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Adherence to Antidepressants and Healthcare Resource Utilization and Costs among Medicare Advantage Beneficiaries with Parkinson's Disease and Depression

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by

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Adherence to Antidepressants and Healthcare Resource Utilization and Costs among Medicare Advantage Beneficiaries with Parkinson's Disease and Depression

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Depression is the most common comorbid psychiatric disorder in patients with Parkinson's disease (PD) and imposes a significant negative impact on PD. Studies have shown that antidepressants (ADs) may both treat depression and ameliorate its negative effects on PD. However, little has been reported regarding how improved adherence to antidepressants affects the outcomes among PD patients with depression. The purpose of this study was to examine antidepressant use patterns (adherence, persistence, switching, and combination therapy) and evaluate the associated healthcare utilization and costs in PD patients with comorbid depression.

A retrospective cohort analysis using claims data from the Humana healthcare insurance plan (2007-2010) was conducted. Medicare Advantage with Prescription Drug (MAPD) Plan insured patients with ADs and a diagnosis of both depression and PD were identified and followed for one year. Healthcare resource utilization and costs were compared between

adherent and non-adherent AD users while adjusting for demographic and clinical covariates. Adherence was defined as having at least 80 percent of AD coverage for the year, using proportion of days covered (PDC) calculations. A total of 856 PD patients initiating AD treatment were included. Less than half (N= 355 (41.5%) were considered adherent. The mean PDC (±SD) for antidepressants was 0.63 (± 0.31). The mean persistence (using a 30-day gap period) for antidepressants was 194 days. Having a regimen modification, (11% of patients had switching or combination therapy) was associated with a greater likelihood of being adherent (odds ratio = 2.97, 95% CI = [1.88, 4.68], $p < 0.001$) and a lower likelihood of discontinuation (hazard ratio = 0.63, 95% CI = [0.47, 0.84], $p = 0.0016$). After adjusting for covariates, adherent AD users had fewer all-cause and PD-related inpatient visits (all $p < 0.05$). Adherent AD users also had lower all-cause nursing facility, inpatient, emergency room (ER), and total costs (all $p < 0.05$) than non-adherent AD users. However, the results were no longer significant when assessing PD-related costs. In conclusion, regimen modification (switching, or combination therapy) to antidepressants was associated with better adherence and persistence in depressed PD patients. Adherent AD users had some lower healthcare utilization and costs than non-adherent AD users among depressed PD patients.

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CHAPTER 1: LITERATURE REVIEW

This chapter will review the literature on 1) Parkinson's disease (PD); 2) depression as a common comorbidity in PD; 3) the importance of management of depression in PD. The following contents will be described:

- Epidemiology of PD
- Humanistic and economic burden of PD
- Symptoms, diagnosis, and management of PD
- Link between PD and depression
- Epidemiology of depression in PD
- Diagnosis and management of depression in PD
- Impact of depression on PD

1.1 Section 1: Parkinson's Disease (PD)

1.1.1 Definition, Etiology, and Epidemiology of PD

Parkinson's disease (PD) is one of the most common progressive neurologic disorders typically characterized by movement deficits, affecting more than seven million people worldwide.[1,2] PD is associated with both motor and non-motor symptoms.[3] Motor symptoms such as tremor, bradykinesia, rigidity, and postural instability are cardinal clinical features of PD.[1] Non-motor symptoms include sleep, emotional, cognitive, sensory, and autonomic disorders. Both motor and non-motor symptoms may become more prominent as PD progresses and thus limit patients' daily activity and decrease their quality of life.[4]

To date, the cause of PD remains unknown. It is hypothesized that both genetics and environmental factors contribute to the development of PD.[1] The identified environmental factors associated with risk of developing PD include: pesticide exposure, prior head injury, rural living, beta-blocker use, agricultural occupation, and well water drinking.[1] Family history is another important risk factor for PD and several studies have revealed the association between dozens of gene loci and PD.[1]

The worldwide prevalence of PD is estimated to be approximately 320 per 100,000 population among individuals aged 40 years or older.[5] By 2030, it is estimated that the number of people with PD will be between 8.7 to 9.3 million.[6] One meta-analysis conducted by Pringsheim et al. has observed a lower prevalence of PD in Asia than in North America, Europe, and Australia.[5] However, it has been questioned whether the geographic variation in PD prevalence was in fact due to the methodological differences rather than ethnic differences.[7] Both prevalence and incidence of PD are age-dependent.[5] The reported prevalence increases with age: 41 for the 40-49 age group; 107 in the 50-59 age group; 173 in the 55-64 age group; 428 in the 60-69 age group; 425 in the 65-74 age group; 1,087 in the 70-79 age group; and 1,903 in the ≥80 age group, all per 100,000 population.[5] A review by de Lau and Breteler demonstrated that the standardized incidence rates ranged from 8 to 18 cases per 100,000 person-years.[8] The age of onset of PD is relatively late, most often in those aged 60 years or older.[8]

In the United States, there are approximately one million individuals living with PD, with 60,000 new cases diagnosed annually.[9] Van Den Eeden et al. estimated the incidence of PD among commercially insured individuals from a large health maintenance organization and reported an age- and gender-adjusted incidence rate of 13.4 per 100,000 population.[10] Using a

passive surveillance PD registry with a great proportion of elderly people in Nebraska, Strickland and Bertoni found a prevalence of 329.3 per 100,000 population.[11] A more recent study investigated Medicare beneficiaries (≥ 65 years old), which revealed higher prevalence and incidence rate of PD in the US than those reported from the Van Den Eeden study and the Strickland study.[12] Wright-Willis et al. used Medicare research-identifiable files and observed that the mean prevalence of PD was approximately 1,588 cases and the mean annual incidence was approximately 446 cases per 100,000 population among Medicare beneficiaries aged 65 years or older.[12]

The prevalence and incidence rate of PD have been found to vary by gender and ethnicity. Some studies reported that men had a greater susceptibility to PD than women. In 2014, a meta-analysis of 47 studies demonstrated that the prevalence of PD was significantly higher in men than women (134 vs. 41, per 100,000 population) among individuals between 50 to 59 years old.[5] A review from Gillies et al. examined the gender differences in PD and found the male-to-female ratios for incidence rates ranged from 1.37 to 3.7.[13] Although no firm conclusions can be drawn, several studies have suggested that the differences in PD susceptibility by gender may be attributable to estrogenic neuroprotection.[13] With regard to differences by race, Wright-Willis et al. examined Medicare beneficiaries (≥ 65 years old) and found that the prevalence of PD was higher in Whites than Hispanics, Asians, and Blacks (approximate cases in Whites: 2,168; Hispanics: 1,544; Asians: 1,139; Blacks: 1,036, all per 100,000 population). In the same study, the reported annual incidence of PD was higher in Hispanics than White, Blacks, and Asians (approximate annual new cases in Hispanics: 476; White: 452; Black: 362; Asian: 339, all per 100,000 population). Wright-Willis et al. also observed higher prevalence and incidence in the

Midwest and Northeast regions of the United States. Possible explanations for the regional difference may involve pathophysiologic risk factors such as byproducts of industrialization or environmental risk factors such as pesticide and herbicide use.[12]

Many studies have shown that people with PD had a lower life expectancy than the general population.[14-16] One meta-analysis of eight studies suggested that people with PD were approximately two times more likely to die compared to the general population.[14] Macleod et al. conducted another meta-analysis of 88 studies and showed that the mortality ratios for people with PD relative to those without PD range from 0.9 to 3.8. Authors also reported that the pooled estimate of the mortality ratio was approximately 1.5 among studies with participants recruited either at PD diagnosis or shortly afterwards.[15] Commonly reported factors associated with increased mortality in patients with PD include: increasing age, dementia, male gender, disease severity, postural instability and gait difficulties, and the presence of psychotic symptoms.[7,14-16]

