

Parkinson's Disease Psychosis: Symptoms, Management, and Economic Burden

Neal Hermanowicz, MD, and Kari Edwards, PhD

Parkinson's disease psychosis (PDP) is a devastating neuropsychiatric condition that afflicts many patients with Parkinson's disease (PD) over the course of their lives. Although the spotlight traditionally has been on the motor symptoms associated with PD, in the last decade there has been increasing recognition that this focus is overly narrow. Non-motor symptoms, such as psychosis, can be just as debilitating to patients and distressing to caregivers as the motor symptoms, and sometimes more so. Notably, because of the dearth of effective and safe treatment options, patients with PDP are subject to considerable emotional distress and increased risk for admission to nursing homes. With the changing demographics in the United States anticipated over the next few decades, direct and indirect costs associated with PDP will escalate. This paper seeks to highlight the need for increased awareness of PDP; its relationship to health outcomes, disability, and healthcare expenditures; and the need for new treatments in this underserved population. The larger context in which these issues are discussed has bearing on efforts to improve the care of patients with PD and manage associated healthcare resources prudently.

PD Imposes a Significant Burden on the Healthcare System

PD is the second-most common neurodegenerative disease; the first is Alzheimer's disease.¹ Although PD is often regarded as a disease of the elderly, the mean age of diagnosis of PD is 60 years, with approximately 5% to 10% of cases identified in patients aged 20 to 50 years.^{1,2} The risk for being diagnosed with PD increases with advancing age.¹ In the United States alone, PD affects 1 million patients who, by virtue of their diagnosis, are at an almost 4 times greater 6-year risk of death than counterparts matched by age, sex, and race.^{1,3} As the mature population in the United States continues to increase, it

Abstract

Parkinson's disease psychosis (PDP) is a costly, debilitating condition that generally develops several years after diagnosis of Parkinson's disease (PD). PD is the second-most common neurodegenerative disease, and it imposes a significant burden on the healthcare system. Non-motor symptoms commonly manifest in PD, contributing to the severity of a patient's disability. The neuropsychiatric symptoms that are common in PD can be a significant source of distress to patients and caregivers. Recent studies have shown that more than 50% of patients with PD will develop psychosis at some time over the course of the disease. The responsibility for caring for a person with PDP frequently falls on family members. Caregiver distress is frequently predicted when patients with PD have symptoms of psychosis. Hallucinations and delusions are independent predictors of nursing home placement for patients with PDP. The authors sought to examine total healthcare expenditures among patients with PDP compared with patients with PD without psychosis. All costs were higher for patients with PDP than for those with PD without psychosis and all-Medicare cohorts, with the highest cost differentials found in long-term care costs (\$31,178 for PDP vs \$14,461 for PD without psychosis), skilled nursing facility costs (\$6601 for PDP vs \$2067 for PD without psychosis), and inpatient costs (\$10,125 for PDP vs \$6024 for PD without psychosis). Patients with PDP spent an average of 179 days in long-term care, compared with 83 days for patients with PD without psychosis. As expected, long-term care utilization and expenditures were significantly higher for patients with PDP than for patients with PD without psychosis. Reducing long-term care utilization by patients with PDP may significantly lower the overall economic burden associated with PDP.

Am J Manag Care. 2015;21:S199-S206
For author information and disclosures, see end of text.

is anticipated that the number of individuals with PD will almost double by 2030.⁴

The economic burden associated with PD was estimated at \$14.4 billion in 2010—\$8 billion higher than would be expected for a similar patient population without PD.⁴ Patients with PD experience increasing symptom severity as their disease progresses, which leads to an escalation in direct costs for pharmaceuticals, hospitalizations, and nursing home care over the life of a patient.^{4,5} Approximately 15% of patients with PD are in nursing homes, amounting to almost 60% of the direct costs associated with the management of PD (Figure 1).⁴ Indirect costs, with lost productivity as a major contributor, are also extremely high, at \$6.3 billion.⁴

The economic burden associated with PD is expected to increase markedly over the next several decades as baby boomers age.⁴ Forecasts of increasing numbers of patients and the associated economic impact underscore the need for medical innovations that will help prevent, delay, or alleviate the symptoms associated with PD.

