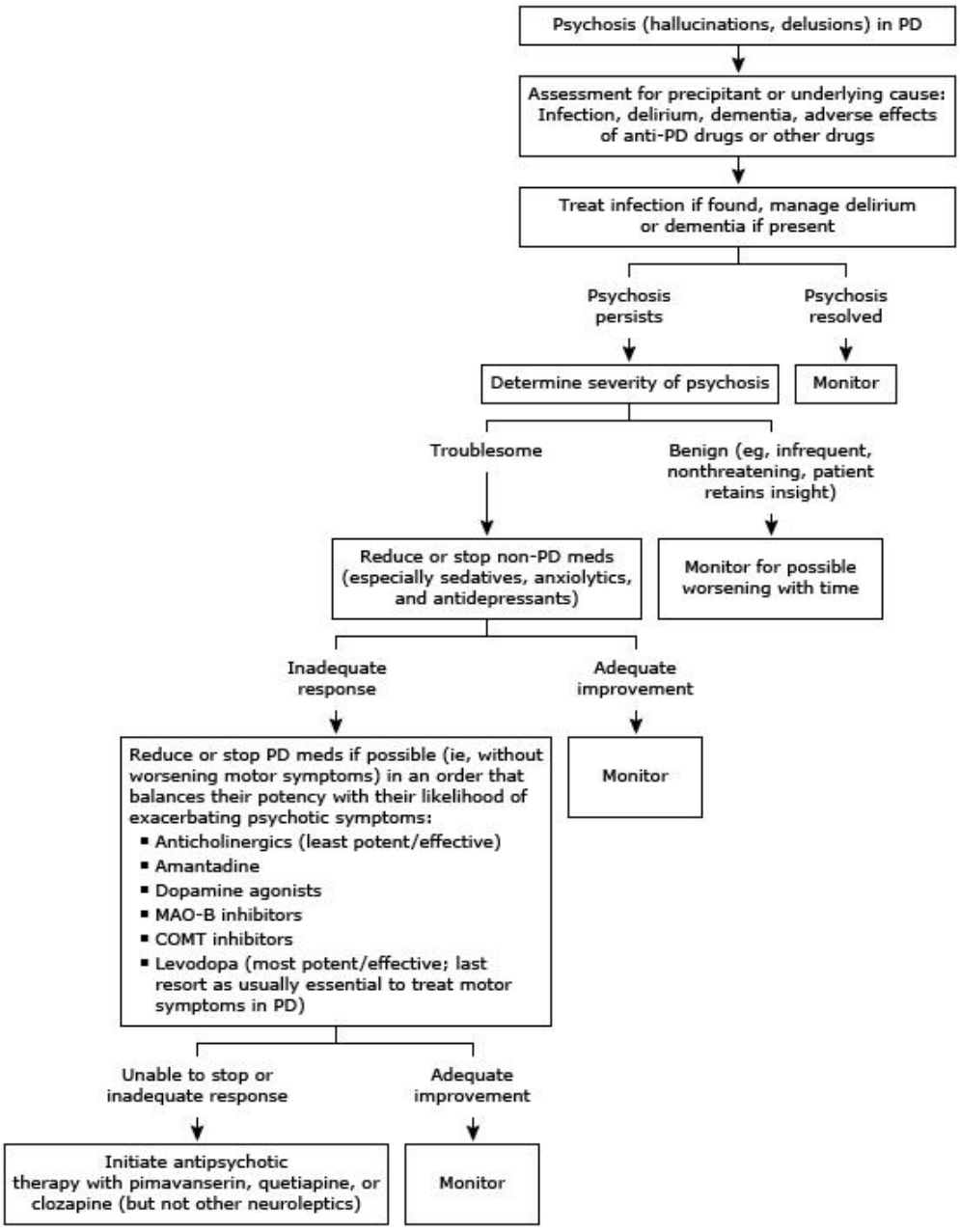

Figure 1. Management of psychosis in Parkinson disease

● Refractory psychotic symptoms—For patients with troublesome hallucinations or delusions despite antiparkinson medication adjustments, pharmacologic treatment directed at the psychotic symptoms may be necessary. If antipsychotic drugs are deemed necessary, preferred agents in patients with PD include pimavanserin, quetiapine, and clozapine. (Seppi K, Ray Chaudhuri K, Coelho M, Fox SH, Katzenschlager R, Perez Lloret S, Weintraub D & Sampaio C, 2019)

