REPORT

Parkinson's Disease and Parkinson's Disease Psychosis: A Perspective on the Challenges, Treatments, and Economic Burden

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An Overview of Parkinson's Disease and Parkinson's Disease Psychosis

Parkinson's disease (PD) is a progressive neurodegenerative illness associated with degeneration of dopaminergic neurons and the consequent decrease in the neurotransmitter dopamine, resulting in both motor and nonmotor changes.[1,2] It is the second most common neurodegenerative disease after Alzheimer's disease,[3] affecting up to 1 million Americans and more than 10 million individuals worldwide.[4] As the elderly population grows, the incidence of PD is expected to double by 2030 in Western Europe's 5 most and the world's 10 most populous nations, including the United States.[5] Approximately 20% of individuals with PD are diagnosed before age 65.[6] The combined direct and indirect costs of PD, including treatment, Social Security payments, and lost income from inability to work, is estimated to be nearly $25 billion per year in the United States alone.[4]

The main clinical features of PD are motor symptoms, as described by the mnemonic TRAP (tremor, rigidity, akinesia, and postural instability),[7] but the cognitive and behavioral nonmotor features of PD are often reported to be more disabling.[8,9] These include autonomic dysfunction, impaired sense of smell, gastrointestinal disturbances, and psychiatric symptoms such as sleep disturbances, depression, impulse control disorders, dementia, and psychosis, as defined by hallucinations and delusions.[10,11] Parkinson's disease psychosis (PDP) is one of the major challenges in the treatment of PD[12] and involves a spectrum of symptoms beyond formed visual hallucinations.[13] These can include presence or passage hallucinations (ie, the perception of an object or person present or moving in the visual periphery)[14]; complex visual hallucinations, usually of people, animals, or objects[15]; auditory, tactile, gustatory, and olfactory hallucinations that can occur on their own or with visual hallucinations[11,16]; and paranoid beliefs of infidelity or abandonment that involve spouses, family members, or other caregivers.[17]

Psychosis has long been thought of as primarily a consequence of dopaminergic therapies used to treat the motor symptoms of PD; however, it is increasingly recognized that dopaminergic therapy is neither necessary nor sufficient to completely account for the development of psychosis.[13,18] More recently, these symptoms

ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disease associated with a decrease in the neurotransmitter dopamine and characterized by the cardinal motor hallmarks of resting tremor, rigidity, bradykinesia/akinesia, and postural instability. Lesser-known features of PD revolve around nonmotor concerns including psychosis, dementia, sleep disturbances, autonomic dysfunction, and sensory abnormalities. Parkinson's disease psychosis (PDP) contributes significantly to morbidity, mortality, nursing home placement, and quality of life (QOL). PDP management suffers from a lack of safe, effective pharmacological agents and the opposing nature of atypical antipsychotics and dopaminergic therapies. Pimavanserin, the only atypical antipsychotic currently approved by the FDA for treating PDP-related hallucinations and delusions, has no appreciable affinity for dopaminergic receptors, and a controlled clinical study demonstrated its efficacy in treating PDP-associated hallucinations and delusions without affecting motor function. A recent analysis of all health resource utilization (HRU) and total costs attributable to PD and PDP found that mean 12-month HRU services per patient were 2.3 times higher and costs were 2.1 times higher in the PDP cases, while falls were 3.4 times higher and fractures 2.3 times higher, respectively. Products or services that prevent, delay, or lessen the severity of PDP may contribute to reduced healthcare system costs and improve the QOL of patients with PDP and of their caregivers.

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For author information and disclosures, see end of text.

IMPORTANT SAFETY INFORMATION AND INDICATION FOR NUPLAZID® (PIMAVANSERIN) 17-MG TABLETS

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. NUPLAZID is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis.

QT Interval Prolongation: NUPLAZID prolongs the QT interval. The use of NUPLAZID should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong QT interval including Class 1A antiarrhythmics or Class 3 antiarrhythmics, certain antipsychotic medications, and certain antibiotics. NUPLAZID should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and presence of congenital prolongation of the QT interval.

