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Top Ten Tips Palliative Care Clinicians Should Know About Parkinson's Disease and Related Disorders

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Abstract

Parkinson's disease (PD) affects 1%–2% of individuals older than 60 years and is the 14th leading cause of death in the United States. People with PD, across all stages of the disease, suffer from a significant symptom burden that includes many nonmotor symptoms (such as depression, fatigue, pain, and dementia), and most will ultimately die from complications of this degenerative and incurable illness. Even at diagnosis, a palliative care (PC) approach can help the patient adjust to his or her diagnosis and maintain an optimal quality of life. We brought together a team of PD and PC experts to assemble practical tips for the care of people with PD. The ''Top 10'' format emphasizes the most relevant issues to enable PC clinicians to provide optimal care for those suffering with this complex neurodegenerative disease.

Keywords: neurodegenerative disorder; neurological disease; nonmotor symptoms; palliative care; Parkinson's disease; symptom control

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting 1%–2% of individuals older than 60 years.[1] While it is primarily known for its effects on movement, PD also causes a tremendous nonmotor symptom burden (e.g., depression, fatigue, and pain), as well as social, and spiritual distress that typically impairs quality of life more than motor dysfunction does.[2,3] Ultimately, about 70% of afflicted individuals die from PD-related complications, making it the 14th leading cause of death in the United States.[4,5]

Currently, nonmotor symptoms in PD are underdiagnosed and undertreated; psychosocial, spiritual, caregiver, and practical issues are underrecognized; and high rates of hospital deaths and low rates of hospice use suggest a lack of discussion regarding prognosis and goals of care.[6,7] There is a significant need for the integration of palliative care (PC) into the treatment of people with PD to address these gaps in care. As a small but dedicated group of individuals work to improve access to PC for those with PD,[8] we hope that this article helps to inform those PC specialists who have the opportunity to care for individuals with PD. The many motor and nonmotor manifestations of PD, as well as the changing landscape of recommended pharmacological and surgical treatments in this disorder, require PC clinicians to learn about PD and collaborate closely with neurologists to provide the highest quality care to these patients and their families.

Tip 1: PD Is More Than a Movement Disorder

People with PD report an average of at least eight nonmotor symptoms, which are often more difficult to recognize and treat than motor symptoms.[9–11] As described in Table 1, nonmotor symptoms include autonomic dysfunction, gastrointestinal disorders, pain disorders, sensory deficits, cognitive dysfunction, ophthalmologic abnormalities, neuropsychiatric disorders, skin abnormalities, speech dysfunction, and sleep dysfunction. In fact, the symptom burden in PD has been shown to be similar to metastatic cancer.[12]

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Table 1. Treatment Strategies for the Nonmotor Symptoms Caused by Parkinson's Disease

Categories	*Common nonmotor symptoms in PD*	*Treatment strategies*	
		Nonpharmacological treatments	*Pharmacological/invasive treatments*
Autonomic dysfunction	Orthostatic hypotension	Encourage hydration Elevate head of bed 20–30° Exercises to activate calf muscles before standing Abdominal compression band Liberalize salt in the diet Eat smaller meals Avoid extreme heat	Reduce antihypertensive and dopaminergic medications, if possible Salt tablets Caffeine Midodrine Droxidopa Fludrocortisone Pyridostigmine (in cases of supine hypertension) NSAIDs
	Erectile dysfunction		Withdraw offending medications, if possible sildenafil, tadalafil, vardenafil
	Hyperhidrosis		Optimize dopaminergic medications to reduce off-time
	Overactive bladder	Rule out and treat UTIs Rule out and treat BPH Timed voiding Kegel exercises Elevated head of bed 20–30° Limit liquids after 6 pm Condom catheter overnight Electroacupuncture	Specific anticholinergic medications (trospium, darifenacin, solifenacin) Mirabegron Desmopressin Imipramine (caution, can worsen confusion) Intravesicular botulinum toxin injections Sacral nerve stimulation
	Rhinorrhea		Anticholinergic nasal spray
	Sialorrhea	Gum and hard candy (reminder to swallow)	Optimize dopaminergic medications Botulinum toxin injections Sublingual atropine ophthalmic solution Glycopyrrolate
Gastrointestinal disorders	Constipation	Dietary changes (e.g., prunes, limit dairy, probiotic- and fiber-rich diet) Encourage hydration Caffeine Electroacupuncture	Probiotic supplements Polyethylene glycol (1–2 times daily) Senna (up to 4 tablets twice daily) Linaclotide or lubiprostone If no BM in 3–5 days: dulcolax suppository±enema If no BM >7 days: magnesium citrate
	Gastroparesis	Small, low-fat meals Avoid carbonated liquids Drink fluids throughout meals Consume more calories as liquid Stay upright for 1 hour after meals	Erythromycin (tachyphylaxis is common) Domperidone Pyridostigmine (case reports) Ondansetron and ginger to reduce nausea Botulinum toxin to the pyloric valve
	Small intestinal bowel overgrowth	Dietary changes: limit dairy, probiotic-rich diet	Course of rifaximin with a daily probiotic supplement
Pain disorders	Central pain syndrome Peripheral neuropathy Nocturnal leg cramps Restless leg syndrome Musculoskeletal pain Dystonia-related pain Dyskinesia-related pain	Rule out and treat B12 deficiency Rule out and treat low ferritin levels (for RLS) Range of motion and stretching exercises Mindfulness-based stress reduction Acupuncture Massage	Optimize dopaminergic medication to reduce off-time and peak dose Dystonia/dyskinesias Duloxetine or venlafaxine Gabapentin or pregabalin Acetaminophen NSAIDs Baclofen or clonazepam Intra-articular steroid injections for shoulder and hip pain Epidural injection for neck pain Magnesium supplement and tonic water for nocturnal leg cramps (anecdotal reports) Botulinum toxin injections for dystonia-related pain Opiates