Among antipsychotics, quetiapine is widely prescribed in patients with PD and clozapine may be the most effective, but the need for hematologic monitoring limited its use as a first-line option. (Friedman JH., 2013; Connolly B & Fox SH., 2014; Morgante L, Epifanio A, Spina E, Di Rosa AE, Zappia M, Basile G, La Spina P & Quattrone A., 2002; Juncos JL, Roberts VJ, Evatt ML, Jewart RD, Wood CD, Potter LS, Jou HC & Yeung PP., 2004; Pollak P, Tison F, Rascol O, Destee A, Pere JJ, Senard JM, Durif F & Bourdeix I., 2004) Pimavanserin is a newer alternative, and long-term safety and efficacy data are more limited. Due to limited comparisons, treatment decisions should be individualized, taking into account these considerations as well as factors that are likely to vary by patient and region, such as drug costs. All three agents have a low likelihood of exacerbating parkinsonism, in contrast to the first-generation antipsychotics as well as other second-generation antipsychotics

such as risperidone and olanzapine.

All antipsychotic drugs carry risk, including an association with a small increase in all-cause mortality and cardiovascular events when used to treat behavioral disorders in older adults with dementia. In patients with PD specifically, data also suggest that antipsychotic use is associated with an increased risk of mortality (Weintraub D, Chiang C, Kim HM, Wilkinson J, Marras C, Stanislawski B, Mamikonyan E & Kales HC., 2016) as well as morbidity and health care utilization. (Weintraub D, Chiang C, Kim HM, Wilkinson J, Marras C, Stanislawski B, Mamikonyan E & Kales HC., 2017) However, these risks must be balanced with the high morbidity and mortality of untreated psychosis. (Miyasaki JM, Shannon K, Voon V, Ravina B, Kleiner-Fisman G, Anderson K, Shulman LM, Gronseth G & Weiner WJ, 2006) When the potential risks are felt to outweigh the benefits, antipsychotics should be prescribed cautiously, starting with low doses and using the lowest dose necessary to achieve clinical response. The need for ongoing dosing should be reviewed regularly.

7. Insomnia and Other Sleep Disorders

Disorders of sleep are common in PD, including sleep onset and maintenance insomnia, restless legs syndrome (RLS), and rapid eye movement (REM) sleep behavior disorder (RBD). They affect between 55 and 80 percent of patients with PD.

There are many potential causes of frequent awakenings in PD, but the most common are nocturia, difficulty turning over in bed, cramps, vivid dreams or nightmares, and pain (especially in the neck or back). (Gjerstad MD, Wentzel-Larsen T, Aarsland D & Larsen JP., 2007; Stefani A & Hogl B., 2020; Cochen De Cock V, Benard-Serre N, Driss V, Granier M, Charif M, Carlander B, Desplan M, Croisier Langenier M, Cugy D & Bayard S., 2015) Tremor may also contribute to sleep fragmentation. The rest tremor in PD disappears with REM sleep, but recurs during light sleep and may awaken the patient as a result. (Askenasy JJ & Yahr MD., 1990) Some patients may have painful dystonia, especially of the legs, which typically occurs in the early morning and disrupts sleep. Depression is also commonly associated with poor sleep efficiency, decreased sleep time, and early morning awakening. (Wang YQ, Li R, Zhang MQ, Zhang Z, Qu WM & Huang ZL., 2015)

Goals of treatment should be well defined with the patient and their caregivers before initiating treatment. Goals can vary depending on the predominant symptom and may include decreased arousal, increased total sleep duration, or improved daytime sleepiness.

● Safe sleeping environment—The frequency of dream enactment behaviors is not predictive of injury, so all patients with RBD and their bed partners should be counseled on modifying the sleeping environment to prevent injury. For patients with mild symptoms, this may be all that is needed.

● Reversible factors—Medications known to cause or exacerbate RBD, such as serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants, should be discontinued or avoided if possible. High-dose melatonin and low-dose clonazepam are effective therapies in patients with frequent, disruptive or injurious behaviors. Clonazepam should be used with caution in light of the risk of increased confusion and unsteadiness with middle of the night awakenings.