Adverse Reactions: The most common adverse reactions (≥2% for NUPLAZID and greater than placebo) were peripheral edema (7% vs 2%), nausea (7% vs 4%), confusional state (6% vs 3%), hallucination (5% vs 3%), constipation (4% vs 3%), and gait disturbance (2% vs <1%).

Drug Interactions: Strong CYP3A4 inhibitors (eg, ketoconazole) increase NUPLAZID concentrations. Reduce the NUPLAZID dose by one-half. Strong CYP3A4 inducers may reduce NUPLAZID exposure, monitor for reduced efficacy. Increase in NUPLAZID dosage may be needed.

Renal Impairment: No dosage adjustment for NUPLAZID is needed in patients with mild to moderate renal impairment. Use of NUPLAZID is not recommended in patients with severe renal impairment.

Hepatic Impairment: Use of NUPLAZID is not recommended in patients with hepatic impairment. NUPLAZID has not been evaluated in this patient population.

Pregnancy: Use of NUPLAZID in pregnant women has not been evaluated and should therefore be used in pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Pediatric Use: Safety and efficacy have not been established in pediatric patients.

Dosage and Administration: Recommended dose: 34 mg per day, taken orally as two 17-mg tablets once daily, without titration.

INDICATION

NUPLAZID is an atypical antipsychotic indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis.

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have been linked to the intrinsic processes of the disease itself. The complex pathophysiology of PDP remains unclear, but it may include visual processing abnormalities, sleep dysfunction, and specific neurochemical changes involving dopamine, serotonin, and acetylcholine.[13] Risk factors/associations for PDP are listed in **Table 1**.[19]

Psychosis symptoms in patients with PD are a strong predictor of caregiver burden.[20] PDP has a critical impact on both patients and caregivers; it is associated with a diminished quality of life (QOL),[18] nursing home placement,[21] worsening patient outcomes, and increased patient mortality.[13,22-24] Once psychotic features are present, they tend to be recurrent and persistent.[13,25]

The Scope of PDP

The burden of PDP exists among patients with PD of all ages.[26] Neuropsychiatric symptoms of PD, especially dementia, depression, and psychosis,[27] significantly increase health service utilization and the risk for disability, hospitalization, and institutionalization.[28,29] In contrast to motor symptoms, nonmotor symptoms are often unrecognized and untreated.[30]

The prevalence of PDP has been difficult to determine, primarily because of nonuniform methods of defining and measuring symptoms.[13] Aarsland and colleagues reported an 8-year prevalence of dementia of 78.2% among patients with PD followed prospectively,[31] while Hely and colleagues found a 20-year prevalence of 83%.[10] In their 2010 study, Reidel and colleagues found that the prevalence of neuropsychiatric symptoms was greatest for insomnia (49.0%), anxiety (19.6%), and hallucinations (11.5%).[27] Others have reported a lifetime prevalence rate for PDP of 25% in community-based populations and nearly 50% in clinic-based populations. However, the proposed diagnostic criteria developed by the National Institute of Neurological Disorders and Stroke and the National Institute of Mental Health, which include the presence of illusions or a false

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TABLE 1. Risk Factors/Associations for PDP[19]

Exposure to PD medications
Increasing severity of executive impairment
Increasing severity and duration of PD
Comorbid depression or anxiety
Comorbid sleep disorder, including REM, sleep behavior disorder, and insomnia
Older age
Global cognitive impairment or dementia
Increasing daytime fatigue
Visual impairment
Polypharmacy

PD indicates Parkinson's disease; PDP, Parkinson's disease psychosis; REM, rapid eye movement.

sense of presence or passage in addition to the historical criteria of hallucinations and delusions, could raise the prevalence over the lifetime course of the disease.[13]

Common neuropsychiatric features of PD include the following:

- Psychosis (hallucinations and delusions)[13]
- Cognitive dysfunction (up to 44%, depending on the diagnostic criteria applied)[32]
- Depression (52% occurrence in people with PD[33]; associated with higher daily doses of levodopa, the presence of mild cognitive impairment, and hallucinations)[12,34]
- Dementia (48% prevalence in PD patients followed over 15 years)[12]
- Confusion or delirium[35]
- Impulse control disorders (occur in up to 14% of PD patients. The most commonly reported impulse control disorders in PD are compulsive gambling, buying, sexual behavior, and binge eating)[36]
- Anxiety (also associated with depression)[37]
- Apathy[38,39]