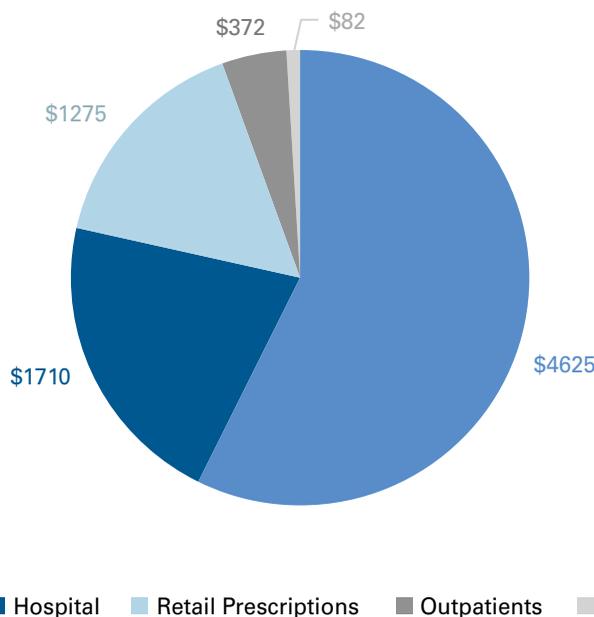
PD Is More Than a Movement Disorder

Motor symptoms—namely tremor, rigidity, bradykinesia, postural instability, and gait impairment—are the cardinal features of PD and historically have been the primary focus of pharmacologic interventions.¹ Non-motor symptoms, while long recognized as prominent in PD, have received increased attention in recent years.⁶

Non-motor symptoms commonly manifest in PD and contribute to the severity of a patient’s disability.⁷ A survey of 99 patients with PD, using validated questionnaires to assess the presence of non-motor symptoms such as anxiety, depression, sensory disturbance, fatigue, and sleep problems, revealed that 88% of patients had at least 1 such symptom.⁸ In a study of patients with PD in neurology clinics that utilized a range of validated clinometric scales to assess both motor and non-motor symptoms, a mean of 11 of 30 non-motor symptoms were reported per patient with PD. In this study, psychosis was one of the non-motor symptoms that correlated with health-related quality-of-life worsening ($r = 0.55, P < .0001$).⁹ The prevalence of non-motor

The financial burden of Parkinson’s disease, along with several other chronic conditions, is projected to increase dramatically over the next several decades as the size of the elderly population grows. Such forecasts underscore the need for medical innovations that will help prevent, delay onset of, or alleviate symptoms of this devastating disease.

■ **Figure 1.** Direct Costs Attributed to Parkinson’s Disease, 2010 (millions)⁴



symptoms in this study was similar to that reported in other studies with heterogeneous patient samples.^{10,11}

Neuropsychiatric Symptoms in PD

In his original characterization of the disease, James Parkinson noted that the senses and intellect were undamaged in patients with what we now refer to as the disease that bears his name.¹² However, it has become increasingly clear that this observation was incorrect. Neuropsychiatric symptoms are common in Parkinson's disease and can be a significant source of distress to patients and caregivers. In fact, several reports indicate that neuropsychiatric symptoms can often be even more distressing and disruptive than the primary motor symptoms.¹³⁻¹⁵ Dementia, depression, and psychosis, in particular, impact the quality of life of patients and caregivers, and substantially add to the risk of needing long-term care.^{9,15}

PDP

Characterization and Clinical Features of PDP

PDP involves an array of neuropsychiatric symptoms that are well characterized clinically and temporally, particularly with respect to hallucinations and delusions.^{16,17} The clinical profile of PDP is distinct from that associated with substance-induced psychosis and other psychotic disorders.^{16,18} Current literature suggests that symptoms of psychosis generally arise later in the course of disease, about 10 years or more after initial diagnosis of PD¹⁷; however, a recent survey of physicians found that the length of time between PD diagnosis and PDP presentation was less than 4 years in almost 60% of patients.¹⁹ Typically, as symptoms of psychosis begin to emerge, a patient main-

tains clear sensorium and retained insight.¹⁷ Over time, symptoms become more severe and insight may become degraded or lost altogether.²⁰

Visual hallucinations and false, idiosyncratic beliefs maintained despite evidence to the contrary occur with variable frequency and duration from one patient to another, as well as within a particular patient. Although these symptoms may occur at any time of day, they are more likely to occur in the evening and under conditions of dim lighting.²¹ Auditory, olfactory, gustatory, and tactile hallucinations also may occur in patients, although they are less common than visual hallucinations.^{17,22}