1.1.2 Humanistic and Economic Burden of PD

Because PD is a progressive disease, the motor and non-motor symptoms may become more severe as PD progresses over time. These symptoms of PD adversely affect patients' health-related quality of life (HRQoL) and pose significant burden on patients and society.[17]

Several studies have assessed HRQoL in PD patients by using either generic or disease-specific questionnaires. The results have shown that PD is associated with HRQoL deterioration.[4] Reuther et al. conducted a prospective longitudinal study and assessed the HRQoL in PD patients. They found a lower HRQoL among patients with PD relative to the general population by using the EuroQOL five dimensions questionnaire (EQ-5D).[18] In another cross-

sectional study, the World Health Organization Disability Assessment Schedule (WHO-DAS II) and the 36-Item Short-Form Health Survey (SF-36) PD patient scores were also lower than the normative values.[19] Among those with disabling motor symptoms, gait impairments and complications due to medications were independent predictors of impaired HRQoL. Studies in recent years have also suggested that non-motor symptoms such as depression, fatigue, and sleep problems were stronger determinants of lower HRQoL than motor symptoms.[4,20]

PD has been described as a disease associated with significant economic burden.[21] Because of the expected continuing increase in the portion of elderly in the population, escalating costs associated with PD in the future are predicted. Kowal et al. evaluated excess healthcare use, medical, and non-medical costs in PD compared to those without PD using combined national representative surveys in the United States.[22] The researchers projected costs based on the U.S. Census Bureau's 2010 to 2050 demographic data. The estimated medical costs attributed to PD were predicted to increase from approximately $8 billion in 2010 to $18.5 billion in 2050.

Many studies have reported high direct and indirect costs associated with PD. The reported total direct costs for the population with PD in the United States were about $14 billion in 2010.[22] The estimated annual direct cost among PD patients ranged from $5,176 to $80,904 per patient depending on the patients' disease severity, disease progression, complications, and compliance.[21] Huse et al. assessed costs for PD using Medstat's MarketScan Research Database, which included medical and pharmacy claims data among enrollees under an employer-funded health plan or Medicaid. They found that the total annual direct costs for patients with PD were $23,101 per patient, which were approximately two times higher than the controls without PD

($11,247).[23] Noyes et al. analyzed Medicare Current Beneficiary Survey data and reported annual health care expenses of $18,528 for PD patients and $10,818 for the beneficiaries without PD.[24] Based on resource use and cost profiles from statewide hospital discharge data, O'Brien and colleagues reported an annual PD-related direct cost of $12,491.[25]

Several studies have also shown that direct costs of PD were significantly associated with the level of disease disability and increased progressively over time.[21] Kaltenboeck et al. used samples from Medicare to estimate direct medical costs among PD patients aged 65 and older.[26] Compared to the matched controls without PD, patients with PD had excess costs of $28,422 ($61,622 vs. $33,200) from the year prior to the quarter with first PD diagnosis to the end of 5-year follow-up. The authors also analyzed the difference in direct medical costs between matched controls without PD and PD patients at different levels of disability. Relative to the matched controls without PD, the excess cumulative costs in the same observation period among patients with PD who received an ambulatory assistance device (a walker or wheelchair) or were in a skilled nursing facility were $50,923 ($78,042 vs. $27,119) and $102,750 ($142,008 vs. $39,258), respectively. Another study used a commercially insured claims database to calculate direct and indirect costs of PD patients under the age of 65 years.[27] Compared to the matched controls without PD, after one-year follow-up, the excess mean direct PD-related costs were $4,072 ($9,175 vs. $5,103) for the newly diagnosed PD patients, $26,467 ($31,800 vs. $5,333) for those PD patients with an ambulatory assistance device, and $37,410 ($43,506 vs. $6,096) for the institutionalized PD patients.

The identified main contributors to direct costs of PD included medications, hospitalization, nursing home, and outpatient costs. The study conducted by Kowal et al. showed

that the total direct costs were $22,129 per PD patient in 2010.[22] They found that nursing home expenses accounted for the greatest percentage (37.4%) of direct costs ($8,272), followed by costs of hospitalization (29.1%, $6,444), and medications (17.1%, $3,780). Richy et al. assessed healthcare costs incurred by PD patients using the PharMetrics claims database.[28] The reported total direct costs were $80,905 per PD patient. Approximately 27% of the direct costs were from outpatient costs ($21,851), 25% were from medications ($20,336), 22% were from hospitalization ($17,743), and 18.6% were from emergency room visits ($15,038). The total direct costs in the Richy study were much higher than the costs in the Kowal study ($80,905 vs. $22,129). This may due to the difference in methodology and data source: Kowal et al. used combined nationally representative surveys and integrated the US Census Bureau's population data, while Richy et al. retrospectively analyzed a nationally representative claims database for the commercially insured population in the US.

Studies regarding indirect costs of PD due to productivity loss, early retirement, and reduced employment have been published. By integrating data from a claims database and simulation of lifetime earnings loss, Johnson et al. demonstrated that newly diagnosed PD patients and PD patients with ambulatory assistance devices (AAD) were more likely retire early.[29] They reported that the earnings loss for newly diagnosed PD patients was $43,928 over 3 years after PD diagnosis and $205,832 over 3 years after AAD use. Another study analyzed commercially insured claims data and found that the newly diagnosed PD patients' indirect costs were $3,311 higher than matched controls without PD after one year follow-up. Among the newly diagnosed PD patients, the costs associated with absenteeism and disability were $2,315 and $2,055 after one year, respectively. Kowal et al. revealed that patients with PD were less

likely to be employed than those without PD, which translated into $1.7 billion in loss of national productivity in 2010.[22] The reported annual indirect costs were $10,046 per PD patient. Among those employed PD patients, they had eight more medically related absenteeism days per year relative to those without PD and generated a loss of $823 million.

In addition to the humanistic and economic burden to patients who suffered from PD, several studies reported the burden to informal caregivers of PD patients.[21] Most PD patients receive informal care performed by their spouse or child. Many informal caregivers take work leaves or quit their jobs to take care of their loved ones.[30] A study conducted by Bhimani revealed that taking care of PD patients poses a significant burden on informal caregivers' physical, psychological, and socioeconomic domains.[30]

In summary, PD was associated with significant burden to patients, their families, and society. PD patients have impaired HRQoL and the economic burden of PD rises progressively over time. Previous studies have also demonstrated that both direct and indirect costs contribute substantially to the economic burden of PD.

1.1.3 Symptoms and Disease Progression of PD

Clinical features of PD can be categorized into motor and non-motor symptoms. Motor symptoms are caused by deficiency of dopamine in the striatum which degenerate patients' movement abilities. Motor symptoms usually begin on one side of the body and extend gradually to the other side as the disease progresses. The core features of motor symptoms are tremor, bradykinesia, rigidity, and postural instability. Tremor is the shaking movement that is most noticeable when PD patients are at rest, occurring in approximately 70% of the PD patients.