Patients often exhibit more than 1 symptom, with depression and/or dementia appearing as the most frequent comorbidities compared with other neuropsychiatric symptoms.[27] Neuropsychiatric symptoms, especially depression and cognitive dysfunction, have the most detrimental impact on patient health-related QOL (HRQoL).[8,40-42] Clinicians are frequently focused on treatment for the motor aspects of PD and may be inattentive to nonmotor and HRQoL issues,[9,43,44] which can adversely affect adherence to treatment and negatively impact cost of care.[45,46] Caregiver HRQoL can also be poor due to the physical and psychological disability associated with PD.[47,48] In a study by von Campenhausen and colleagues (2011), more than half of family members providing care suffered from health problems themselves.[49]

Economic Burden of PDP

While the economic costs of PD are significant, they are magnified in those patients also diagnosed with PDP. An oft-cited study found that the odds ratio for nursing home placement is 16 times higher for PD patients with psychosis (hallucinations) than for patients with PD remaining in the community.[21]

Of the total economic burden for PD, Huse and colleagues (2005) attributed almost 70% to indirect costs related to productivity loss and provision of uncompensated care by family members.[6] There is evidence that productivity loss is greatest in the later stages of the disease[50]; however, even in the first year after diagnosis, indirect costs due to loss of patient and caregiver productivity represented 45% of total expenses.[51]

Parkinson's Disease Psychosis Impact on Long-Term Care Utilization

Symptoms of psychosis are strongly correlated to nursing home placement, regardless of age.[21,25] In a 10-year analysis of costs utilizing claims data for commercially insured members with Parkinson's disease (PD) under age 65 years (n = 1151), patients requiring an ambulatory assistance device and institutionalization incurred 6 to 7 times the direct costs of their matched controls. Among all patients with PD, 24% had diagnosed mental disorders, 11% had neuropsychiatric disorders, and 10% had sleep disorders. Among the institutionalized cohort of patients with PD versus matched controls, 57% versus 10% had mental disorders, and 29% versus 4% had neuropsychiatric disorders.[51]

Analysis of Medicare claims data from 2000-2010 provides evidence of the heavy burden associated with PDP[52]:

- 74.6% of patients with Parkinson's disease psychosis (PDP) spent time in a long-term care (LTC) facility (average, 179 days) compared with 55.8% of patients with PD without psychosis (average, 83 days).
- In LTC specifically, the average annual all-cause cost was $31,178 for patients with PDP compared with $14,461 for PD without psychosis.
- Annual all-cause reimbursement across all components of care for patients with PDP averaged $67,251, while that for PD patients without psychosis was $38,742.

Traditional and New Approaches to PDP Management

The pathophysiology of PDP and pharmacological rationale for treatment are associated with 3 main neurotransmitter systems: dopamine, acetylcholine, and serotonin.[53,54] Medical management of PDP aims to reduce the frequency and severity of psychotic symptoms with minimal worsening of PD motor symptoms. Traditional management of PDP has been challenged by the lack of effective and safe pharmacological treatment options and the opposing nature of atypical antipsychotics and dopaminergic therapies given to treat motor symptoms. Frequently, an initial step in treating hallucinations and delusions associated with PD is to first reduce anti-PD medications, such as anticholinergics, selegiline, amantadine, dopamine agonists, catechol-O-methyltransferase inhibitors, and lastly, levodopa. Reducing dopaminergic therapies, however, may worsen motor symptoms.[54] To treat symptoms of psychosis when reduction of dopaminergic therapies is not a viable option, 2 alternatives exist: use of recently approved pimavanserin[55] or off-label use of atypical antipsychotics, particularly clozapine and quetiapine. However, off-label use of some atypical antipsychotics may worsen motor symptoms by antagonizing dopaminergic therapy.[53]