Visual hallucinations may be simple and involve a mundane experience such as seeing ants on the floor. More common early in the disease, such simple hallucinations may not be especially disturbing and may, in some instances, be reported as interesting or even entertaining by patients. Because these types of hallucinations are not disruptive, patients may not be as likely to spontaneously report their occurrence to caregivers or physicians. Over time, and with the progression of disease, the benign quality tends to diminish and the hallucinations can become alarming and disruptive. Patients may call 911 to report intruders in their

home, or even flee their home to escape perceived danger. Although delusions are less common than hallucinations in PDP, delusions often signify more advanced disease and can contribute to a highly complex and challenging care situation. Delusions often are characterized by paranoid thoughts, with common recurring themes of spousal infidelity or intent of harm by unidentified people or even those providing care to the

ACTUAL PATIENT CASE

At the age of 78 years, Mrs D had been living with Parkinson's disease for more than 15 years. Although she required assistance for all basic daily activities—dressing, cutting her food, bathing, and using the toilet—she remained at home, with her husband of 56 years as her sole caregiver.

Mrs D had long experienced hallucinations, both visual and auditory, with the latter initially consisting of hearing music from a radio. The music was distracting but not upsetting; however, more recently, her auditory hallucinations had changed. Instead of hearing music, she now heard the voice of their son calling for her, asking for her help. Her son had died from cancer 2 years earlier, and hearing his voice and his call for help reignited her grief over his loss.

Mrs D now also had the delusional idea that her husband had a girlfriend who was living hidden in their home. She had never seen the girlfriend but nonetheless believed she was present, and thought she heard the girlfriend complaining to Mr D that he spent too much time caring for his wife and not enough time with her—a belief Mrs D communicated to her husband.

Mr D, a man dedicated for years to the care and comfort of his wife, was understandably devastated by the accusation. "All I do all day and every day is care for my wife," he said with sad exasperation. "When would I even have time for a girlfriend?"

—Neal Hermanowicz, MD, UC Irvine Medical Center

patient. The resulting distrust and groundless accusations by the patient can rapidly transform a difficult care situation into one that is intolerable to the patient and caregiver alike.^{17,22}

The urgency of treatment will depend on a number of factors, including the type and characteristic of the psychosis as well as patient tolerance—even benign symptoms can be disturbing for both patients and caregivers. Some clinicians will choose to postpone treatment if the symptoms are infrequent and non-threatening, and if the patient retains insight. Other clinicians will start treatment based on the understanding that psychosis will continue to get worse over time; thus, early intervention is warranted.

Prevalence of PDP

More than 50% of patients with PD will develop psychosis at some point over the course of their disease.²³ Visual hallucinations are common, occurring in up to one-third of patients with PD on chronic dopaminergic therapy; delusions are less common, occurring in 5% to 10% of patients.²⁴

Underdiagnosis of PDP

In the United States, 50,000 to 60,000 new cases of PD are diagnosed each year, adding to the 1 million already diagnosed.²⁵ Despite the high prevalence of symptoms of psychosis among patients with PD, there is an increasing concern that many patients with PDP may not be receiving a proper diagnosis or treatment for their symptoms.²⁶

In a survey by Fernandez and colleagues, 1 in 5 patients with PD were diagnosed as exhibiting symptoms of psychosis. Of those designated as undiagnosed, 14% were later identified through chart review as experiencing moderate or severe psychotic symptoms.²⁷ Such findings may be a reflection of either a comparatively greater emphasis in clinical practice on treating motor symptoms associated with PD or a low awareness among some physicians of the features of PDP.^{8,27} It is also possible that the lack of appealing treatment options for PDP symptoms diminishes the value of formal diagnosis. Additionally, patients, family members, and caregivers may not always report PDP symptoms, either because they do not associate symptoms of psychosis with PD or because they are reluctant to discuss such symptoms due to their associated stigma.^{9,21}