● Pharmacotherapy—All patients with frequent, disruptive, or injurious behaviors should be treated with pharmacotherapy to reduce behaviors and lower risk of injury. Melatonin is an endogenous hormone normally secreted by the pineal gland in response to evening darkness, entraining circadian rhythms. Like melatonin, the therapeutic mechanisms of clonazepam in RBD are not fully understood, although it is thought that clonazepam may reduce the frequency of unpleasant dreams, thus decreasing violent dream enactment behavior. (Li SX, Lam SP, Zhang J, Yu MW, Chan JW, Liu Y, Lam VK, Ho CK, Zhou J & Wing YK., 2016) In patients who fail melatonin and clonazepam therapy, cholinergic agents may be useful.

In several observational studies and one small randomized trial, the majority of patients treated with melatonin experienced at least partial improvement in the frequency and severity of RBD symptoms and a reduced likelihood of injury. (McGrane IR, Leung JG, St Louis EK & Boeve BF., 2015; Kunz D & Mahlberg R., 2010; Anderson KN & Shneerson JM., 2009; McCarter SJ, Boswell CL, St Louis EK, Dueffert LG, Slocumb N, Boeve BF, Silber MH, Olson EJ & Tippmann-Peikert M., 2013) In a retrospective study that included 45 patients with RBD, melatonin and clonazepam were similarly effective, and melatonin was better tolerated. (McCarter SJ, Boswell CL, St Louis EK, Dueffert LG, Slocumb N, Boeve BF, Silber MH, Olson EJ & Tippmann-Peikert M., 2013) Approximately two-thirds of patients treated with melatonin reported at least mild improvement in symptoms, and 12 percent had complete resolution of RBD behaviors. Patients on melatonin reported fewer falls and injuries post-treatment compared with clonazepam.

In one small, placebo-controlled, crossover trial, the acetylcholinesterase inhibitor rivastigmine reduced the number of dream-enactment behavior episodes (as noted by bed partners) in patients with Parkinson disease (PD) and RBD. (Liebenthal J, Valerio J, Ruoff C & Mahowald M., 2016) Rivastigmine is administered by transdermal patch, and dosing typically starts at 4.6 mg applied every 24 hours. The dose can be titrated up to a maximum of

13.3 mg daily. Donepezil, another cholinesterase inhibitor, has also been reported to improve RBD symptoms in three patients. (Arnulf I, Bonnet AM, Damier P, Bejjani BP, Seilhean D, Derenne JP & Agid Y., 2000)

These agents are both commonly used in the treatment of dementia with Lewy bodies and PD dementia and thus may be a good choice for patients with RBD who also have cognitive impairment. However, rivastigmine should be used with caution among patients with autonomic symptoms.

8. Daytime Sleep

Excessive daytime sleepiness (EDS) has long been recognized as a problem in PD. (Arnulf I, Bonnet AM, Damier P, Bejjani BP, Seilhean D, Derenne JP & Agid Y., 2000; Factor SA, McAlarney T, Sanchez-Ramos JR & Weiner WJ., 1990; van Hilten JJ, Weggeman M, van der Velde EA, Kerkhof GA, van Dijk JG & Roos RA., 1993) The prevalence of EDS in PD varies according to study methodology, but estimates range from 33 to 76 percent. (Brodsky MA, Godbold J, Roth T & Olanow CW., 2003; Hogl B, Seppi K, Brandauer E, Glatzl S, Frauscher B, Niedermuller U, Wenning G & Poewe W., 2003; Henderson JM, Lu Y, Wang S, Cartwright H & Halliday GM., 2003; Bargiotas P, Lachenmayer ML, Schreier DR, Mathis J & Bassetti CL., 2019) Some patients may just be sleepy, while others have additional unintended sleep episodes or sudden sleep “attacks”. (Roth T, Rye DB, Borchert LD, Bartlett C, Bliwise DL, Cantor C, Gorell JM, Hubble JP, Musch B, Olanow CW, et al., 2003) EDS and sudden somnolence can be a hazard for patients with PD who drive. (Frucht S, Rogers JD, Greene PE, Gordon MF & Fahn S., 1999) EDS in PD is likely multifactorial. Possible risk factors include difficulty sleeping at night, depression, dementia, dopaminergic treatment, high comorbid disease burden, and male sex. (Biglan KM, Holloway RG, Jr., McDermott MP, Richard IH & Parkinson Study Group C-PDI, 2007; Razmy A, Lang AE & Shapiro CM., 2004; Avorn J, Schneeweiss S, Sudarsky LR, Benner J, Kiyota Y, Levin R & Glynn RJ., 2005; Gjerstad MD, Alves G, Wentzel-Larsen T, Aarsland D & Larsen JP., 2006; Bliwise DL, Trotti LM, Wilson AG, Greer SA, Wood-Siverio C, Juncos JJ, Factor SA, Freeman A & Rye DB., 2012) It has also been argued that EDS may be intrinsic to the disease process. (Arnulf I, Konofal E, Merino-Andreu M, Houeto JL, Mesnage V, Welter ML, Lacomblez L, Golmard JL, Derenne JP & Agid Y., 2002) Management requires a multipronged approach involving nonpharmacologic and pharmacologic strategies.