(*continued*)

TABLE 1. (CONTINUED)

Categories	*Common nonmotor symptoms in PD*	*Treatment strategies*	
		Nonpharmacological treatments	*Pharmacological/invasive treatments*
Sensory deficits	Hyposmia Ageusia	Eat more flavorful and spicy foods	
Cognitive dysfunction	Mild cognitive impairment dementia	Rule out and treat toxic/metabolic causes Rule out and treat severe depression, OSA, and B12 deficiency Recommend cognitive leisure activities and regular exercise	Withdraw offending medications Optimize dopaminergic medications Cholinesterase inhibitors Memantine
Ophthalmologic abnormalities	Diplopia Blurriness	Rule out and treat cataracts and glaucoma Avoid progressive lenses, bifocals, and trifocals Wear prisms for convergence insufficiency	Optimize dopaminergic medications
	Eyelid opening apraxia		Botulinum toxin injections
Neuropsychiatric symptoms	Fatigue	Rule out and treat insomnia and depression Strength training and forced exercise (e.g., Theracycle) Group exercise classes Acupuncture	Withdraw offending medications Modafinil Methylphenidate
	Depression Anxiety	Psychotherapy mindfulness-based stress reduction gratitude therapy	Optimize dopaminergic medications to reduce nonmotor off symptoms Mirtazapine Duloxetine or venlafaxine Sertraline Buspar Citalopram or escitalopram Deplin Transcranial magnetic stimulation Electroconvulsive therapy
	Pseudobulbar affect		SSRIs Dextromethorphan/quinidine
	Apathy	Rule out and treat depression and chronic insomnia schedule activities weekly	Optimize dopaminergic medications
	Psychosis	Rule out and treat toxic/metabolic causes reduce risk of delirium (e.g., optimize use of glasses and hearing aids)	Withdraw offending medications Reduce dopaminergic medications, if possible Cholinesterase inhibitors Consider stopping memantine (case reports of psychosis on this medication) Antipsychotics: quetiapine, pimavanserin, Clozaril
	Agitation	Rule out and treat toxic/metabolic causes reduce risk of delirium (e.g., optimize use of glasses and hearing aids)	Withdraw offending medications Melatonin to improve sleep quality, reduce delirium Consider standing acetaminophen for nonverbal patients Cholinesterase inhibitors Quetiapine Benzodiazepines (caution, can cause paradoxical agitation and delirium)

(*continued*)

Table 1. (Continued)

Categories	*Common nonmotor symptoms in PD*	*Treatment strategies*	
		Nonpharmacological treatments	*Pharmacological/invasive treatments*
Skin abnormalities	Seborrheic dermatitis		Ketoconazole cream Hydrocortisone cream
Speech dysfunction	Dysarthria	Speech therapy Singing therapy SpeechVive device	Optimize dopaminergic medications to reduce nonmotor off symptoms
	Dysphagia	Alert and sitting upright for all meals Stay upright 30 minutes after a meal Consider brushing teeth after meals Chin-tuck position when swallowing Reduce distractions while eating Alternate between one bite of food and one sip of liquid between meals Double swallow and clear throat every 2–3 bites Caution with dry foods and nuts Consider using Provale cup and Nosey cup Switch to carbonated liquids and nectar-thick liquids SLP evaluation	Optimize dopaminergic medications to reduce nonmotor off symptoms
Sleep dysfunction	REM behavior disorder (dream enactment)	Maintain safe sleep environment (e.g., padding on furniture corners)	Withdraw offending medications Melatonin clonazepam quetiapine
	Impaired sleep onset and maintenance	Rule out and treat OSA Review good sleep hygiene Mindfulness-based stress reduction Cognitive behavioral therapy for insomnia Exposure to bright light (natural sunlight or 10,000 Lux lamp)	Adequate carbidopa/levodopa dosing overnight Melatonin Mirtazapine Trazodone Quetiapine Doxepin
	Excessive daytime sleepiness	Rule out and treat OSA Optimize sleep onset and maintenance Bright light (natural sunlight or 10,000 Lux lamp) during the day	Withdraw offending medications Caffeine (last dose before 2 pm) Modafinil Armodafinil Methylphenidate

BM, bowel movement; BPH, benign prostatic hypertrophy; NSAIDs, nonsteroidal anti-inflammatory drugs; OSA, obstructive sleep apnea; PD, Parkinson's disease; REM, rapid eye movement; RLS, restless leg syndrome; SLP, speech language pathology; SSRIs, selective serotonin reuptake inhibitors; UTI, urinary tract infections.