Pathophysiology of PDP

In the past, dopaminergic medications were considered the primary cause of PDP.^{17,27} Today, however, there is more widespread acceptance that the symptoms of PDP are not necessarily attributable to dopaminergic drugs and that the medications singularly are not sufficient to account for the psychotic symptomatology. Evidence supports the involvement of factors both intrinsic to the disease (duration and severity of PD) and extrinsic to the disease in the emergence of the symptoms of PDP.¹⁷ Hallucinations and delusions in patients with PD have been associated intrinsically with sleep disturbances (eg, rapid eye movement behavior disorder, nocturnal hallucinations, vivid dreams, nightmares),^{28,29} and also with deficits in visual processing attributable to dopamine deficiency.³⁰ Family history of dementia has also been shown to be a significant risk factor for hallucinations in PD.³¹ Extrinsic factors associated with the emergence of

psychosis include the effects of medications, including those used to treat PD.

Impact of PDP on Caregiver Burden and Risk of Nursing Home Admission

The responsibility of caring for a person with PDP frequently falls with spouses and

other family members and, in some cases, hired caregivers. These individuals play a vital role in assuring the well-being of the patient, providing physical, emotional, and financial support; in so doing, they help prevent or delay placement into nursing homes. It is well documented that the care of patients with PD, as with other chronically ill patients, can be a source of persistent social and emotional stress for caregivers, especially as the disease advances and patient disability increases.^{22,32}

In a number of studies looking at predictors of caregiver distress, symptoms of psychosis, including delusions and hallucinations, arise as among the most impactful.^{14,15} Psychosis accompanying PD is associated with greater caregiver distress than the effect of other neuropsychiatric symptoms or the motor symptoms of PD.^{12,33}

The presence of these symptoms affects caregivers initially by restricting their ability to pursue activities of daily life as before.³⁴ As symptoms worsen for the patient with PDP, caregivers may experience considerable stress and a decline in emotional and physical health.¹⁴ At some point, the psychosis may become so serious and disrupt-

Although it was once thought that the symptoms of Parkinson's disease psychosis were attributable to side effects from dopaminergic drugs, in recent years the understanding of the pathophysiology has changed to involve an array of more complex factors that are intrinsic and extrinsic to the disease.¹⁷

tive that caregivers are no longer able to manage a patient at home.¹³ In fact, psychosis is one of the major reasons for admitting patients with PD into nursing homes and long-term care facilities.^{22,35} A 4-year prospective study of 178 community-dwelling patients with PD in Norway revealed that hallucinations, dementia, and Hoehn and Yahr score were some of the main independent predictors of nursing home admission (Table 1).³⁵

Economic Burden of PDP

A recent analysis of a Medicare survey of claims data from 2000 to 2010 and a claims-based definition of PDP provide compelling evidence of the burden associated with PDP in terms of disability, long-term care utilization, and cost to the healthcare system.³⁶

The following trends emerged from this analysis:

- 74.6% of patients with PDP spent time in a long-term care facility—an average of 179 days—compared with 55.8% of patients with PD without psychosis (average, 83 days). Among those in the non-PD Medicare cohort, 36.1% spent time in long-term care (average, 22 days).
- Across all components of care, annual all-cause reimbursement for patients with PDP averaged \$67,251, of which \$27,428 was borne by Medicare. Patients with PDP averaged higher total reimbursement relative both to patients with PD (\$38,742) and the non-PD Medicare cohort (\$18,757) (Figure 2, page S204).³⁶

Effective treatment of psychotic symptoms may improve the quality of life of patients and their caregivers, and may enable caregivers to maintain patients with Parkinson's disease at home longer or indefinitely.

In an evaluation of each of the major components of care, all-cause costs and resource utilization were higher for patients with PDP than for patients with PD without psychosis or the non-PD Medicare cohort. The highest annual cost differentials were found in long-term care (\$31,178 for patients with PDP vs \$14,461 for patients with PD without psychosis) and skilled nursing facilities (\$6601 for patients with PDP vs \$2067 for patients with PD without psychosis) (Figure 3, page S205).³⁶ Results confirm other published reports that have suggested that symptoms of psychosis are a predictor of long-term care placement of patients with PD.^{7,12}