● Optimal nighttime sleep—Common factors that contribute to poor nighttime sleep, such as poor sleep hygiene and nocturia, may improve EDS when treated accordingly.

Reduction or discontinuation of dopamine agonists—In some patients, EDS is due to antiparkinson’s therapy. Dopamine agonists can cause EDS, sometimes severe enough to suddenly develop narcolepsy-like sleep episodes. At this time, it is necessary to reduce or discontinue dopamine agonists. Levodopa also has a sedative effect, but its role in controlling motor symptoms is important, so it can only be reduced to some extent. Among the options for patients with PD, case-by-case evidence suggests that the MAO inhibitor selegiline helps relieve daytime sleepiness because the drug is metabolized to amphetamine derivatives, making it suitable for the treatment of motor symptoms in patients with EDS.

● Patient education and safety—Regardless of the cause of EDS, a strong focus needs to be placed on patient driving safety and other activity-related issues. Some patients should stop driving.

● Bright light therapy and physical activity—Data on nonpharmacological treatments for EDS in patients with PD are limited, but bright light therapy is a promising new therapy. In a randomized trial of 31 patients with PD and EDS, bright light therapy (1 hour twice daily for 14 days) improved Epworth Sleepiness Scale (ESS), multiple self-rated sleep quality measures, and physical activity levels compared with dim red-light control. (Videnovic A, Klerman EB, Wang W, Marconi A, Kuhta T & Zee PC., 2017) Structured physical activity and exercise also hold promise for the treatment of daytime sleepiness in patients with PD, but there is no evidence to guide specific exercise regimens. (Reynolds GO, Otto MW, Ellis TD & Cronin-Golomb A., 2016) Patients with PD should generally be encouraged to achieve the recommended level of physical activity for adults. The National Institute on Aging provides patients with useful online resources. The benefits of exercise may be similar to those of the average adult and may benefit other aspects specific to PD, including EDS.

● Medical therapy—If nonpharmacologic measures are insufficient, pharmacologic options for EDS in patients with PD include modafinil and methylphenidate. Appropriate use of caffeine during the day also has some benefits. (Postuma RB, Anang J, Pelletier A, Joseph L, Moscovich M, Grimes D, Furtado S, Munhoz RP, Appel-Cresswell S, Moro A, et al., 2017)

Data on the efficacy of modafinil in EDS in patients with PD are sparse and inconsistent. (Hogl B, Saletu M, Brandauer E, Glatzl S, Frauscher B, Seppi K, Ulmer H, Wenning G & Poewe W., 2002; Adler CH, Caviness JN, Hentz JG, Lind M & Tiede J., 2003; Ondo WG, Fayle R, Atassi F & Jankovic J., 2005) Some studies suggest that modafinil results in subjective improvement in EDS in some patients with PD, (Hogl B, Saletu M, Brandauer E, Glatzl S, Frauscher B, Seppi K, Ulmer H, Wenning G & Poewe W., 2002; Adler CH, Caviness JN, Hentz JG, Lind M & Tiede J., 2003) but objective sleep improvement has not been demonstrated. The largest of these small

trials randomized 40 patients with PD with EDS to modafinil (200 to 400 mg/day) or placebo. Modafinil treatment did not improve the primary outcome [i.e., ESS (calculator 1)] or any secondary outcomes. The U.S. FDA has approved the use of modafinil for the treatment of narcolepsy in the general population, but has not yet approved it for the treatment of drowsiness in patients with PD. Patients with PD can try modafinil for EDS, but it is important to set patient expectations, and even if the treatment is beneficial, it is usually mild and not durable. (Seppi K, Ray Chaudhuri K, Coelho M, Fox SH, Katzenschlager R, Perez Lloret S, Weintraub D & Sampaio C, 2019)

9. Dysphagia

Swallowing difficulty is prevalent in PD, particularly at advanced stages. All phases of swallow are impacted due to abnormalities in both striated and smooth muscle function, ineffective tongue movements, delayed swallow responses, and weak cough-expectoration response. Dysphagia contributes to sialorrhea and increases risk of aspiration and pneumonia.