Tip 2: PD Is the Most Common Cause of Parkinsonism; However, a Group of Conditions Called Atypical Parkinsonian Disorders Are More Rapidly Progressive and Have Limited Response to Therapies Compared with PD

Parkinsonism is a syndrome characterized by several motor signs and symptoms, including muscle stiffness (rigidity), slow movements (bradykinesia), imbalance (postural instability), shuffling gait, and a rest tremor. While PD is the most common cause of parkinsonism, other neurodegenerative conditions, also called atypical parkinsonian disorders or Parkinson-plus syndromes, are important to consider given therapeutic and prognostic implications. The most common atypical parkinsonian conditions and their characteristic features include the following:

(1) Dementia with Lewy Bodies: dementia and visual hallucinations early in the disease course, significant fluctuations in consciousness, and high risk of side effects from neuroleptics (worsening parkinsonism and delirium).[13]
(2) Progressive Supranuclear Palsy: early and significant dysarthria, dysphagia, and imbalance and supranuclear gaze palsy (particular difficulty with downgaze).[14]
(3) Multiple System Atrophy: formerly Shy-Drager syndrome and prominent and severe autonomic dysfunction (orthostatic hypotension, sexual dysfunction, and neurogenic bladder).[15]
(4) Corticobasal Degeneration: myoclonus (rapid jerks), dystonia (abnormal muscle contractions and posturing), apraxia (difficulty with skilled movements and use of tools), and alien limb phenomena.[16]

Compared with PD, these associated conditions have a faster progression to disability, higher rates of dementia, reduced benefit from dopaminergic therapies, and worse overall prognosis (five- to nine-year typical life expectancy from diagnosis).[17] Notably, the PC needs of this patient population and the caregivers are similar to PD, and thus, the majority of the discussion that follows is pertinent.[18]

Tip 3: Individuals with PD Derive Significant Benefit from Dopaminergic Medications Throughout the Course of Their Disease, But Motor Fluctuations and Dyskinesias May Occur at Even Moderate Stages of the Disease, and Adverse Neuropsychiatric and Autonomic Effects of These Medications at Later Stages of Disease May Limit Their Dosing

Dopaminergic medications should be continued throughout the course of PD, given the significant motoric benefit derived from these medications. Approximately five years after diagnosis of PD, most patients will begin to develop ''motor fluctuations,'' characterized by motor deterioration (also called ''off-time'') up to several hours before their next dose of medication. Initially, these motor fluctuations can be ameliorated with medication changes such as increased frequency of dosing, the initiation of long-acting formulations of levodopa, the addition of dopamine extenders, and/or adding dopamine agonists (Table 2).[19] Within a few years, however, dopaminergic therapy might unpredictably and suddenly stop working (called ''sudden off-time'') or a dose may fail to produce any benefits at all (called ''dose failures'').[20] Oral dosing of dopaminergic medications in the setting of neurodegeneration often leads to irregular swaying, rocking, and writhing movements that are called dyskinesias, which may be more debilitating than the underlying motor symptoms caused by PD.[21]

Simplifying medications in advanced PD to focus mostly on levodopa is preferable to reduce medication burden and ameliorate prominent neuropsychiatric and autonomic side effects from dopaminergic therapy.[22] Dopamine agonists, amantadine, and trihexyphenidyl typically have to be tapered off as the disease progresses, given that psychosis, inattention, and delirium can result from continued use of these medications at the advanced stages of the disease. These psychiatric symptoms can even occur at early to moderate stages of PD in those older than 70 years.[23] In addition, medication-induced sedation and orthostatic hypotension can limit the use of levodopa at all stages of PD but may be more prominent at later stages and should be carefully monitored.

Finally, abrupt cessation or withholding of dopaminergic medications is contraindicated in PD in almost all circumstances. In particular, people can experience severe disability due to motor and nonmotor symptoms in the ''off-medication'' state, and there is a very rare risk of a potentially fatal condition called parkinsonism/hyperpyrexia syndrome. In the case of dopamine agonists, there can be significant withdrawal when dopamine agonists are not tapered off slowly, called dopamine agonist withdrawal syndrome, which is associated with severe agitation, psychosis and/or depression, and worsening of motor symptoms that may persist for months to years.[24]

Tip 4: Surgical Therapies (Deep Brain Stimulation, Thalamotomy, and Levodopa Intestinal Infusion Therapy) May Be Used to Control Motor Symptoms

Deep brain stimulation (DBS) is the most commonly performed PD surgery today. A neurostimulator is surgically implanted in the patient's chest wall with electrodes implanted in specific deep brain nuclei. DBS alleviates disabling motor symptoms (tremor, rigidity, slowness, dystonia, dyskinesia, and on/off fluctuations) that persist despite optimized medical management.[25,26] It typically does *not* help axial symptoms (such as balance, speech, and swallowing impairment) or nonmotor symptoms (such as cognitive, behavioral, and autonomic impairment). Furthermore, DBS is contraindicated in patients with dementia or unstable psychiatric problems, as it can make these issues worse. Risks of DBS include intraoperative stroke, postoperative infection, battery depletion, other hardware complications, and stimulation-induced side effects (such as strained speech and behavioral complaints). It is important to note that DBS usually continues to benefit people throughout the course of PD. Therefore, to prevent severe motor worsening (return of disabling tremor, dyskinesia, and painful dystonia and stiffness), DBS therapy should be considered palliative therapy and continued (with battery replacements, if necessary) even in end-stage PD.

Two other surgical therapies are sometimes used to alleviate motor symptoms, usually when DBS is contraindicated. Ablative brain surgery is an older stereotactic technique in