Atypical Antipsychotics

Atypical antipsychotics, also known as second-generation antipsychotics, have long been used to treat PDP, but they are generally not well tolerated because the doses needed to block limbic D_2 receptors also result in blockage of the dorsal striatal D_2 receptors, reducing the therapeutic effects of dopamine treatment on motor symptoms.[56] These medications are associated with a higher risk of mortality when used in elderly patients with dementia.[54] Only clozapine (Level B evidence), with monitoring of absolute neutrophil count, or quetiapine (Level C evidence) have been considered as appropriate for use by the American Academy of Neurology. One Class I study and 1 Class II study found that clozapine improved psychosis and, in some cases, motor function. One Class II study demonstrated that quetiapine possibly improves psychosis. However, it is important to note that the American Academy of Neurology guidelines were last updated in 2006,[53] prior to the introduction of an FDA-approved agent.[55]

At this time only 1 atypical antipsychotic, pimavanserin (NUPLAZID®, ACADIA Pharmaceuticals Inc.), is approved by the FDA for the treatment of hallucinations and delusions associated with PDP.[55] Pimavanserin acts as an inverse agonist/antagonist at serotonin 5-HT_{2A} receptors with high binding affinity and at serotonin 5-HT_{2C} receptors with lower binding affinity. In vitro, pimavanserin has no appreciable affinity for dopaminergic (including D_2) receptors. A clinical study demonstrated the efficacy of pimavanserin as a treatment for hallucinations and delusions associated with PDP and also showed that pimavanserin does not have an effect on motor function compared with placebo, nor does it have appreciable effects on blood cell counts or metabolic parameters. While pimavanserin shares the class warning regarding increased risk of death in elderly patients with dementia, the boxed warning is modified to permit treatment of the hallucinations and delusions associated with PDP in this population.[57] Atypical antipsychotics used to treat PDP are listed in **Table 2**.[26,55,57-60]

Parkinson's Disease Benchmarks® Database Analysis

To better understand the population of patients with PD who develop PDP, ACADIA Pharmaceuticals Inc. completed a retrospective claims analysis utilizing Havas Gemini, LLC's proprietary PD/PDP Disease Benchmarks® Database.[61] Patients with integrated medical and pharmacy claims had to have continuous enrollment within any 12-month period from October 1, 2011, to September 30, 2014, as well as data identifying gender and age. A 6-month runout period, the time given to file a claim following the study period, was used. Patients were identified using specific ICD-9 codes (**Table 3**[61]) and were required to have a minimum of 2 claims for PD, at least 30 days apart, to be included in the PD patient cohort. Those patients meeting the PD inclusion criteria and having a minimum of 2 claims for the identified PDP ICD-9 codes, at least 30 days apart, were included in the PDP patient cohort. Patients meeting the PDP patient cohort criteria were excluded from the PD cohort to avoid double counting of patients.

For patients with PD only, the index date (date of the start of the study) was the date of the first claim for PD, and the study stop date was that date plus 364 days. For patients with PDP, the index date was the date of the first claim for PDP, and the study stop date was that date plus 364 days. Thus, all patients in the study in both cohorts were analyzed for a continuous 12-month period, but the start date for each patient was determined by their unique index date. In all cases, the study stop date had to be less than or equal to the last date of claims available in the dataset.

All healthcare resource utilization (HRU) and total costs that could be attributed to PD and PDP were included in these analyses. HRU attribution methods for the PDP population, for example, meant that once the patient met the inclusion criteria for the PDP patient cohort, patients matching any medical claim linked with an associated ICD-9 diagnosis code for PD *or* any of the additional codes for psychosis, hallucinations, or delusions were considered PDP-related. Since ICD-9 diagnosis codes are not used in pharmacy claims, only drug claims known to treat the disease/condition relating to the above ICD-9 diagnosis codes used for inclusion criteria were considered.

A total of 28,250 PD patients and 1066 PDP patients were identified (**Table 4**[61-63]) for the analyses based on the applied inclusion criteria. Two variables drive this fact: 1) the inclusion criteria used in this analysis are stricter than what are reported in most prevalence data, and 2) the analysis was based on a commercial population. The prevalence of PDP in a Medicare population would be considerably higher.[27]

TABLE 2. Atypical Antipsychotics Used to Treat PDP[26,55,57-60]