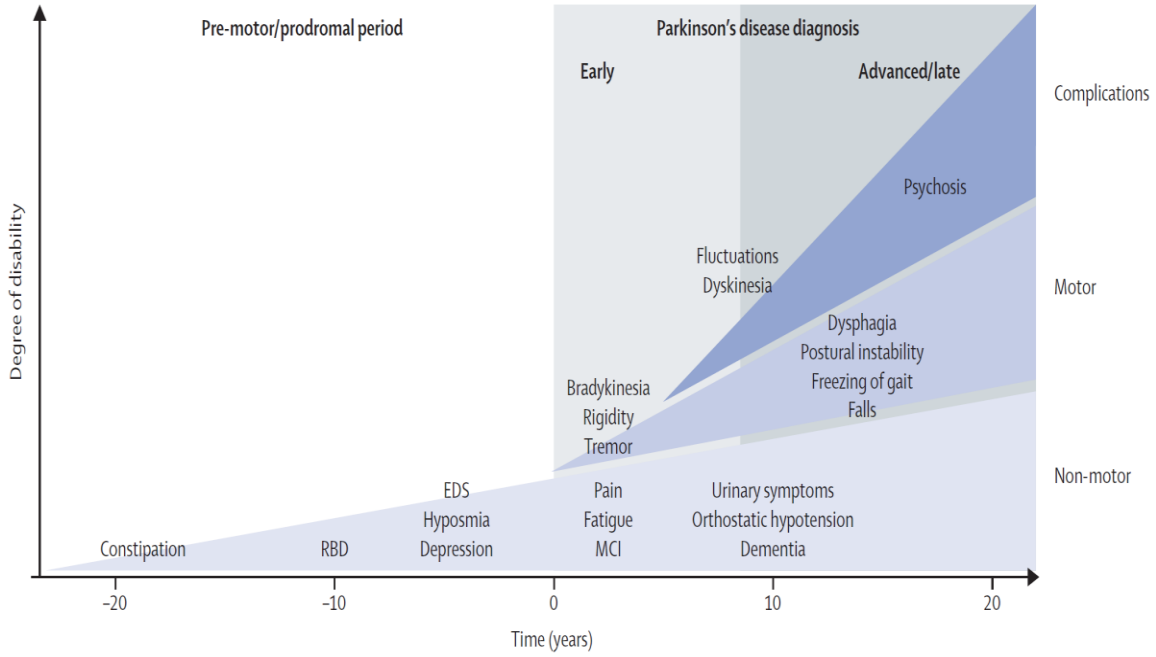
Bradykinesia (slow movement) makes PD patients difficult to initiate movement. This is the most debilitating feature of motor symptoms which limits patients' ability to perform daily living tasks, such as buttoning clothes, brushing teeth, and bathing. Rigidity, characterized by stiffness of limbs, neck, or trunk, is caused by failure of reciprocal relaxation of antagonist muscles. Postural instability refers to the motor symptom where patients lose the automatic reflexes required to retain balance, resulting in difficulty in walking and an increase the risk of falling. The term "parkinsonism" is used to describe the motor symptom complex such as tremor, rigidity, bradykinesia, and postural instability. Although PD causes the majority of cases of parkinsonism, many diseases can present with signs and symptoms of parkinsonism as well.[31]

A wide spectrum of non-motor symptoms have been reported: cognitive problems and dementia, psychosis and hallucinations, mood disorders, sleep disorders, daytime sleepiness, autonomic dysfunction, loss of sense of smell, and pain. Non-motor symptoms are common and nearly all PD patients have experienced non-motor symptoms.[32,33] The neurochemical changes associated with non-motor symptoms have not been fully understood to date. Although motor symptoms are more noticeable, previous studies have shown that non-motor symptoms have a greater impact on PD patients' quality of life than motor symptoms.[34-36]

The symptoms and progression of PD vary from patient to patient. Non-motor symptoms usually present before the onset of motor symptoms and progress during the course of PD (See Figure 1.1).[37] As the disease progresses, both motor and non-motor symptoms may become more severe and increase the degree of functional disability. In the late phase of PD, many patients develop complications due to long-term symptomatic treatment such as psychosis, fluctuations in response, and dyskinesia. For motor symptoms, the majority of the advanced PD patients

experienced freezing of gait and falls. As for the non-motor symptoms, autonomic dysfunction and dementia are common in advanced PD patients.

Figure 1.1 Clinical symptoms and time course of Parkinson's disease progression



EDS=excessive daytime sleepiness. MCI=mild cognitive impairment. RBD= REM (rapid eye movement) sleep behavior disorder.

Source: Kalia LV, Lang AE. Parkinson's disease. *Lancet (London, England).* Aug 29 2015;386(9996):896-912.

1.1.4 Diagnosis of PD

Currently, there is no definitive test available to specifically assess PD. The diagnosis of PD can be confirmed by histopathological examination of neuronal loss with Lewy bodies at autopsy. However, in clinical practice, the diagnosis of PD is usually based on different symptoms and findings from the patient's history and a physical examination. Both the International Parkinson and Movement Disorder Society's (MDS) Task Force and the UK

Parkinson's Disease Society Brain Bank have published diagnostic criteria of PD (See Table 1.1 and Table 1.2).[38-40] In general, the diagnosis of PD involves identification of parkinsonism (bradykinesia, rigidity, 4-6 Hz rest tremor, and postural instability), exclusion of other diseases that manifest in a similar fashion, and assessment of response to dopaminergic therapy. The clinicians often review the patient's history such as onset of the symptoms, whether symptoms are unilateral, changes in mood, sleeping habits, or autonomic dysfunction, recent injury/falls, medication use, etc. A series of physical and neurologic examinations are performed to assess the patient's ability to regain balance and coordination. When the diagnosis of PD is uncertain or the symptoms become incapacitating for a patient's everyday life, a medication challenge test (i.e., giving dopaminergic therapy to patients for diagnostic purpose) may be conducted to support the diagnosis of PD. If the patient's symptoms significantly improve after the medication challenge test, it suggests the diagnosis of PD.[31,41,42]

Table 1.1 Movement Disorder Society's (MDS) diagnostic criteria for Parkinson's disease (PD)

The first essential criterion is parkinsonism, which is defined as bradykinesia, in combination with at least 1 of rest tremor or rigidity. Examination of all cardinal manifestations should be carried out as described in the MDS–Unified Parkinson Disease Rating Scale. Once parkinsonism has been diagnosed:

Diagnosis of Clinically Established PD requires:

1. Absence of absolute exclusion criteria
2. At least two supportive criteria, and
3. No red flags

Diagnosis of Clinically Probable PD requires:

1. Absence of absolute exclusion criteria
2. Presence of red flags counterbalanced by supportive criteria
   - If 1 red flag is present, there must also be at least 1 supportive criterion
   - If 2 red flags, at least 2 supportive criteria are needed
   - No more than 2 red flags are allowed for this category

Table 1.1 Movement Disorder Society's (MDS) diagnostic criteria for PD (continued)

Supportive criteria
(Check box if criteria met)
☐ 1. Clear and dramatic beneficial response to dopaminergic therapy. During initial treatment, patient returned to normal or near-normal level of function. In the absence of clear documentation of initial response a dramatic response can be classified as:
a) Marked improvement with dose increases or marked worsening with dose decreases. Mild changes do not qualify. Document this either objectively (>30% in UPDRS III with change in treatment), or subjectively (clearly-documented history of marked changes from a reliable patient or caregiver).
b) Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off.
☐ 2. Presence of levodopa-induced dyskinesia
☐ 3. Rest tremor of a limb, documented on clinical examination (in past, or on current examination)
☐ 4. The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy

Absolute exclusion criteria: The presence of any of these features rules out PD:
☐ 1. Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (e.g., sustained gaze evoked nystagmus, macro square wave jerks, hypermetric saccades)
☐ 2. Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades
☐ 3. Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia, defined according to consensus criteria within the first 5 y of disease
☐ 4. Parkinsonian features restricted to the lower limbs for more than 3 y
☐ 5. Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism
☐ 6. Absence of observable response to high-dose levodopa despite at least moderate severity of disease
☐ 7. Unequivocal cortical sensory loss (i.e., graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia
☐ 8. Normal functional neuroimaging of the presynaptic dopaminergic system
☐ 9. Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or, the expert evaluating physician, based on the full diagnostic assessment feels that an alternative syndrome is more likely than PD

Red flags
☐ 1. Rapid progression of gait impairment requiring regular use of wheelchair within 5 y of onset
☐ 2. A complete absence of progression of motor symptoms or signs over 5 or more y unless stability is related to treatment
☐ 3. Early bulbar dysfunction: severe dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, NG tube, or gastrostomy feeding) within first 5 y
☐ 4. Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs
☐ 5. Severe autonomic failure in the first 5 y of disease. This can include:
a) Orthostatic hypotension32—orthostatic decrease of blood pressure within 3 min of

Table 1.1 Movement Disorder Society's (MDS) diagnostic criteria for PD (continued)

standing by at least 30 mm Hg systolic or 15 mm Hg diastolic, in the absence of dehydration, medication, or other diseases that could plausibly explain autonomic dysfunction, or

b) Severe urinary retention or urinary incontinence in the first 5 y of disease (excluding long-standing or small amount stress incontinence in women), that is not simply functional incontinence. In men, urinary retention must not be attributable to prostate disease, and must be associated with erectile dysfunction

☐ 6. Recurrent (>1/y) falls because of impaired balance within 3 y of onset

☐ 7. Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 y

☐ 8. Absence of any of the common nonmotor features of disease despite 5 y disease duration. These include sleep dysfunction (sleep-maintenance insomnia, excessive daytime somnolence, symptoms of REM sleep behavior disorder), autonomic dysfunction (constipation, daytime urinary urgency, symptomatic orthostasis), hyposmia, or psychiatric dysfunction (depression, anxiety, or hallucinations)

☐ 9. Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response)

☐ 10. Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, and no side predominance is observed on objective examination

Criteria Application:

1. Does the patient have parkinsonism, as defined by the MDS criteria? Yes ☐ No ☐
   If no, neither probable PD nor clinically established PD can be diagnosed. If yes:
2. Are any absolute exclusion criteria present? Yes ☐ No ☐
   If "yes," neither probable PD nor clinically established PD can be diagnosed. If no:
3. Number of red flags present ____
4. Number of supportive criteria present ____
5. Are there at least 2 supportive criteria and no red flags? Yes ☐ No ☐
   If yes, patient meets criteria for clinically established PD. If no:
6. Are there more than 2 red flags? Yes ☐ No ☐
   If "yes," probable PD cannot be diagnosed. If no:
7. Is the number of red flags equal to, or less than, the number of supportive criteria?
   Yes ☐ No ☐
   If yes, patient meets criteria for probable PD

Source: Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society.* Oct 2015;30(12):1591-1601.

Table 1.2 UK Parkinson's Disease Society Brain Bank (UKPDSBB) clinical diagnostic criteria for idiopathic Parkinson's disease

Step 1 Diagnosis of Parkinsonian syndrome - Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions) - and at least one of the following: • muscular rigidity • 4-6 Hz rest tremor • postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction
Step 2 Exclusion criteria for idiopathic Parkinson's disease - Repeated strokes with stepwise progression of parkinsonian features - Repeated head injury - History of definite encephalitis - Oculogyric crises - Neuroleptic treatment at onset of symptoms - More than one affected relative - Sustained remission - Strictly unilateral features after 3 years - Supranuclear gaze palsy - Cerebellar signs - Early severe autonomic involvement - Early severe dementia with disturbances of memory, language, and praxis - Babinski sign - Presence of cerebral tumor or communicating hydrocephalus on computed tomography scan - Negative response to large doses of levodopa (if malabsorption excluded) - MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) exposure
Step 3 Supportive prospective positive criteria for idiopathic Parkinson's disease (Three or more required for diagnosis of definite Parkinson's disease) - Unilateral onset - Rest tremor present - Progressive disorder - Persistent asymmetry affecting side of onset most - Excellent response (70-100%) to levodopa - Severe levodopa-induced chorea - Levodopa response for 5 years or more - Clinical course of 10 years or more

Source: National Institute for Health and Care Excellence (NICE). Parkinson's disease in over 20s: diagnosis and management. NICE Guidelines. https://www.nice.org.uk/guidance/cg35/chapter/1-Guidance#diagnosing-parkinsons-disease. Accessed April

3, 2016. (Adapted from Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *Journal of neurology, neurosurgery, and psychiatry.* Mar 1992;55(3):181-184.)

Ruling out diseases that mimic PD is an essential step in diagnosis of PD. However, distinguishing PD from other neurodegenerative disorders that also share similar symptoms and signs of parkinsonism is challenging.[42] PD may be confused with other diseases such as essential tremor, dementia with Lewy bodies (DLB), corticobasal degeneration (CBD), multiple system atrophy, and progressive supranuclear palsy (PSP), or other conditions such as secondary parkinsonism (See Table 1.3).[43] The American Academy of Neurology (AAN) suggests the following clinical features to identify alternative diagnoses other than PD: "Falls at presentation or early in the disease course, poor response to levodopa, symmetry of motor signs, rapid progression, lack of tremor, and early dysautonomia".[41] Although imaging tests cannot help the confirmation of PD diagnosis, they may be used to distinguish PD from other diseases. These include magnetic resonance imaging (MRI), 123I-FP-CIT single photon emission tomography (also known as DaTscan), positron-emission tomography (PET), and brain parenchyma sonography.[41] In addition to the imaging tests, olfactory screening may help in the differential diagnosis of PD because impairment of olfaction is more common in PD patients than CBD or PSP patients.[41]

Table 1.3 Disorders that can mimic Parkinson's disease

Neurodegenerative causes: - Alzheimer disease - Corticobasal degeneration - Dementia with Lewy bodies - Frontotemporal dementia - Huntington disease - Multiple system atrophy - Parkinsonism-dementia-ALS complex of Guam - Progressive supranuclear palsy - Spinocerebellar ataxias
Symptomatic: - Drug-induced (neuroleptics, other dopamine receptor antagonists) - Infectious (post-encephalitic, Creutzfeldt-Jakob disease) - Metabolic (Wilson disease, neurodegeneration with brain iron accumulation, hepatocerebral degeneration, parathyroid disorders) - Neoplastic - Post-traumatic - Toxic (carbon monoxide, manganese, MPTP) - Vascular
Other: - Essential tremor - Normal pressure hydrocephalus - SWEDD (Scans Without Evidence of Dopaminergic Deficit): patients with relatively isolated upper extremity tremor resembling early Parkinson disease who lack evidence of nigrostriatal dopamine deficiency on dopamine transporter imaging

Source: Chou K, Hurtig HI, Dashe JF. Diagnosis of Parkinson Disease. 2015; http://www.uptodate.com/contents/diagnosis-of-parkinson-disease?source=search_result&search=parkinson&selectedTitle=3~150#H13. Accessed Dec 6, 2015.

1.1.5 Management of PD

PD is associated with both motor and non-motor complications. For non-motor complications management (e.g., anxiety, depression, impulse-control disorders, psychosis, cardiovascular or urogenital disorders), each typical complication can have a corresponding pharmacologic and

non-pharmacologic management strategy.[44] The following section will focus on motor complications management in PD.

Currently, there is no cure for PD, and the current treatment goal is symptom control. There are a variety of management techniques that attempt to restore balance, reduce motor inhibitory control, and improve health-related quality of life (HRQoL) for PD patients. The management of PD can be divided into 3 categories — non-pharmacologic, pharmacologic, and surgical interventions.