Table 2. Medications Prescribed for Parkinson's Disease Motor Symptoms

Medication	*Dose range*	*Potential side effects*
Carbidopa/levodopa	150–1000+ mg/day in divided doses	Nausea, vomiting, confusion, dyskinesia, low blood pressure
Carbidopa/benserazide	150–1000+ mg/day in divided doses	Nausea, vomiting, confusion, dyskinesia, low blood pressure
Carbidopa/levodopa oral disintegrating [Parcopa]	150–10000+ mg/day in divided doses	Nausea, vomiting, confusion, dyskinesia, low blood pressure
Carbidopa levodopa extended release	150–1000+ mg/day in divided doses	Nausea, vomiting, confusion, dyskinesia, low blood pressure
Carbidopa/levodopa entacapone [Stalevo]	150–1000+ mg/day in divided doses	Nausea, vomiting, confusion, dyskinesia, low blood pressure
Carbidopa/levodopa extended release capsules [Rytary]	855–2340 mg total daily	Nausea, vomiting, confusion, dyskinesia, low blood pressure
Carbidopa/levodopa enteral solution [Duopa]	Up to 2000 mg over 16 hours	Nausea, vomiting, confusion, dyskinesia, low blood pressure
Dopamine agonists		
Ropinirole	6–24 mg/day divided in 3–4 doses	Low blood pressure, nausea, vomiting, leg swelling and discoloration, confusion, excessive daytime sleepiness, impulse control disorders
Ropinirole XL	2–24 mg once/day	Low blood pressure, nausea, vomiting, leg swelling and discoloration, confusion, excessive daytime sleepiness, impulse control disorders
Pramipexole	1.5–4.5 mg/day divided in 3–4 doses	Low blood pressure, nausea, vomiting, leg swelling and discoloration, confusion, excessive daytime sleepiness, impulse control disorders
Pramipexole ER	1.5–4.5 once daily	Low blood pressure, nausea, vomiting, leg swelling and discoloration, confusion, excessive daytime sleepiness, impulse control disorders
Rotigotine patch	2–8 mg once daily	Low blood pressure, nausea, vomiting, leg swelling and discoloration, confusion, excessive daytime sleepiness, impulse control disorders
Apomorphine	2–6 mg	Significant nausea; must take antinausea medication with dose
MAOB inhibitors		
Selegiline	5 mg/twice daily divided in 1–2 doses	Nausea, dry mouth, light-headedness, constipation, may worsen dyskinesias, serotonin syndrome (rare)
Rasagiline	1 mg once daily	Nausea, dry mouth, light-headedness, constipation, may worsen dyskinesias, serotonin syndrome (rare)
Selegiline HCl oral disintegrating (Zydis)	1.25–2.5 once daily	Nausea, dry mouth, light-headedness, constipation, may worsen dyskinesias, serotonin syndrome (rare)
COMT inhibitors		
Entacapone	200 mg up to 4 times daily	Diarrhea, discolored urine, dyskinesias, confusion
Tolcapone	100 mg 3 times daily	Liver failure (rare, must have liver function monitoring)
Other classes		
Amantadine	100 mg 2–3 times daily	Nausea, confusion, leg discoloration, dry mouth, blurred vision, constipation, urinary retention, confusion, hallucinations
Anticholinergics		
Trihexyphenidyl	1–2 mg 2–3 times daily	Blurred vision, confusion, hallucinations, dry mouth, urinary retention, constipation
Benztropine	0.5–2 mg 2–3 times daily	Blurred vision, confusion, hallucinations, dry mouth, urinary retention, constipation

COMT, catechol-O-methyltransferase inhibitor; MAOB, monoamine oxidase B inhibitor.

which a brain lesion is created to relieve disabling tremor. It still carries the risks of intracranial surgery and can only be unilateral, but has the benefits of having no implanted hardware and no need for complicated postoperative management. Duodopa (AbbVie, North Chicago, IL) is a therapy in which levodopa enteral suspension is continually infused from an external pump directly into the jejunum via a percutaneous endoscopic gastrostomy with a jejunal tube (PEG-J tube). It is most commonly used in patients who are not candidates for DBS, but carries the risk of gastrointestinal complications.

Tip 5: Isolation Due to Multiple Factors, Including Mobility and Communication Difficulties, Is a Major Cause of Suffering in PD

People with PD face many impediments that lead to a diminished number and quality of social interactions, eroding relationships, and fostering feelings of alienation and loss of identity. Motor symptoms such as rigidity, bradykinesia, and postural instability, as well as other nonmotor symptoms such as pain and autonomic dysfunction, make travel outside of the home challenging, decreasing opportunities to participate in social activities.[27–29] Neuropsychiatric changes such as dementia, psychosis, depression, anxiety, daytime somnolence, and apathy decrease the frequency of opportunities to interact with the outside world and can impair effective communication when these opportunities are present.[30] In addition, the extent of neuropsychiatric symptoms influences caregiver burden and distress.[31] Hypophonia (quiet speech) and bradyphrenia (slowness of thought) make conversations difficult. Furthermore, the reduced facial expression (hypomimia) seen in PD, often called ''masked facies,'' can render emotional connection difficult.[32] The social stigma experienced by those with Parkinson's further erodes social connections and creates a sense of outsiderness and devaluation, which can lead to feelings of shame, embarrassment, and demoralization, ultimately leading many of those affected to withdraw socially.[30,33]

Treating underlying issues whenever possible is the first step; speech therapy and the use of speech amplifying devices to improve hypophonia, antidepressants and psychotherapy to reduce depression, and melatonin to improve sleep quality and ameliorate daytime sleepiness are several examples. Educating friends and family on how to communicate with PD patients is valuable (e.g., allowing for additional time for the individual with PD to process information and respond). Also crucial are ongoing conversations between patients, their families, and their interdisciplinary medical team to discuss challenges faced, normalize experiences, and discover targeted tools for coping, adjusting, and retaining social connections.