Current Management of PDP and Limitations

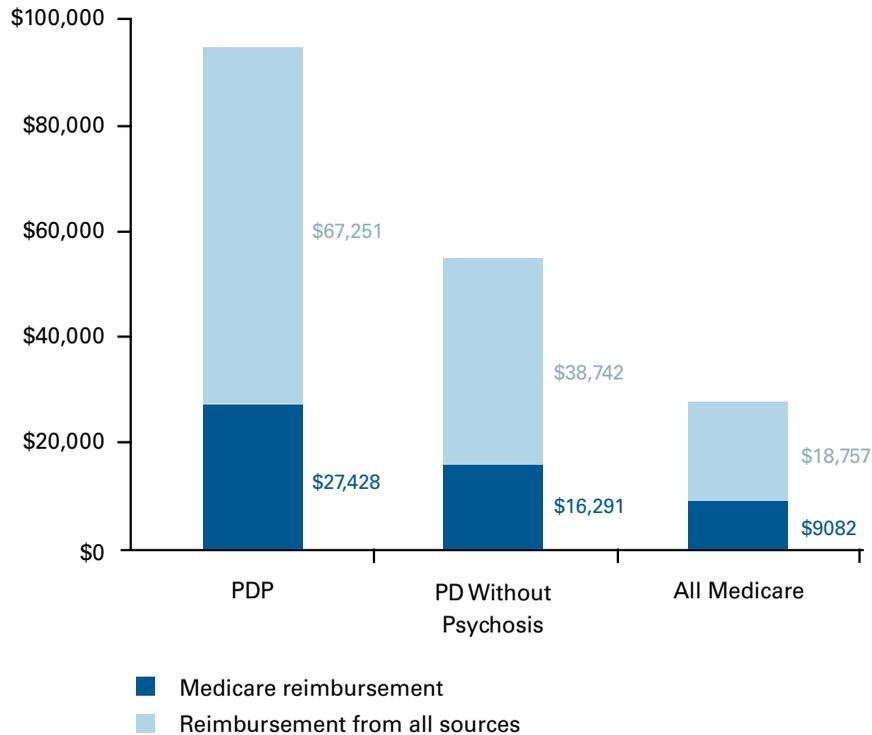
The proportion of adequately treated patients with PDP is low because of a general lack of effective treatment strategies.³⁷ Although PDP previously was considered a side effect of dopaminergic therapies, increasing evidence suggests that its development is multifactorial and a manifestation of the underlying disease process.³⁸ Historically, the first-line strategy for managing psychosis in PD, after ruling out other factors such as infection or dehydration, has been to selectively lower the dose of, or discontinue, anti-PD medications. No FDA-approved medications are currently available to treat PDP; atypical antipsychotics are sometimes used, but they may worsen motor function. In addition, the use of atypical antipsychotics raises other concerns:

■ **Table 1.** Risks for Nursing Home Placement³⁵

	Score	Total (n)	Institutionalized n (%)	Relative Risk	95% CI
Age (y)	≤75	91	11 (12)	3.5	1.9-6.4
	>75	86	36 (42)		
Hallucinations (UPDRS Thought Disorder Item)	≤1	159	37 (23)	2.5	1.6-4.1
	>1	17	10 (59)		
Dementia	Yes	22	12 (55)	2.4	1.5-3.9
	No	154	35 (23)		
Hoehn and Yahr	≤2.5	111	20 (18)	2.3	1.4-3.8
	>2.5	65	27 (42)		
UPDRS ADL	≤11	94	14 (15)	2.7	1.6-4.7
	>11	82	33 (40)		

ADL indicates activities of daily living; UPDRS, Unified Parkinson's Disease Rating Scale. Adapted from Aarsland D, Larsen P, Tandberg E, Laake K. *J Am Geriatr Soc.* 2000;48(8):938-942.

■ **Figure 2.** Average Costs Across All Components of Care (Medicare Survey Data 2000-2010)³⁶



PD indicates Parkinson's disease; PDP, Parkinson's disease psychosis.

- Atypical antipsychotics carry black box warnings for increased mortality and morbidity in elderly patients with dementia.³⁹
- Use of these drugs may not only worsen motor symptoms but also increase risk of tardive dyskinesia, a potentially irreversible movement disorder.^{17,40}
- Overall, evidence is limited to support the efficacy of this drug class in this patient population.⁴¹
- Atypical antipsychotics may require frequent blood tests and careful monitoring for potential side effects.
- Some atypical and typical antipsychotics may worsen Parkinsonism (drug-induced Parkinsonism).