1.1.5.1 Non-pharmacologic Management of PD

Although non-pharmacologic interventions cannot resolve the cardinal symptoms of PD, they may help maintain the overall functioning of PD patients. Exercise and physical therapy may help alleviate the pain due to muscular rigidity or flexed posture and improve balance and gait speed.[45] Because PD patients commonly experience speech and voice disorders, speech therapy may help them restore communication abilities.[46] Although no specific diet restrictions are required for PD patients, a high fiber diet is advised to prevent constipation while high-fat foods should be avoided as they may interfere with levodopa absorption by delaying gastric emptying.[47,48] In patients in an advanced phase of PD, dietary protein restriction may be considered since dietary neutral amino acids may compete with levodopa for intestinal absorption and blood-brain barrier transportation.[49]

1.1.5.2 Pharmacologic Treatment of PD

Pharmacotherapy remains the mainstream treatment for the management of PD. The current pharmacologic treatment of PD focuses on symptomatic therapy and cannot modify the disease progression. Because the medication treatment effect may diminish over time as the disease advances, how to optimize and implement medication treatment is critically important. Optimal control of PD with pharmacotherapy requires an individually tailored strategy, as well as monitoring the balance between continued efficacy and side effects.[50] The major PD medications for motor symptoms treatment can be categorized into the following classes according to different mechanisms: levodopa, dopamine agonists (DAs), monoamine oxidase B (MAO-B) inhibitors, amantadine, anticholinergic agents, and catechol-O-methyltransferase (COMT) inhibitors.[51]

(1) Levodopa

Levodopa, also known as L-dopa, is a prodrug of dopamine. It is metabolized by L-aromatic amino acid decarboxylate to dopamine after crossing the blood-brain barrier (BBB), and hence replaces the neurotransmitter deficiency.[50] Because levodopa can be extensively absorbed in the gastrointestinal tract and cause premature conversion of levodopa to dopamine outside of the brain, this may lead to nausea, vomiting, and orthostatic hypotension. To prevent the above symptoms, levodopa is usually administered in combination with a peripheral decarboxylase inhibitor — carbidopa.[50] The current available carbidopa-levodopa products in the United States include Sinemet®, Sinemet CR®, and Parcopa®. Although levodopa is an effective medication for PD management, patients may develop motor complications (e.g., motor

fluctuations, dyskinesia, and dystonia) after prolonged levodopa use.[50] Other common adverse effects associated with levodopa include nausea, vomiting, postural hypotension, somnolence, sleep attacks, dizziness, sedation, confusion, and a range of mental disorders (e.g., isolated hallucinosis, delusions, and psychosis).[50,52,53]

(2) Dopamine agonists

Dopamine agonists (DAs) bind and activate the post-synaptic dopamine receptors directly without metabolic conversion from other compounds.[50] DAs can be further divided into two groups — ergot and nonergot derivatives. Ergot derivatives used to treat PD include bromocriptine, lisuride (not available in the United States), and pergolide.[50,54] Though it is uncommon, ergot derivatives may have potential side effects such as fibrosis due to its affinity to both serotonin (5-HT_{2B}) and dopamine receptors.[50] In March 2007, pergolide was withdrawn from the market because of cardiac valvular fibrosis concerns.[55] Unlike ergot derivatives, nonergot derivatives have relatively safe profiles compared to ergot derivatives because of their low affinity to serotonin (5- hydroxytryptamine 2B receptor or 5-HT_{2B}) receptors.[50] Nonergot derivatives for PD treatment include ropinirole, and pramipexole, injectable apomorphine, and rotigotine transdermal patch. Because of a delivery mechanism problem, rotigotine patches were recalled in 2008, and were released back to the market after approval of the new formulation in 2012.[56,57] In general, DAs tend to cause similar side effects as levodopa. These include nausea, vomiting, somnolence, orthostatic hypotension, and psychiatric disorders (e.g., confusion, cognitive changes, hallucination, and delusion). Other side effects associated with DAs are edema of the lower extremities, sleep attacks, and impulse-control disorders (ICDs).[50]

Pramipexole, ropinirole, and rotigotine have been implicated in causing sleep attacks, which may result in dangerous consequences if patients are driving.[50] The ICDs in PD patients are hypothesized to be linked to dysfunction in the mesocorticolimbic dopaminergic pathway, and can be expressed through excessive gambling or shopping, hyper-sexuality, binge eating, and pathological collecting.[50]

(3) Monoamine oxidase B (MAO-B) inhibitors

Monoamine oxidase B (MAO-B) inhibitors prolong dopamine activation by blocking MAO-B, the major enzyme of dopamine degradation.[58] These medications include selegiline and rasagiline. Both selegiline and rasagiline can be used as monotherapy for patients with mild-to-moderate motor features in order to delay the use of carbidopa/levodopa or DAs.[58] MAO-B inhibitors can also be used as adjunctive treatment to boost the effect of carbidopa/levodopa or DAs for patients with advanced PD.[58] Some studies suggest that selegiline and rasagiline may have a neuroprotective effect against PD, yet more research is needed before this can be concluded.[58-62] MAO-B inhibitors are generally well tolerated with minor adverse reactions such as nausea, vomiting, dizziness, orthostatic hypotension, and dyskinesias.[63] There are also reported cases of impulse control disorders induced by rasagiline.[64,65] Because MAO-B inhibitors can also inhibit serotonin breakdown and activate 5HT receptors, co-administration with serotonergic agents should be avoided.[58,63]

(4) Catechol-O-methyltransferase (COMT) inhibitors

Catechol-O-methyltransferase (COMT) inhibitors, such as entacapone and tolcapone, indirectly increase dopamine availability by blocking methylation of levodopa.[58] The COMT inhibitors are usually used as adjunctive treatment with carbidopa/levodopa among PD patients who experience motor fluctuations.[58] The adverse events associated with COMT inhibitors are similar to those with increased dopaminergic stimulation, such as nausea and vomiting. Delayed-onset diarrhea has also been reported in COMT inhibitors use.[58] In addition, the use of tolcapone requires monitoring of liver function tests because its hepatotoxicity.[58]

(5) Anticholinergic agents

Anticholinergic agents were first introduced to PD treatment in the 1960s based on the concept that dopamine deficiency may cause subsequent imbalance between dopaminergic and cholinergic activity and result in PD symptoms.[58] Anticholinergic agents act by blocking the action of acetylcholine and have shown effective control of tremor in patients younger than 60 years.[58] Currently available anticholinergics for PD treatment include benztropine, biperiden, trihexyphenidyl, and procyclidine. The side effects of anticholinergics have limited their use in elderly patients. These include CNS-related adverse events (e.g., confusion, memory loss, and hallucinations) and peripheral antimuscarinic adverse events (e.g., dry mouth, constipation, and urinary retention).[58] Anticholinergics should be used with caution for PD patients with comorbid closed-angle glaucoma, dementia, or prostatic hypertrophy.[58]

(6) Amantadine

Although the mechanism of amantadine in PD treatment has not been fully elucidated, it appears that N-methyl-D-aspartate (NMDA) receptor blockade is involved and thus increases dopamine release.[58] Amantadine has shown its effectiveness in improving motor symptoms and carbidopa/levodopa-induced dyskinesia.[58] Amantadine may cause peripheral side effects (e.g., mottled skin, ankle edema), CNS effect (e.g., confusion, hallucinations), gastrointestinal symptoms, or corneal edema.[58] Because amantadine also has anticholinergic properties, caution should be taken when using this with other medications to avoid additive anticholinergic effects.[58]