Tip 6: Dementia and Dementia-Related Behavioral Disturbances Are Common in PD

Mild cognitive impairment (MCI) is common in PD even at the time of diagnosis and will progress to PD dementia in up to 80% of afflicted individuals.[34] Cognitive assessment is thus imperative in this population to guide goals-of-care discussions, treatment decisions, and anticipate the needs of both patients and caregivers. Cognitive screening may be reliably performed with several brief global screening instruments, including the Montreal Cognitive Assessment (MoCA).[35] The prevalence of progressive cognitive impairment makes early goals-of-care discussions and advance care planning critical in this population.[36]

Dementia in PD is commonly associated with other behavioral disturbances, including psychosis (hallucinations and delusions), agitation, sundowning, and apathy. Not surprisingly, dementia is a strong predictor and contributor to caregiver burden and distress in this population. Psychosis and apathy further increase this burden.[31]

When advanced MCI or dementia is present, it is imperative to assess safety concerns, such as driving ability and firearm possession. Verbal, physical, and/or sexual threats or abuse may be directed at either the caregiver or patient so routine screening should occur.[37] Financial risk may also be placed on families through scams targeted at older adults with impaired cognitive abilities.[38] The use of cash allowances or low-limit credit cards may minimize risks while maintaining the patient's sense of independence. Wandering behaviors may place patients at risk for adverse outcomes and necessitate full-time supervision or institutional placement.[39]

Before beginning treatment, determine whether there is a secondary cause for the behavioral disturbance, such as a medical condition (e.g., urinary tract infection or medication side effect).[40] Agitation and irritability may result from unrecognized or untreated depression, anxiety, boredom, sleep disorders, or pain.[41] Treatment of symptoms should begin with nonpharmacological approaches whenever possible, including caregiver education, environmental modifications (e.g., bright lights during the day and removal of unsafe stimuli), daytime activities, and exercise.[42,43] Pain may be difficult to assess in patients with severe cognitive or language disturbances; screening tools such as the PAINAD exist to evaluate pain based on other behaviors (e.g., moaning, grimacing).[44] Data further suggest that an empiric trial of acetaminophen may improve not only untreated pain but also resulting behavioral disturbances.[45] Melatonin at bedtime may reduce nighttime delirium and improve sleep quality without the increased risk of falls or morning sedation seen with benzodiazepines.[46] Pharmacological agents to treat dementia-related behavioral disturbances may also include antidepressants, cholinesterase inhibitors, and specific antipsychotics (quetiapine, pimavanserin, and clozapine).[41] Valproic acid and benzodiazepines can be cautiously considered, but carry a risk of a paradoxical worsening of parkinsonism, dementia, and agitation.[41,47]

Tips 7: Some Commonly Used Medications in the PC Setting Should NOT be Used in People with PD

Several classes of drugs frequently used in PC settings (including hospice comfort kits) are relatively or absolutely contraindicated in the PD population. Antiemetic and antipsychotic dopamine receptor blocking agents (DRBAs) are of chief concern because they block the D2 dopamine receptor with high affinity. Antiemetic DRBAs (e.g., metoclopramide, promethazine, and prochlorperazine) are contraindicated. Ondansetron (Zofran) is the antiemetic of choice in PD patients.

Regarding neuroleptics, all typical (e.g., haloperidol) and most atypical (e.g., olanzapine, ziprasidone, risperidone, and

aripiprazole) antipsychotics are similarly contraindicated.[48,49] It is important to highlight that, contrary to common medical practice, even the newer atypical antipsychotics present a serious risk for Parkinson's patients. In fact, risperidone has an affinity for the D2-receptor equal to that of haloperidol. Unfortunately, because of high rates of sleep dysfunction, delirium, anxiety, agitation, and psychosis in those with PD, medical management of these issues is frequently required. In general, the *only* relatively safe antipsychotics in PD are low-dose quetiapine, Clozaril, and pimavanserin. Given this information, we recommend that hospice programs develop a separate PD comfort kit that uses quetiapine as the neuroleptic agent and ondansetron as the antiemetic agent.

Tip 8: People with PD Can Often Benefit from Physical Therapy and Dopaminergic Therapy Even at the Latest Stages of Their Disease to Reduce Pain and Improve Range of Motion

Physical activity is important to continue as a part of PD care in the last few years of life. Even when a person with PD is wheelchair bound or bedbound, active and passive movement and breathing exercises have been shown to maintain residual mobility and prevent complications such as contractures, decubiti, and pneumonia.[19] As hospice services do not routinely offer these therapies, the benefits of these interventions should be carefully considered when planning for end-of-life care.

Furthermore, people with late-stage PD continue to obtain significant motor benefit from levodopa, and there are often improvements in nonmotor symptoms as well (e.g., insomnia and depression) with this medication. In later stages of the disease, patients often need to reduce dopaminergic therapy due to levodopa-induced dyskinesias, psychosis, and delirium.[50] Thus, weaning of dopaminergic medications, if considered, should seek to find a balance between benefits and side effects.[19] Consulting with a movement disorder specialist to help guide dosing of levodopa in this setting is preferred.

Oral dissolving carbidopa/levodopa or rectally delivered carbidopa/levodopa can be administered for PD patients with pill dysphagia.[51,52] While continuous infusions of levodopa gel through a PEG-J tube (called Duodopa) can be considered for people with PD who have motor fluctuations, it is the opinion of the authors that the high risk of the PEG-J device insertion (e.g., aspiration, intraperitoneal infection, wound infection, abdominal pain, abdominal distention, intestinal hemorrhage, pneumoperitoneum, ileus, delirium, agitation, and nausea)[53] outweighs the likely minimal benefit an individual with end-stage PD would have with this medication, given that most of those afflicted in the end-stage of the disease are bedbound, demented, and psychotic from the disease itself. Of note, a PEG tube used for nutrition will require placement of an FDA-approved jejunal extension for concurrent Duodopa delivery.