Considering the number of older patients affected by PDP, the safety risks associated with antipsychotic use in this population are a cause for concern. Together, these

issues underscore the need for new treatments to manage PDP—treatments for which there is evidence to support safe and effective use in this patient population.

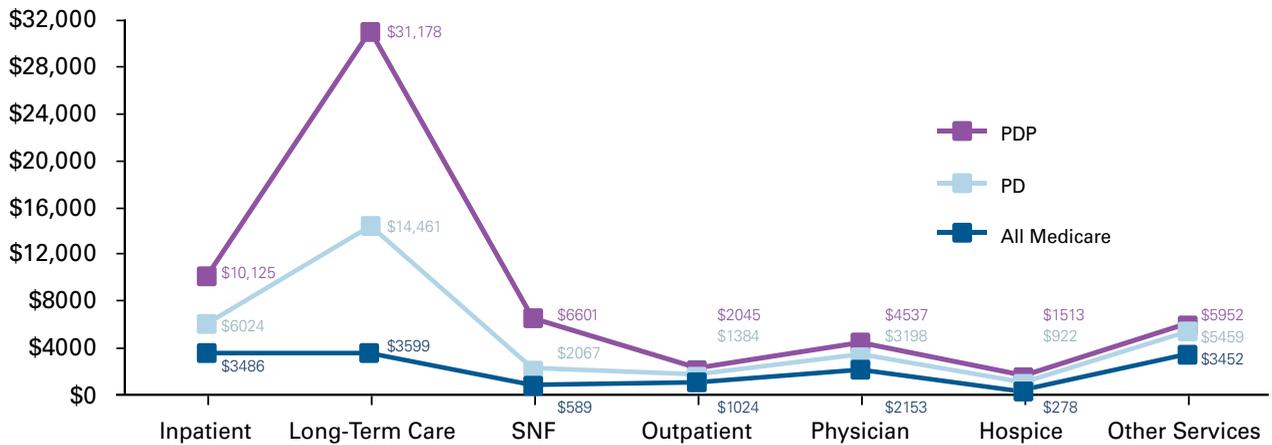
SUMMARY

Antipsychotic medications come with a black box warning for risk of increased morbidity and mortality in elderly patients with dementia. Clinicians should consider the potential for adverse consequences with these medications.

PD is a progressive disease with complex, debilitating symptoms. The non-motor aspects of the disease, such as psychosis, are often under-recognized and may become worse with disease severity. These aspects may exact a serious toll on patient and caregiver quality of life. Increased awareness of PDP and more

effective and safe pharmacologic treatments are needed to improve the quality of care for patients with PDP, alleviate the substantial burden placed on their caregivers, and reduce the risk of nursing home admissions and their attendant costs to the system.

■ **Figure 3.** Average Costs of Major Components of Care (Medicare Survey Data 2000-2010)³⁶



PD indicates Parkinson's disease; PDP, Parkinson's disease psychosis; SNF, skilled nursing facility.

ACTUAL PATIENT CASE

Dr C was diagnosed with Parkinson's disease just 2 years after retiring from his successful OB/GYN practice in the Midwest. Ten years later, he struggled with cognitive decline but remained largely independent in basic daily activities and was able to manage the changes in his life imposed by his diagnosis with a sense of humor and steadfast perseverance—qualities shared by his wife. He had stopped all driving and delegated his medication management to his wife, who attended all of his appointments with him.

On his most recent visit, strain was evident in her face and voice. "Don has been more confused lately," she reported. "Sometimes he thinks I'm somebody else." Her husband sat beside her without a discernible change in his calm smile as he silently listened to her words. "Sometimes he asks me what I have done with Dolores," she said, referring to herself. I inquired if this was frightening or threatening. She hesitated a moment. "Sometimes."

I discussed with the couple the fact that these symptoms were not uncommon for patients with Parkinson's disease and explained the treatment options, including low doses of antipsychotic medication, along with the potential side effects of these medications. Mrs C was uneasy about the warning of sudden death in the medication package insert and chose to not pursue use of one of these medications, opting instead for a reduction of the Parkinson's medication, an increase in her husband's cholinesterase inhibitor, and cautious observation.

Dr C's paranoid delusions escalated in the ensuing days. Ten days later, Mrs C called 911 after her husband attacked her in the kitchen of their home, striking her in the head. Dr C was admitted to a geriatric psychiatry hospital program, and after soul-searching discussions with their children, Mrs C arranged discharge placement of her husband into a skilled nursing facility, where he spent the remainder of his days.