Dysphagia is important to recognize in patients with PD as there are compensatory strategies available to help retain safe and effective oral feeding for as long as possible. Assessment and management strategies are reviewed in detail separately.

● Swallowing interventions—More recently, greater attention has been placed on optimizing health and preserving functional reserve starting in early diagnostic stages. Resistive strength swallowing exercises may help to maintain physiologic swallowing function for longer. (Rogus-Pulia NM & Plowman EK., 2020)

The physiologic information obtained from clinical and instrumental swallowing assessment facilitates the selection of interventions that are aimed at increasing swallowing safety and efficiency. These strategies may compensate for impaired swallowing function by altering head or neck posture to redirect bolus flow, heighten sensory awareness, or change bolus characteristics to improve the safety of swallowing. The chin tuck posture, a commonly recommended strategy, narrows the lumen of the pharynx by increasing tongue base retraction and pressure on the bolus and decreases the opening of the larynx during swallowing. These functional effects potentially reduce the risk of laryngeal penetration and aspiration. However, in cases of delayed onset of the swallow response, the chin tuck posture may induce or exacerbate aspiration, and therefore it is not safe in all cases. Only a direct imaging of swallowing during food and liquid trials with laryngoscopy or fluoroscopy can determine its effectiveness.

● Diet considerations—The guiding principle is to ingest the maximum amount of calories and hydration for the least amount of effort, with the understanding that the patient may be unlikely to consume the same volume as before the illness. Nutritionists can provide individualized suggestions for calorie-dense foods or high-calorie supplements, taking the patient's metabolic status into consideration. Modifying the texture of solid foods and consistency of liquids is widely used in the management of patients with dysphagia and may improve the safety and/or ease of oral consumption. (Steele CM, Alsanei WA, Ayanikalath S, Barbon CE, Chen J, Cichero JA, Coutts K, Dantas RO, Duivestein J, Giosa L, et al., 2015; Logemann JA, Gensler G, Robbins J, Lindblad AS, Brandt D, Hind JA, Kosek S, Dikeman K, Kazandjian M, Gramigna GD, et al., 2008) However, low acceptability, resulting in poor adherence to modified food textures and liquids, can contribute to an increased risk of inadequate nutrition and hydration. As such, these modifications should be used judiciously and in the context of shared decision-making. Alterations in texture and viscosity must be balanced with foods that are pleasurable and appetizing for the patient in spite of their texture modification.

● Maintaining airway clearance — An overabundance of secretions or change in secretion viscosity and composition may result from impaired swallowing. Airway clearance can be compromised in dysphagic individuals because of weak cough and/or capacity to expel secretions from the upper airways. This significant functional deficit can increase the risk for infections as well as affect oxygenation and respiration. Additionally, a struggle to clear the airway and resume comfortable respiration is concerning and potentially frightening for patients and their caregivers. A reliable and readily available mechanism for physical removal of secretions can be extraordinarily helpful. (Strickland SL, Rubin BK, Drescher GS, Haas CF, O'Malley CA, Volsko TA, Branson RD, Hess DR & American Association for Respiratory Care IT, 2013)

10. Autonomic Dysfunction

10.1 Constipation

Constipation is one of the most common nonmotor problems related to autonomic dysfunction and slowed colonic transit time in PD.

Treatment of constipation in PD does not generally differ from the treatment of constipation in other patient populations. The approach includes patient education, dietary changes (e.g., increased fluid and fiber intake), and laxative therapy beginning with bulk-forming laxatives.

● Patient education — Patient education involves efforts to reduce dependency on laxatives by emphasizing that daily bowel movements are not the norm or necessary for health, and to increase fluid and fiber intake. Patients who overuse laxatives should be advised to try to taper their use, as they introduce new measures to improve bowel function. Patients should be advised to try to defecate after meals, thereby taking advantage of normal postprandial increases in colonic motility. This is particularly important in the morning when colonic motor activity is highest.