Tip 9: PD Contributes to Mortality, and There Are Certain Signs and Symptoms That Predict the Terminal Phase of This Disease

When individuals with PD ask about their prognosis, a common response from neurologists can offer false hope: ''Don't worry, you'll die with Parkinson's and not from it.'' Unfortunately, the majority of those with PD (71%) will actually die from complications of their neurodegenerative disease.[54,55] Challenges with prognostication in PD include limited existing research on this topic and the variability of the duration and progression of disease. While there is limited information on predicting the terminal stages of PD, some data can guide information we share with patients and families.

The Hoehn and Yahr (H&Y) scale is the only disease severity staging system for PD; it includes stages 1 through 5 (Table 3). The chances of dying from a PD-related cause is 78% for those who survive long enough (8–12 years on average) to reach H&Y stage 3 (characterized by significant imbalance with falls, but ambulating without an assistive device). Common underlying causes of death in these cases include sepsis, respiratory failure, wasting syndrome, and choking.[5,54,56,57] There has been only one study that evaluated predictors of mortality in PD within 6–12 months.[56] This study indicated that a body mass index <18.5, accelerated weight loss, and a significant reduction in dopaminergic medications due to neuropsychiatric side effects, all predicted a 6- to 12-month life expectancy. In the authors' clinical experience, weight loss (with or without loss of appetite), dysphagia for liquids and aspiration, recurrent infections, and accelerating loss of function and mobility should encourage consideration of hospice. The most common causes of terminal hospital admissions include aspiration pneumonia, sepsis, failure to thrive, and falls.[5,54,56,57]

Tip 10: End-Stage PD Is Characterized by Psychosis, Dementia, and an Inability to Ambulate Independently

H&Y stage 5 is considered end-stage PD and is characterized by dementia, psychosis, and wheelchair-bound/bedbound status (unless aided). The typical life expectancy for a person with PD ranges from 12 to 20 years,[58] and this final stage of PD (H&Y stage 5) typically lasts about 2 years.[59] Severe dysphagia and bedridden status are the final common pathways for many neurodegenerative

Table 3. Hoehn and Yahr Staging System of Parkinson's Disease Severity

H&Y stage	*Clinical description*
Stage 1	Unilateral mild motor symptoms (tremor, rigidity, bradykinesia). Independent ambulation.
Stage 2	Bilateral mild motor symptoms. Independent ambulation.
Stage 3	Bilateral mild to moderate motor symptoms. Postural instability present. Independent ambulation.
Stage 4	Severe bilateral motor symptoms. Severe disability. Needs an assistive device to walk and stand.
Stage 5	Severe bilateral motor symptoms. Severe disability. Wheelchair bound or bedridden. Can only ambulate with another person assisting.

H&Y, Hoehn and Yahr.

diseases, including PD. Artificial hydration/nutrition is not recommended for these individuals since it has not been shown to prolong life or improve/maintain quality of life for those with end-stage neurodegenerative disease.[60] Notably, as with other aspects of PD, there is significant variability in end-stage disease ranging from ambulatory persons dying of complications of dementia to others with a sound mind dying of complications of physical debility and dysphagia.

In addition to management of motor symptoms, it is important to continue to monitor and treat nonmotor symptoms that can arise in the last few years of life for someone with PD,[61] such as eyelid opening apraxia (difficulty raising the eyelids, which can contribute to social isolation). Should a person with end-stage PD enroll in hospice services, carbidopa/levodopa and other symptom-targeted medications (e.g., cholinesterase inhibitors) should be continued for as long as tolerated. Another consideration is that psychological burden and depression among caregivers become more prominent with late-stage PD as well; providers should check on caregivers' well-being routinely and discuss supportive services such as social work, spiritual care, and respite as indicated.[62]

Currently, there is a significant underuse of PC and hospice in the terminal stage of PD. Less than 5% of those with PD receive hospice at the end of life (although use may be higher in nursing home residents),[63] and the majority die in the acute inpatient hospital setting.[55,64] A part of this may be due to a lack of training in serious illness communication among neurologists. One study that examined patients with Parkinson's who died in the inpatient hospital setting showed that 97% lacked a documented goals-of-care discussion or advance directive.[64] Patients who do complete an advance directive are much more likely to die at home.[65] Another reason for the low rate of hospice use at the end of life for those with PD could be the lack of clear hospice eligibility guidelines for PD. Additional research on predictors of a six-month life expectancy in PD is needed to optimize timing of hospice referrals.

Conclusion

The introduction of PC to the treatment of those with PD represents a paradigm shift in the care of patients with neurodegenerative diseases.[66] The top 10 tips in this article summarize core information and pearls from a group of movement disorder neurologists and PC clinicians who are engaged in research and clinical work at the intersection of neurology and PC. Lack of training and exposure to PC in neurology training can lead to misunderstandings about PC in the neurology community and mean that PC clinicians should actively engage their neurology colleagues to foster collaboration.