1.1.5.3 Surgery and Other Treatments for PD

Surgical procedures may be advised for certain advanced PD patients with troublesome motor symptoms which cannot be controlled by the medications.[58] Currently, the main surgical practice for PD is deep brain stimulation (DBS) — a surgery that implants an electrode into the brain. The implanted electrode can control the motor symptoms and reduce dyskinesia by sending electrical impulses to certain parts of the brain, such as subthalamic nucleus, the globus pallidus, and the thalamus.[58] DBS is not recommended for PD patients who have comorbid psychiatric and cognitive problems.[58] Other treatments such as transplantation of stem cells and gene therapy are still under development.[58]

1.1.6 Guidelines for the Management of PD

Several clinical practice guidelines have been developed for the management of PD. These include guidelines published by the American Academy of Neurology (AAN), the European

Federation of Neurological Societies/the Movement Disorders Society (EFNS/MDS), the UK's National Institute for Health and Clinical Excellence (NICE), the Canadian Neurological Sciences Federation (CNSF), and the Scottish Intercollegiate Guidelines Network (SIGN). In general, the management of PD can be divided into two phases — early stage and late stage therapy. There is no universal first choice medication for these two phases.[45,66,67] Instead, the medications for PD management should be tailored for individuals, and are based on several factors such as the clinical characteristics, disease progression, lifestyle, and patient preference.[45,66,67]

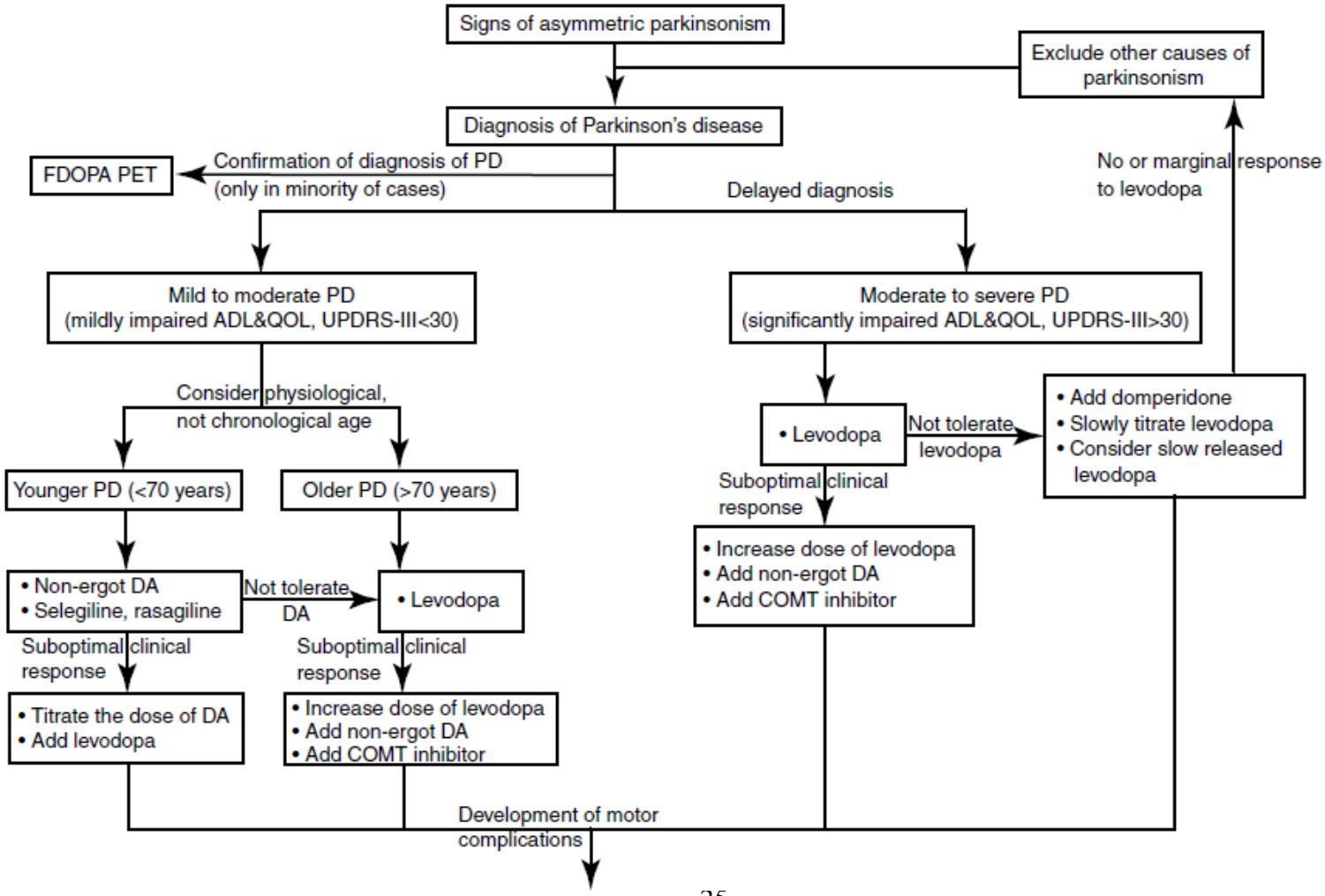
Early stage therapy is for PD patients who have not developed motor complications due to levodopa use. These patients are usually in their 3rd to 5th year after the PD diagnosis. The recommended main medications at this stage include DAs and levodopa. The choice of using a DA or levodopa depends on the age and symptom severity of the patient. DA monotherapy is usually advised for PD patients who are younger than 70 years old and have mild to moderate PD. Although levodopa is the most effective medication to control motor symptoms, the long-term use of levodopa may cause motor complications. Therefore, the delayed use of levodopa has been proposed, and thus levodopa is more often recommended for those aged older than 70 years with moderate to severe PD. Anticholinergics, MAO-B inhibitors, and amantadine are second-line treatment choices for PD management during the early stage.[45,66-68]