Name	Comments	Contraindications/Warnings	Main Side Effects
Clozapine	• Only low-dose clozapine has enough evidence to support its use in PDP[58] • Risk of agranulocytosis and required blood testing may limit use[58,59] • At low doses, low incidence of extrapyramidal side effects[58]	• Avoid in patients with serious hypersensitivity to clozapine (eg, photosensitivity, vasculitis, erythema multiforme, or Stevens-Johnson Syndrome)[59] • Use with caution in patients with cardiac disease, dementia, renal impairment, hepatic impairment, diabetes mellitus, and suicide risk[59] • Associated with QT interval prolongation and fatal arrhythmia. Use with caution when co-administered with medications known to cause QT prolongation[59] • FDA Class Warning of increased mortality in elderly patients with dementia-related psychosis[59] • FDA Boxed Warning of increased risks for severe neutropenia; orthostatic hypotension, bradycardia, and syncope; seizure; myocarditis and cardiomyopathy[59]	• Sedation, tachycardia, orthostatic hypotension, and salivation[59] • Constipation, dry mouth, weight gain, hypercholesterolemia, hyperglycemia[59]
Pimavanserin	• Approved for the treatment of hallucinations and delusions associated with PDP[a] • Efficacy shown in treatment of hallucinations and delusions associated with PDP[57] • No effect shown compared with placebo on motor function[57]	• Prolongs the QT interval. Avoid use in patients with known QT prolongation or in combination with other drugs known to prolong QT interval[57] • FDA Class Warning of increased mortality in elderly patients with dementia-related psychosis[57] • Not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis[57]	• Nausea, constipation, peripheral edema, gait disturbance, hallucination, and confusional state[57]
Quetiapine	• Most commonly prescribed antipsychotic treatment for PDP[26]	• Use with caution in elderly patients and those with seizure history, cardiovascular disease, dementia, diabetes mellitus, hepatic impairment, suicide risk[60] • Avoid use in presence of congenital prolongation of QT interval and in combination with other drugs known to prolong QTc[60] • FDA Class Warning of increased mortality in elderly patients with dementia-related psychosis[60] • FDA Boxed Warning of increased incidence overall of suicidal thoughts and behavior[60]	• Somnolence and sedation[60] • Dizziness, dry mouth, constipation, increased ALT, weight gain, and dyspepsia[60]

ALT indicates alanine aminotransferase; PDP, Parkinson's disease psychosis.
[a]The FDA approved pimavanserin on April 29, 2016.[55]

This analysis shows that mean 12-month HRU and cost estimates are higher in the PDP patient cohort compared with the PD patient cohort in each of the main service categories of inpatient, outpatient, emergency department (ED), and pharmacy (**Table 5**[61]).[61]

Using the same dataset and patient cohorts identified in Table 4, an additional series of descriptive analyses that examined falls and fractures in the PD versus PDP patient cohorts found that both falls and fractures were higher in the PDP cohort. Overall, 2.4% (26/1066) of patients in the PDP cohort had at least 1 fall versus 0.7% (198/28,250) in the PD cohort, and 16.9% (180/1066) of patients in the PDP cohort had at least 1 fracture versus 7.3% (2062/28,250) in the PD cohort.[61]

Subsequent to the PD versus PDP patient cohort analyses, additional analyses were undertaken to better understand the PDP-specific patient cohort. The PDP cohort (N = 1066) was split into 2 subpopulations based on the presence or absence of at least 1 prescription for an atypical antipsychotic medication. Differences between patient ages, age-adjusted Charlson Comorbidity Index, total number of claims, pharmacy claims, pharmacy total costs,

TABLE 3. ICD-9 Codes Identifying Patients With PD and PDP[61]

Parkinson's disease (PD)	332, 332.0, 332.1
Parkinson's disease psychosis (PDP)	Psychosis: 292.0, 292.12, 292.84, 293.0, 298.0, 298.1, 298.9 Hallucinations: 293.82, 295.2, 295.21, 295.22, 295.23, 295.24, 295.25, 368.16, 780.1 Delusions: 293.81, 297.1

TABLE 4. Demographics of PD and PDP Patient Population[61-63]

Cohort	Cohort Size	Average Age[a]	Female: Male
PD only	28,250	69.6	40.8: 59.2
PDP	1066	74.5	45.7: 54.3