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References

1. Walker RW, Hand A, Jones C, et al.: The prevalence of Parkinson's disease in a rural area of North-East England. Parkinsonism Relat Disord 2010;16:572–575.
2. Bostantjopoulou S, Katsarou Z, Karakasis C, et al.: Evaluation of non-motor symptoms in Parkinson's disease: An underestimated necessity. Hippokratia 2013;17:214–219.
3. Shulman LM, Taback RL, Rabinstein AA, Weiner WJ: Non-recognition of depression and other non-motor symptoms in Parkinson's disease. Parkinsonism Relat Disord 2002;8:193–197.
4. Murphy SL, Xu J, Kochanek KD, et al.: Deaths: Final data for 2015. In: *National Vital Statistics Reports, Vol. 66 No. 6.* Hyattsville, MD: National Center for Health Statistics, 2018.
5. Pennington S, Snell K, Lee M, Walker R: The cause of death in idiopathic Parkinson's disease. Parkinsonism Relat Disord 2010;16:434–437.
6. Lyons KE, Pahwa R: The impact and management of nonmotor symptoms of Parkinson's disease. Am J Manag Care 2011;17 Suppl 12:S308–S314.
7. Miyasaki JM: Palliative care in Parkinson's disease. Curr Neurol Neurosci Rep 2013;13:367.
8. Kluger BM, Fox S, Timmons S, et al.: Palliative care and Parkinson's disease: Meeting summary and recommendations for clinical research. Parkinsonism Relat Disord 2017; 37:19–26.
9. Barone P, Antonini A, Colosimo C, et al.: The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov Disord 2009;24:1641–1649.
10. Chaudhuri KR, Healy DG, Schapira AH: Non-motor symptoms of Parkinson's disease: Diagnosis and management. Lancet Neurol 2006;5:235–245.
11. Schapira AH, Chaudhuri KR, Jenner P: Non-motor features of Parkinson disease. Nat Rev Neurosci 2017;18:435.
12. Miyasaki JM, Long J, Mancini D, et al.: Palliative care for advanced Parkinson disease: An interdisciplinary clinic and new scale, the ESAS-PD. Parkinsonism Relat Disord 2012; 18 Suppl 3:S6–S9.
13. McKeith IG, Dickson DW, Lowe J, et al.: Diagnosis and management of dementia with Lewy bodies: Third report of the DLB consortium. Neurology 2005;65:1863–1872.
14. Litvan I, Agid Y, Calne D, et al.: Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): Report of the NINDS-SPSP international workshop. Neurology 1996; 47:1–9.
15. Gilman S, Wenning GK, Low PA, et al.: Second consensus statement on the diagnosis of multiple system atrophy. Neurology 2008;71:670–676.
16. Armstrong MJ, Litvan I, Lang AE, et al.: Criteria for the diagnosis of corticobasal degeneration. Neurology 2013;80: 496–503.
17. Levin J, Kurz A, Arzberger T, et al.: The differential diagnosis and treatment of atypical parkinsonism. Dtsch Arztebl Int 2016;113:61–69.
18. Wiblin L, Lee M, Burn D: Palliative care and its emerging role in multiple system atrophy and progressive supranuclear palsy. Parkinsonism Relat Disord 2017;34:7–14.
19. Varanese S, Birnbaum Z, Rossi R, Di Rocco A: Treatment of advanced Parkinson's disease. Parkinsons Dis 2011; 2010:480260.
20. Cenci MA: Presynaptic mechanisms of l-DOPA-induced dyskinesia: The findings, the debate, and the therapeutic implications. Front Neurol 2014;5:242.
21. Bastide MF, Meissner WG, Picconi B, et al.: Pathophysiology of L-dopa-induced motor and non-motor complications in Parkinson's disease. Prog Neurobiol 2015;132:96–168.
22. Chang A, Fox SH: Psychosis in Parkinson's disease: Epidemiology, pathophysiology, and management. Drugs 2016; 76:1093–1118.