● Dietary changes — Dietary fiber are the most physiologic and effective approach to therapy. Taken together with adequate fluids, this can improve bowel habits in many patients with constipation. Prunes were also shown to be effective in one trial. Fiber supplementation can improve symptoms in patients with constipation. Fiber is available in a large variety of supplements and natural foods. Because fiber supplements are low cost, easy to use, and safe, they are frequently used first in the management of constipation. Cereal fibers generally possess cell walls that resist digestion and retain water within their cellular structures. Fiber found in citrus fruits and legumes stimulates the growth of colonic flora, thereby increasing fecal mass. (Floch MH & Wald A., 1994) There is a dose response between fiber intake, water intake, and fecal output. (Voderholzer WA, Schatke W, Muhldorfer BE, Klauser AG, Birkner B & Muller-Lissner SA., 1997; Anti M, Pignataro G, Armuzzi A, Valenti A, Iascone E, Marmo R, Lamazza A, Pretaroli AR, Pace V, Leo P, et al., 1998) Larger particle size of the fiber source, such as the large particle size of cereal products, enhances fecal bulking effects. In addition to fiber, sugar components (sorbitol and fructose) of foods such as apples, peaches, pears, cherries, raisins, grapes, and nuts are also beneficial.

Specifically in patients with PD, the following therapies have been studied and found to be more effective than placebo in small trials (Seppi K, Ray Chaudhuri K, Coelho M, Fox SH, Katzenschlager R, Perez Lloret S, Weintraub D & Sampaio C, 2019):

● Polyethylene glycol (PEG)—PEG electrolyte solutions (e.g., GoLYTELY) and powdered preparations (e.g., MiraLAX) that do not contain electrolytes are available for the treatment of chronic constipation. (Corazziari E, Badiali D, Bazzocchi G, Bassotti G, Roselli P, Mastropaolo G, Luca MG, Galeazzi R & Peruzzi E., 2000; Dipalma JA, Cleveland MV, McGowan J & Herrera JL., 2007) A systematic review found evidence that polyethylene glycol is effective in improving stool frequency and consistency. (Bharucha AE, Pemberton JH & Locke GR, 2013) A reasonable approach is to start with 17 g of powder dissolved in 8 oz of water once daily and titrate up or down (to a maximum of 34 g daily) to effect. There is no need to use PEG more than once daily. If patients do not respond, one can decrease PEG to 8.5 from 17 g daily and add a stimulant laxative every other to every third day as needed.

● Probiotics—Probiotics including fermented milk containing probiotic strains and prebiotic fiber and multistrain probiotic capsules larger studies of various probiotics for constipation in the general population support a benefit in some but not all trials.

● Lubiprostone—Lubiprostone is a locally acting chloride channel activator that enhances chloride-rich intestinal fluid secretion. Its approval was based upon two placebo-controlled trials that included a total of 479 patients with chronic idiopathic constipation who were randomly assigned to active treatment (either 24 or 48 mcg daily) or placebo for four weeks. (Lang L., 2008) Significantly more patients receiving active treatment achieved the primary endpoint (an increase in spontaneous bowel movements to at least three per week) during each week of observation. Corresponding improvement was observed for abdominal bloating, discomfort, stool frequency, and straining.

Three subsequent open-label trials involving a total of 871 patients showed persistent improvement compared with baseline in abdominal bloating, discomfort, and constipation for 6 to 12 months. (Lang L., 2008) The most common side effect was nausea, which occurred in approximately 30 percent of patients (compared with 5 percent in placebo). The incidence of nausea was dose-dependent and was lower with the 24 mcg dose (17 percent). In addition, diarrhea was reported in 13 percent of patients (compared with 1 percent for placebo). The approved dose is 24 mcg taken twice daily with food, which is believed to decrease the frequency of nausea.

10.2 Sialorrhea

Sialorrhea or drooling are common symptoms of PD related to reduced oromotor control and autonomic dysfunction. For patients with mild symptoms, the use of chewing gum or hard candy to encourage swallowing may reduce drooling in social situations. (Pfeiffer RF., 2011; Cloud LJ & Greene JG., 2011)

For patients with more severe symptoms, treatment with botulinum toxin injections into the salivary glands can be effective and is well tolerated, with dry mouth occurring in approximately five percent or less of patients. (Seppi K, Ray Chaudhuri K, Coelho M, Fox SH, Katzenschlager R, Perez Lloret S, Weintraub D & Sampaio C, 2019; Seppi K, Weintraub D, Coelho M, Perez-Lloret S, Fox SH, Katzenschlager R, Hametner EM, Poewe W, Rascol O, Goetz CG, et al., 2011; Chinnapongse R, Gullo K, Nemeth P, Zhang Y & Griggs L., 2012; Ondo WG,