PD indicates Parkinson's disease; PDP, Parkinson's disease psychosis.
[a]The average age is consistent with a Medicare population. The majority of Medicare beneficiaries are 65 years and older.[62] The average age of Medicare beneficiaries in 2015 was 71 years.[63]

TABLE 5. Benchmarks® Claims Data (Commercial and Medicare Advantage Prescription Drug)[61,a,b]

	Average From *All* Patients With PD (N = 28,250)		Average From *All* Patients With PDP (N = 1066)	
Service Category	Services/ Patient	Costs/ Patient	Services/ Patient	Costs/ Patient
Inpatient Ancillary	1.2	$773.02	2.2	$999.10
Inpatient Facility	0.1	$724.72	0.3	$1746.93
Inpatient Management	0.8	$78.36	3.3	$344.14
Inpatient Surgical	0.0	$23.60	0.0	$26.42
Inpatient Total	**2.2**[c]	**$1599.70**	**5.8**	**$3116.60**[c]
Outpatient Ancillary	6.5	$1777.85	16.9	$4681.32
Outpatient Management	5.2	$502.68	10.0	$1037.24
Outpatient Surgical	0.1	$71.24	0.1	$112.91
Outpatient Total	**11.7**[c]	**$2351.77**	**27.0**	**$5831.47**
Emergency Department	**0.6**	**$70.49**	**1.4**	**$143.63**
Pharmacy	**2.8**	**$619.23**	**5.4**	**$822.44**
Total Costs	**17.3**	**$4641.19**	**39.6**	**$9914.14**

[a]All costs are expressed as total cost amount. The total cost amount is the total amount of money that a medical care provider can ultimately collect for a service rendered. It is a combination of the amount the insurance company will pay plus the amount for which the patient is responsible. The calculation is patient responsible amount + insurance payment = total cost amount. Long-term care costs are excluded because they typically are not paid by a commercial plan.
[b]A propensity score matching analysis was performed; no patients in the 2 study cohorts could be matched by probability score.
[c]Amounts may not sum exactly due to rounding.

and number of distinct diagnostic categories were all statistically significant ($P \leq .05$) in those patients with PDP treated with an atypical antipsychotic versus not treated with an atypical antipsychotic. The ED total cost difference was borderline statistically significant ($P = .057$) between the 2 subpopulations of patients with PDP. In all cases, the higher costs and utilization occurred in the PDP subpopulation that was treated with atypical antipsychotics.[64]

Summary

While long thought to be a side effect of anti-PD drug treatment, the development of psychosis may be a part of the underlying disease process itself.[18,54] The development of PDP has a profoundly detrimental impact and is one of the biggest challenges to PD treatment.

Antipsychotic medications used in the traditional management of PDP may worsen motor symptoms, trigger metabolic and other adverse effects, and require careful monitoring. Low doses of clozapine or quetiapine are prescribed off-label, with quetiapine being more commonly used in the United States.[26] Although clozapine has shown clinical benefit for psychosis without typically causing motor function worsening, it is rarely used because of the risk of agranulocytosis and the associated regular blood monitoring requirement. Quetiapine is the most frequently prescribed therapy, but it has shown variable evidence of efficacy in controlled trials[53] and is associated with increased sedation.[60]

To date, only 1 atypical antipsychotic, pimavanserin, has been approved by the FDA specifically to treat PDP.[55] Pimavanserin has been shown to be efficacious as a treatment for hallucinations and delusions associated with PDP, and it does not have an effect on motor function, nor are there appreciable effects on blood counts or metabolic parameters.[57]

The initial results of the Benchmarks® database claims analyses demonstrate that patients with PDP have greater HRU and incur increased costs compared with patients with PD only, particularly in the inpatient and outpatient service categories. Importantly, these initial findings are consistent with the Medicare analysis of claims data from 2000-2010 and provide evidence of the heavy burden associated with PDP.[52]

Products or services that prevent, delay, or lessen the severity of PDP may contribute to reduced healthcare system costs and improve the QOL of patients with PDP and their caregivers. Evidence for this assumption is supported by analyses showing that psychosis, as well as comorbid mental health disorders, are common reasons for ED admissions and hospitalizations in patients with PD.[65] In addition, the development of PDP is associated with increased nursing home placement, long-term care, and mortality.[21-23,52,66] ■

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