23. Lewis SJ, Gangadharan S, Padmakumar CP: Parkinson's disease in the older patient. Clin Medicine 2016;16:376–378.
24. Pondal M, Marras C, Miyasaki J, et al.: Clinical features of dopamine agonist withdrawal syndrome in a movement disorders clinic. J Neurol Neurosurg Psychiatry 2013;84: 130–135.
25. Okun MS: Deep-brain stimulation for Parkinson's disease. N Engl J Med 2012;367:1529–1538.
26. Sillay KA, Larson PS, Starr PA: Deep brain stimulator hardware-related infections: Incidence and management in a large series. Neurosurgery 2008;62:360–367.
27. Jankovic J: Parkinson's disease: Clinical features and diagnosis. J Neurol Neurosurg Psychiatry 2008;79:368–376.
28. Kadastik-Eerme L, Muldmaa M, Lilles S, et al.: Nonmotor features in Parkinson's disease: What are the most important associated factors? Parkinsons Dis 2016;2016: 4370674.
29. Boersma I, Jones J, Carter J, et al.: Parkinson disease patients' perspectives on palliative care needs: What are they telling us? Neurol Clin Pract 2016;6:209–219.
30. Balestrino R, Martinez-Martin P: Neuropsychiatric symptoms, behavioural disorders, and quality of life in Parkinson's disease. J Neurol Sci 2017;373:173–178.
31. Martinez-Martin P, Rodriguez-Blazquez C, Forjaz MJ, et al.: Neuropsychiatric symptoms and caregiver's burden in Parkinson's disease. Parkinsonism Relat Disord 2015;21: 629–634.
32. Chiong-Rivero H, Ryan GW, Flippen C, et al.: Patients' and caregivers' experiences of the impact of Parkinson's disease on health status. Patient Relat Outcome Meas 2011; 2011:57–70.
33. Koo BB, Chow CA, Shah DR, et al.: Demoralization in Parkinson disease. Neurology 2018;90:e1613–e1617.
34. Hely MA, Reid WG, Adena MA, et al.: The Sydney multicenter study of Parkinson's disease: The inevitability of dementia at 20 years. Mov Disord 2008;23:837–844.
35. Skorvanek M, Goldman JG, Jahanshahi M, et al.: Global scales for cognitive screening in Parkinson's disease: Critique and recommendations. Mov Disord 2018;33:208–218.
36. Snineh MA, Camicioli R, Miyasaki JM: Decisional capacity for advanced care directives in Parkinson's disease with cognitive concerns. Parkinsonism Relat Disord 2017; 39:77–79.
37. Bruno V, Mancini D, Ghoche R, et al.: High prevalence of physical and sexual aggression to caregivers in advanced Parkinson's disease. Experience in the Palliative Care Program. Parkinsonism Relat Disord 2016;24:141–142.
38. Han SD, Boyle PA, James BD, et al.: Mild cognitive impairment and susceptibility to scams in old age. J Alzheimers Dis 2016;49:845–851.
39. Futrell M, Melillo KD, Remington R, Butcher HK: Evidence-based practice guideline: Wandering. J Gerontol Nurs 2014;40:16–23.
40. Lau T, Russell S: A complex case of delirium: From theory to clinical management. In: *Complex Clinical Conundrums in Psychiatry.* Springer, 2018, pp. 15–22.
41. Kales HC, Gitlin LN, Lyketsos CG: Assessment and management of behavioral and psychological symptoms of dementia. BMJ 2015;350:h369.
42. Gitlin LN, Kales HC, Lyketsos CG: Nonpharmacologic management of behavioral symptoms in dementia. JAMA 2012;308:2020–2029.
43. Seitz DP, Brisbin S, Herrmann N, et al.: Efficacy and feasibility of nonpharmacological interventions for neuropsychiatric symptoms of dementia in long term care: A systematic review. J Am Med Dir Assoc 2012;13:503–506 e502.
44. Warden V, Hurley AC, Volicer L: Development and psychometric evaluation of the Pain Assessment in Advanced Dementia (PAINAD) scale. J Am Med Dir Assoc 2003;4: 9–15.
45. Chibnall JT, Tait RC, Harman B, Luebbert RA: Effect of acetaminophen on behavior, well-being, and psychotropic medication use in nursing home residents with moderate-to-severe dementia. J Am Geriatr Soc 2005;53:1921–1929.
46. Choy SW, Yeoh AC, Lee ZZ, et al.: Melatonin and the prevention and management of delirium: A scoping study. Front Med 2017;4:242.
47. Mahmoud F, Tampi RR: Valproic acid-induced parkinsonism in the elderly: A comprehensive review of the literature. Am J Geriatr Pharmacother 2011;9:405–412.
48. Goldman JG, Holden S: Treatment of psychosis and dementia in Parkinson's disease. Curr Treat Options Neurol 2014;16:281.
49. Weintraub D, Chiang C, Kim HM, et al.: Antipsychotic use and physical morbidity in Parkinson disease. Am J Geriatr Psychiatry 2017;25:697–705.
50. Coelho M, Ferreira JJ: Late-stage Parkinson disease. Nat Rev Neurol 2012;8:435–442.
51. Donnelly RF: Stability of levodopa/carbidopa rectal suspensions. Hosp Pharm 2016;51:915–921.
52. Jimenez-Shahed J: A review of current and novel levodopa formulations for the treatment of Parkinson's disease. Ther Deliv 2016;7:179–191.
53. Olanow CW, Kieburtz K, Odin P, et al.: Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: A randomised, controlled, double-blind, double-dummy study. Lancet Neurol 2014;13:141–149.
54. Fall PA, Saleh A, Fredrickson M, et al.: Survival time, mortality, and cause of death in elderly patients with Parkinson's disease. A 9-year follow-up. Mov Disord 2003;18: 1312–1316.
55. Snell K, Pennington S, Lee M, Walker R: The place of death in Parkinson's disease. Age Ageing 2009;38:617–619.
56. Goy ER, Bohlig A, Carter J, Ganzini L: Identifying predictors of hospice eligibility in patients with Parkinson disease. Am J Hosp Palliat Care 2015;32:29–33.
57. Moscovich M, Boschetti G, Moro A, et al.: Death certificate data and causes of death in patients with parkinsonism. Parkinsonism Relat Disord 2017;41:99–103.
58. Morgan JC, Currie LJ, Harrison MB, et al.: Mortality in levodopa-treated Parkinson's disease. Parkinsons Dis 2014; 2014:426976.
59. Zhao YJ, Wee HL, Chan YH, et al.: Progression of Parkinson's disease as evaluated by Hoehn and Yahr stage transition times. Mov Disord 2010;25:710–716.
60. Ayman AR, Khoury T, Cohen J, et al.: PEG insertion in patients with dementia does not improve nutritional status and has worse outcomes as compared with PEG insertion for other indications. J Clin Gastroenterol 2017;51:417–420.
61. Miyasaki JM, Kluger B: Palliative care for Parkinson's disease: Has the time come? Curr Neurol Neurosci Rep 2015;15:26.
62. Schmotz C, Richinger C, Lorenzl S: High burden and depression among late-stage idiopathic Parkinson disease and

progressive supranuclear palsy caregivers. J Geriatr Psychiatry Neurol 2017;30:267–272.
63. Safarpour D, Thibault DP, DeSanto CL, et al.: Nursing home and end-of-life care in Parkinson disease. Neurology 2015;85:413–419.
64. Moens K, Houttekier D, Van den Block L, et al.: Place of death of people living with Parkinson's disease: A population-level study in 11 countries. BMC Palliat Care 2015;14:28.
65. Tuck KK, Zive DM, Schmidt TA, et al.: Life-sustaining treatment orders, location of death and co-morbid conditions in decedents with Parkinson's disease. Parkinsonism Relat Disord 2015;21:1205–1209.
66. Boersma I, Miyasaki J, Kutner J, Kluger B: Palliative care and neurology: Time for a paradigm shift. Neurology 2014; 83:561–567.

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