Hunter C & Moore W., 2004; Lagalla G, Millevolte M, Capecci M, Provinciali L & Ceravolo MG., 2009; Jost WH, Friedman A, Michel O, Oehlwein C, Slawek J, Bogucki A, Ochudlo S, Banach M, Pagan F, Flatau-Baque B, et al., 2019; Isaacson SH, Ondo W, Jackson CE, Trosch RM, Molho E, Pagan F, Lew M, Dashtipour K, Clinch T, Espay AJ, et al., 2020) Glycopyrrolate (e.g., 1 mg three times daily) is also effective and has only a limited ability to cross the blood-brain barrier, which may reduce the risk of central anticholinergic side effects. Other anticholinergic medications (e.g., oral hyoscyamine and amitriptyline; sublingual ipratropium bromide and sublingual atropine [1 percent ophthalmic solution, one to two drops applied sublingually once or twice daily]) have also been used to control sialorrhea and drooling. (Hyson HC, Johnson AM & Jog MS., 2002; Thomsen TR, Galpern WR, Asante A, Arenovich T & Fox SH., 2007)

10.3 Rhinorrhea

Rhinorrhea is another nonmotor complication of PD that is commonly triggered by eating certain foods (gustatory rhinorrhea). Affected patients report a profuse runny nose that is unrelated to allergy, upper respiratory infection, or sinus disease. (Friedman JH & Amick MM., 2008; Sedig L, Leibner J, Ramjit AL, Wu SS, Dai Y, Okun MS, Rodriguez RL, Malaty IA & Fernandez HH., 2010; Chou KL, Koeppe RA & Bohnen NI., 2011)

There is no proven treatment for gustatory rhinorrhea in PD, but limited data and clinical experience suggest that ipratropium nasal spray, an anticholinergic agent, is effective. (Thomsen TR, Galpern WR, Asante A, Arenovich T & Fox SH., 2007) Similar to the treatment of sialorrhea with anticholinergic agents, care should be exercised to watch for peripheral and central anticholinergic side effects.

10.4 Sexual Dysfunction

Patients may not spontaneously discuss sexual dysfunction, making it important for the clinician to bring up this topic.

Sexual dysfunction can range from underactivity to hypersexuality and may affect up to 25 percent of patients with PD. Hypersexuality tends to occur more often in younger men and patients treated with dopamine agonist therapy or deep brain stimulation.

In some patients, improving motor function with dopaminergic treatment may lead to improved sexual function. Men with erectile dysfunction may benefit from treatment with sildenafil taken one hour prior to sex. (Raffaele R, Vecchio I, Giammusso B, Morgia G, Brunetto MB & Rampello L., 2002) Sildenafil should be used cautiously in patients with orthostatic hypotension. (Seppi K, Ray Chaudhuri K, Coelho M, Fox SH, Katzenschlager R, Perez Lloret S, Weintraub D & Sampaio C, 2019) Other medications such as tadalafil and vardenafil appear to be effective as well. Intrapenile injections of vasoactive drugs are effective in treatment-refractory cases. Women may benefit from vaginal lubricants and urinating prior to sexual activity.

10.5 Orthostatic Hypotension

Orthostatic hypotension is common and disabling in PD. It may occur as a feature of the disease itself or the medications used to treat PD, including levodopa, dopamine agonists, and monoamine oxidase type B (MAO B) inhibitors.

Treatment should be initiated in symptomatic cases, but no treatments are specific for PD. Nonpharmacologic should be tried first, including boluses of oral fluid intake, salt supplementation, physical counter-maneuvers, abdominal bands, stockings, and elevating the head of the bed. (Newton JL & Frith J., 2018) Conditioning with exercise, such as resistance training, holds promise as a nonpharmacologic treatment option of orthostatic hypotension in PD. (Kanegusuku H, Silva-Batista C, Pecanha T, Nieuwboer A, Silva ND, Jr., Costa LA, de Mello MT, Piemonte ME, Ugrinowitsch C & Forjaz CL., 2017)

Pharmacologic treatments are reserved for symptomatic patients who do not respond to these measures. Options include droxidopa, fludrocortisone, and midodrine, though these may lead to supine hypertension. (Seppi K, Ray Chaudhuri K, Coelho M, Fox SH, Katzenschlager R, Perez Lloret S, Weintraub D & Sampaio C, 2019) Pyridostigmine may also be useful and is less likely to cause supine hypertension.

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