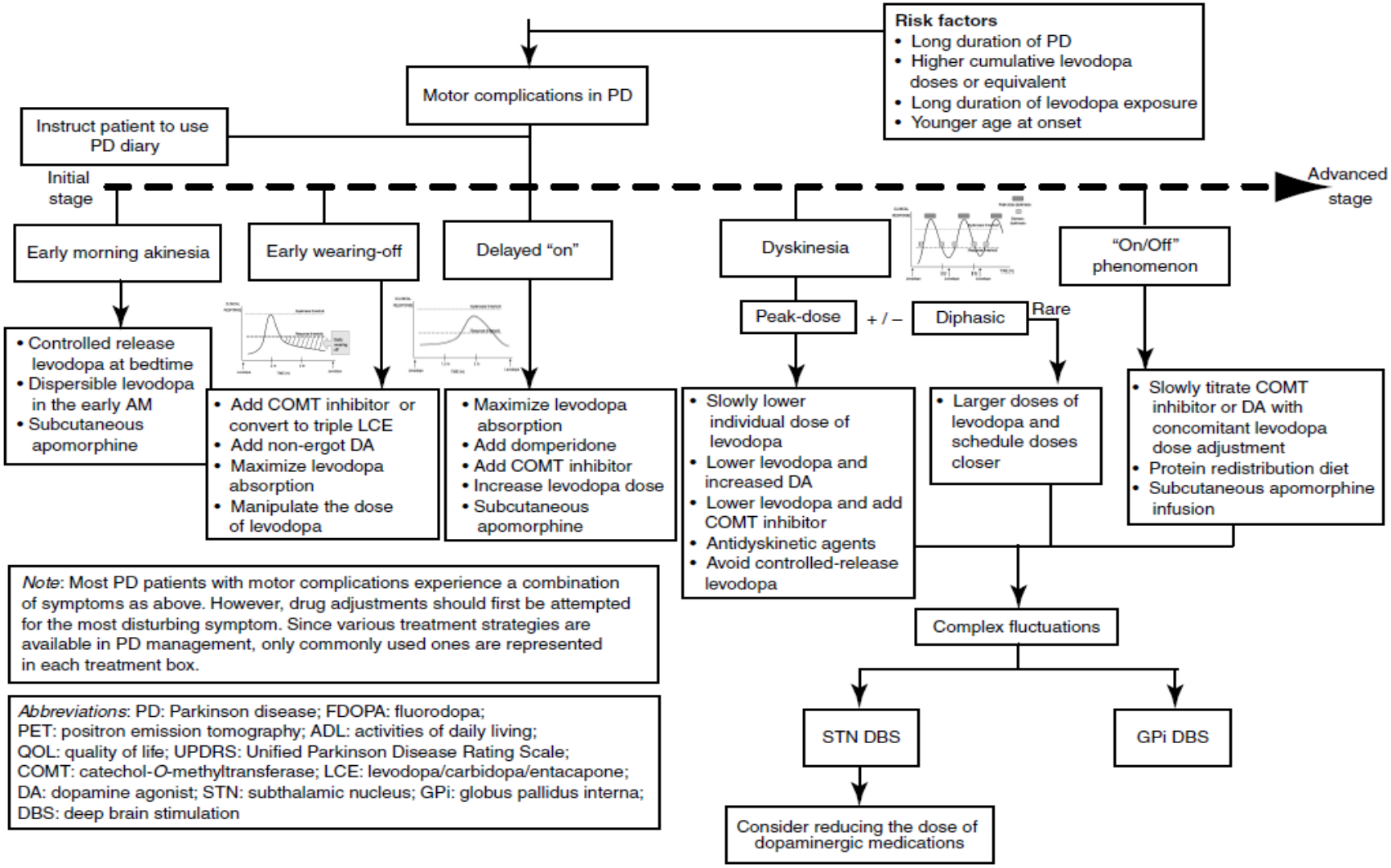
Late stage therapy is for patients who have developed motor complications after long-term use of levodopa. These patients usually have had a PD diagnosis for more than five years. At this stage, many patients experience a wearing-off effect (shorter duration of parkinsonian symptoms control), an on-off effect (unpredictable and abrupt fluctuation between controlled and worsen parkinsonian symptoms), or dyskinesia. In addition to levodopa, MAO-B inhibitors, COMT

inhibitors, or DAs can be added as the combination therapy to reduce motor fluctuations. Amantadine may be considered as an adjunct therapy with levodopa to reduce dyskinesia. For those PD patients with severe motor complications, apomorphine may be used to alleviate "off" time (parkinsonian symptoms worsen period). If pharmacotherapy still cannot control the motor symptoms and complex fluctuations, a surgical procedure can be considered.[45,66,67,69]

The following algorithm (Figure 2.2) illustrates the general concept of PD management:[70]

Figure 1.2 The treatment algorithm for PD





Source: Appendix: Treatment Algorithm for Parkinson's Disease. *International Neurology*: Wiley-Blackwell; 2010:681-682.

1.1.7 Antiparkinson Medication Taking Behavior in PD Patients

1.1.7.1 Antiparkinson Medication Adherence

The term, adherence (or compliance), refers to "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen."[71] Another term, persistence, can be defined as "the duration of time from initiation to discontinuation of therapy."[71] Adherence and persistence are two constructs used to describe a patient's medication taking behavior. Many factors may be associated with low medication adherence. These include forgetfulness, ineffectiveness of the medications, complexity of the treatment, side effects of medications, higher costs of the medications, polypharmacy, cognitive diseases, mental disorders, socioeconomics, and others.[72]

The identified factors associated with poor adherence include age greater than 65 years old, more comorbid diseases, PD regimen modifications and complexity, disease progression, cognitive impairment, and a lower level of family support. As PD progresses, patients may need more than one medication to control motor symptoms. Also, advanced PD patients may need to take dopaminergic agents more frequently than early PD patients (e.g., 3-4 times/day in early PD; 6-10 times/day in advanced PD). In addition, physicians modify PD regimens often to optimize treatment effect. All of these contribute to suboptimal adherence to PD medications.[73]

The reported non-adherence rate to PD medications ranged between 0 and 70 percent upon the methodology employed.[73] Leopold et al. used a computerized medication event monitoring system to measure adherence and found that 20.5% of the PD patients missed ≥ 3 doses per week.[74] For those studies using electronic monitoring bottles, 20% of PD patients were non-adherent (less than 80% of prescribed doses) in a single-center observational study, while a

lower non-adherence rate was observed (12.5%) in a multi-center observational study.[75,76] Valldeoriola et al. administered the Morisky-Green Test (MGT) questionnaire to capture adherence and reported a non-adherence rate of 40%.[77] Elm et al. compared adherence results measured by using a patient self-reported questionnaire versus using pill counts from two clinical trials. They observed a lower non-adherence rate using the pill count method compared to the MGT questionnaire (10% vs. 44%) among these PD patients.[78] Although the authors did not discuss the possible explanation of the different results generated by these two adherence measure approaches, they pointed out that the wording of the MGT questionnaire may be somewhat ambiguous and less reliable. Some other studies measured adherence by calculating the medication possession ratio (MPR) and defined non-adherence as having an MPR < 80%. Davis et al. reported a non-adherence (MPR < 80%) rate of 61% by assessing MPR from a claims database with 30 managed care plans in the US.[79] Kulkarni et al. tracked the MPR for PD medications in a Medicare population over five years and revealed that 67% of patients were non-adherent (MPR < 80%).[80] Tarrants et al. compared medication adherence across PD medications and reported an average non-adherence (MPR < 80%) rate of 46.5%.[81] Wei et al. calculated a 37.3% rate of non-adherence (MPR < 80%) using a 5% random sample of Medicare beneficiaries.[82] Richy et al. performed a retrospective database analysis and found 45.7% of the PD patients were non-adherent (MPR < 80%).[28] Persistence, or duration of therapy, was also reported in some studies. Tarrants et al. used a gap of 45 days and obtained a mean persistence of 133 days across all PD medications.[81] Wei et al. reported a mean persistence of 472 days using a 30-day gap.[83]

Several studies have reported that suboptimal adherence to PD medications is associated with higher healthcare resource utilization and costs as well as reduced quality of life in PD patients.[28,79,83] Using the USA PharMetrics claims database, Richy et al. observed a higher mean healthcare cost in non-adherent PD patients than those who were adherent ($84,949 vs. $77,499, $p < 0.0001$).[28] Davis et al. found similar patterns - non-adherent patients had extra mean medical (+$3,451, $P < 0.0001$) and total healthcare costs (+$2,383, $P = 0.0053$).[79] The retrospective study conducted by Wei et al. revealed that compared with non-adherent PD patients, adherent PD patients had lower rates of hospitalization (RR = 0.86), emergency room visits (RR = 0.91), skilled nursing facility episodes (RR = 0.67), home health agency episodes (RR = 0.83), and physician visits (RR = 0.93). The authors also found lower total health care expenditures in adherent PD patients than those who were non-adherent (-$2242, $p < 0.001$).[83]