—Neal Hermanowicz, MD, UC Irvine Medical Center

Author affiliation: University of California, Irvine (NH); ICON plc Commercialisation and Outcomes, Los Angeles, CA (KE).

Funding source: The publication of this article was supported by ACADIA Pharmaceuticals Inc. The views and opinions expressed are those of the authors and not necessarily those of ACADIA Pharmaceuticals Inc.

Author disclosures: Dr Hermanowicz reports serving on an advisory board, receiving consultant honoraria, and receiving speaker honoraria

from ACADIA Pharmaceuticals Inc. Dr Edwards reports no relevant commercial financial relationships or affiliations.

Authorship information: Concept and design (KE, NH); analysis and interpretation of data (KE); drafting of the manuscript (KE, NH); and critical revision of the manuscript for important intellectual content (NH).

Address correspondence to: Neal Hermanowicz, MD, 100 Irvine Hall, Irvine, CA 92697; nhermano@uci.edu.

REFERENCES

1. Olanow C, Schapira A. Parkinson's disease and other movement disorders. In: Longo D, Fauci A, Kasper D, et al. *Harrison's Principles of Internal Medicine*. 18th ed. New York, NY: McGraw-Hill; 2012.
2. Samii A, Nutt JG, Ransom BR. Parkinson's disease. *Lancet*. 2004;363(9423):1783-1793.
3. Willis AW, Schootman M, Kung N, et al. Predictors of survival in patients with Parkinson disease. *Arch Neurol*. 2012;69(5):601-607.
4. Kowal SL, Dall TM, Chakrabarti R, Storm MV, Jain A. The current and projected economic burden of Parkinson's disease in the United States. *Mov Disord*. 2013;28(3):311-318.
5. Dowding CH, Shenton CL, Salek SS. A review of the health-related quality of life and economic impact of Parkinson's disease. *Drugs Aging*. 2006;23(9):693-721.
6. O'Sullivan SS, Williams DR, Gallagher DA, et al. Nonmotor symptoms as presenting complaints in Parkinson's disease: a clinicopathological study. *Mov Disord*. 2008;23(1):101-106.
7. Fernandez HH, Aarsland D, Fénelon G, et al. Scales to assess psychosis in Parkinson's disease: critique and recommendations. *Mov Disord*. 2008;23(4):484-500.
8. Miyasaki JM, Shannon K, Voon V, et al. Practice parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2006;66(7):996-1002.
9. Gallagher DA, Lees AJ, Schrag A. What are the most important nonmotor symptoms in patients with Parkinson's disease and are we missing them? *Mov Disord*. 2010;25(15):2493-2500.
10. Martinez-Martin P, Schapira AH, Stocchi F, et al. Prevalence of nonmotor symptoms in Parkinson's disease in an international setting; study using nonmotor symptoms questionnaire in 545 patients. *Mov Disord*. 2007;22(11):1623-1629.
11. Cheon SM, Ha MS, Park MJ, Kim JW. Nonmotor symptoms of Parkinson's disease: prevalence and awareness of patients and families. *Parkinsonism Relat Disord*. 2008;14(4):286-290.
12. Pearce JM. Aspects of the history of Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 1989;(suppl 6-10).
13. Aarsland D, Larsen JP, Karlsen K, Lim NG, Tandberg E. Mental symptoms in Parkinson's disease are important contributors to caregiver distress. *Int J Geriatr Psychiatry*. 1999;14(10):866-874.
14. Schrag A, Hovris A, Morley D, Quinn N, Jahanshahi M. Caregiver-burden in Parkinson's disease is closely associated with psychiatric symptoms, falls, and disability. *Parkinsonism Relat Disord*. 2006;12(1):35-41.
15. Aarsland D, Karlsen K. Neuropsychiatric aspects of Parkinson's disease. *Curr Psychiatry Rep*. 1999;1(1):61-68.
16. Ravina B, Marder K, Fernandez HH, et al. Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS, NIMH work group. *Mov Disord*. 2007;22(8):1061-1068.
17. Zahodne LB, Fernandez HH. Pathophysiology and treatment of psychosis in Parkinson's disease: a review. *Drugs Aging*. 2008;25(8):665-682.
18. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
19. Norton J, Fredericks D, Suresh R, Mills R. Parkinson's disease psychosis (PDP): characteristics of the PDP patient in clinical practice [abstract]. *Mov Disord*. 2015;30(suppl 1):160.
20. Goetz CG, Fan W, Leurgans S, Bernard B, Stebbins GT. The malignant course of "benign hallucinations" in Parkinson disease. *Arch Neurol*. 2006;63(5):713-716.
21. Fénelon G, Mahieux F, Huon R, Ziegler M. Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. *Brain*. 2000;123(pt 4):733-745.
22. Marsh L, Margolis R. Neuropsychiatric aspects of movement disorders. In: Sadock BJ, Virginia AS, Ruiz P, ed. *Kaplan & Sadock's Comprehensive Textbook of Psychiatry*. 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009.
23. Forsaa EB, Larsen JP, Wentzel-Larsen T, et al. A 12-year population-based study of psychosis in Parkinson disease. *Arch Neurol*. 2010;67(8):996-1001.
24. Goldman JG, Holden S. Treatment of psychosis and dementia in Parkinson's disease. *Curr Treat Options Neurol*. 2014;16(3):281.
25. Statistics on Parkinson's. Parkinson's Disease Foundation website. http://www.pdf.org/en/parkinson_statistics. Accessed March 5, 2015.
26. Schneider F, Althaus A, Backes V, Dodel R. Psychiatric symptoms in Parkinson's disease. *Eur Arch Psychiatry Clin Neurosci*. 2008;258(suppl 5):55-59.
27. Fernandez H, Lio FM, Kaiser JJ, et al. P1.181 Parkinson's disease psychosis (PDP): an under-diagnosed condition in spite of its prevalence and impact. *Parkinsonism & Related Disorders*. 2009;15(suppl 2):S75.
28. Pacchetti C, Manni R, Zangaglia R, et al. Relationship between hallucinations, delusions, and rapid eye movement sleep behavior disorder in Parkinson's disease. *Mov Disord*. 2005;20(11):1439-1448.
29. Larsen JP, Tandberg E. Sleep disorders in patients with Parkinson's disease: epidemiology and management. *CNS Drugs*. 2001;15(4):267-275.
30. Bodis-Wollner I. Visual deficits related to dopamine deficiency in experimental animals and Parkinson's disease patients. *Trends Neurosci*. 1990;13(7):296-302.
31. Paleacu D, Schechtman E, Inzelberg R. Association between family history of dementia and hallucinations in Parkinson disease. *Neurology*. 2005;64(10):1712-1715.
32. Carter JH, Stewart BJ, Lyons KS, Archbold PG. Do motor and nonmotor symptoms in PD patients predict caregiver strain and depression? *Mov Disord*. 2008;23(9):1211-1216.
33. Marsh L, Williams JR, Rocco M, et al. Psychiatric comorbidities in patients with Parkinson disease and psychosis. *Neurology*. 2004;63(2):293-300.
34. O'Reilly F, Finnan F, Allwright S, Smith GD, Ben-Shlomo Y. The effects of caring for a spouse with Parkinson's disease on social, psychological and physical well-being. *Br J Gen Pract*. 1996;46(410):507-512.
35. Aarsland D, Larsen JP, Tandberg E, Laake K. Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study. *J Am Geriatr Soc*. 2000;48(8):938-942.
36. Data on File. ACADIA Pharmaceuticals Inc. 2015.
37. Lio F, Fernandez H, Kaiser JJ, et al. P1.183 Parkinson's disease psychosis (PDP): a condition which is undertreated. *Parkinsonism & Related Disorders*. 2009;15(suppl 2):S76.
38. Isaacson S. Parkinson's disease psychosis - a symptom complex signaling risk for increased disability and caregiver burden. *US Neurology*. 2015;11(1):23.
39. Public health advisory: deaths with antipsychotics in elderly patients with behavioral disturbances. FDA website. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm053171.htm>. Accessed May 27, 2015.
40. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA*. 2005;294(15):1934-1943.
41. Weintraub D, Chen P, Ignacio RV, Mamikonyan E, Kales HC. Patterns and trends in antipsychotic prescribing for Parkinson disease psychosis. *Arch Neurol*. 2011;68(7):899-904.