1.1.7.2 Antiparkinson Medication Switch and Augmentation

In order to optimize the therapeutic effect, regimen modifications such as dose escalation, switching, or augmentation are common in PD treatment.[66] The regimen modification could result from ineffective dose, poor tolerance, or side effects of the PD treatment. However, previous studies also revealed that poor adherence may result in regimen modifications in PD treatment.[73] Physicians may not be aware that this ineffective treatment is due to non-adherence, and thus may prescribe unnecessary regimen modifications. One study demonstrated that prior non-adherence to antiparkinson medications was associated with subsequent antiparkinson drug regimen modifications.[84]

Two studies examined PD regimen modification patterns. Huse et al. analyzed the initial PD medication use among patients in employer-funded health insurance plans and Medicaid. Among the PD patients, 14.1% had augmentation of their initial PD therapy, while 2.7% switched their initial PD therapy — together, this accounted regimen modifications in 16.8% of PD patients. For PD patients who initiated monotherapy, levodopa users had the lowest rate of augmentation or switching compared to other medication users.[85] Wei et al. examined patterns of antiparkinson medication use in Medicare beneficiaries. The authors reported that 21.1% of the PD patients had augmentation and 16.4% had switches during the 19-month follow-up. In line with the Huse study, Wei et al. also found that PD patients who used levodopa had the lowest rates of switching or augmentation compared to other drug classes.[82]

1.1.7.3 Link between PD, Depression, and Antidepressants Use

Depression has been found to be more prevalent in PD patients than the general population.[86] Because depression and PD both involve neurobiological changes in the brain, several studies have been conducted to find the link between the two diseases. So far, the evidence has supported the hypothesis that depression may be a pre-symptom of PD.[7,87-89] Studies have also found that adequate depression treatment may not only control depression itself but may also reverse the negative impact brought about by depression in PD. Paumier et al. conducted a patient-level meta-analysis and reported that tri-cyclic antidepressants (TCAs) were associated with a delayed need of dopaminergic therapy among PD patients.[90] In addition, the Ricci study found that depressed PD patients receiving selective serotonin reuptake inhibitor (SSRIs) had improved motor function compared to those not receiving antidepressants.[91]

Kulisevsky et al. examined the motor changes among depressed PD patients using sertraline and found a similar result.[92] One randomized controlled double-blind trial also suggested that longer-term treatment for depression may improve certain cognitive domains.[93]

1.1.7.4 Summary of Section

PD is a prevalent neurodegenerative disorder in elderly people. It has been associated with a substantial humanistic and economic burden for PD patients. The symptoms of PD include motor- and non-motor symptoms, and both largely affect patients' daily function and quality of life. The main management of PD is pharmacologic treatment. However, due to the complexity of the regimen and the need for lifelong treatment, among other issues, suboptimal adherence to antiparkinson medications has been observed. Depression could be a pre-symptom of PD. A detailed discussion of depression in PD patients is presented in the next section.

1.2 Section 2: Depression in PD

1.2.1 Epidemiology and Pathophysiology of Depression in PD

Depression is a common non-motor symptom of PD, affecting roughly 20 to 50% of PD patients.[94] The wide range of reported prevalence and incidence rates is due to the methodology to identify depression and the patient population. Generally, higher prevalence rates were observed when using depression rating scales than using diagnostic criteria (the Diagnostic and Statistical Manual for Mental Disorders (DSM) or the International Classification of Diseases (ICD) codes) to capture depression in PD patients. Lower prevalence rates were found in studies

analyzing a general ambulatory population compared with outpatient or inpatient settings. The reported prevalence of depression also varied according to the severity of depression. A systematic review concluded that the weighted mean prevalence of depression in PD patients was 17% for major depressive disorder, 22% for minor depression, and 13% for dysthymia. Those who had clinically relevant-depressive symptoms accounted for 35% of the PD patients.[86] Similarly, other recent studies have shown the prevalence rate ranged between 30 to 35% for clinically-relevant depression in PD patients.[95] One study also observed that among PD patients, 36.3% were diagnosed with minor depression while 12.9% were diagnosed with major depression.[96] Another factor associated with some dissimilarity in the reported prevalence of depression may be attributed to method used to identify depression. The studies with structured interviews for DSM criteria reported higher prevalence in major depressive disorders than those without structured interviews (19% vs. 7%).[86] Factors associated with depression prevalence among PD patients included autonomic symptoms, motor fluctuations, severity and frequency of symptoms, staging of the disease, as well as PD onset and duration.[97] Some studies investigated the incidence rate of depression in PD patients. Aarsland et al. reviewed articles before 2011 and found the annual incidence rates for the two largest studies were 2.6 and 13.0%. Both older age and longer duration of PD were reported to be risk factors associated with a higher incidence of depression in PD. [95]

Although the etiology of depression in PD remains uncertain, research suggests that both psychosocial and neurobiological factors may be involved.[98,99] Receiving the diagnosis of PD can be a stressful life event to patients. They may proceed through different emotional reactions such as sadness, anger, fear, and demoralization when coping with a PD diagnosis as well as its

associated disability and symptoms, which may contribute to the development of depression.[99,100] However, one study compared depression symptom severity between PD patients and non-PD patients with other chronic disabling diseases not involving loss of endogenous neurotransmitters. The result showed PD patients had more severe depression symptoms than the non-PD patients with other functional disabilities, which might indicate that disability is not the sole factor that accounts for depression in PD.[101]

In addition to the psychosocial aspects, neurobiological factors may also play a role in depression in PD. The onset of depression is not parallel with the onset of motor disturbance in PD. In fact, depression usually occurs years before a PD diagnosis and has been considered as either a risk factor or a prodromal symptom.[102] Besides the degeneration of midbrain dopaminergic neurons, PD may affect noradrenergic and serotonergic neurons, which in turn regulate reward and mood.[98] Some studies showed that PD patients with depression had greater loss of striatal dopamine transporters and white matter within the cortical-limbic network than non-depressed counterparts. Different cerebral glucose metabolic and frontal perfusion features were also found between PD patients with and without depression.[95] These findings suggest a correlation between neurodegeneration and depression in PD.[98]

Mood changes leading to suicide attempts, mania, aggression, and depression are reported complications after deep brain stimulation (DBS) treatment. Post-DBS mood changes were more likely to be observed after subthalamic nucleus (STN) DBS, but not after thalamic and pallidal DBS. Researchers have suggested that mood changes may result from serotonin inhibition in neuronal circuits caused by STN stimulation. However, mood changes could also be due to the stimulation spreading to adjacent pathways mediating non-motor functions as well as improper

electrode placement or contact. Alternatively, depression could exist before DBS and occur when reducing dopaminergic medication dose after DBS.[98,99]

Genetic susceptibility to depression has been postulated because a higher rate of depression was observed in non-PD first-degree relatives of PD patients with depression.[89] The reported genes that may be associated with depression in PD include SLC6A4 and n LRRK G2019S mutations.[103-105] Nonetheless, further research is needed to verify the relationship between genetic determinants and depression in PD.[98]

1.2.2 Diagnosis of Depression in PD

The main clinical features of depression are depressed mood and loss of interest. Depressed patients may also present somatic or vegetative symptoms (e.g., psychomotor retardation, poor appetite, decreased energy or fatigue, sleep disturbance, pain, trouble concentrating, decreased memory, and loss of libido). However, many of these features may overlap with PD symptoms, and thus make it challenging to differentiate depressed from non-depressed PD patients.[94] The Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria have been widely used to diagnose depression. But due to the overlapping symptoms of depression and PD, the National Institute of Neurological Disease and Stroke (NINDS)/National Institute of Mental Health provide following recommendations of diagnosing depression in PD: 1) All symptoms should be counted toward the assessment of depression regardless of the presumed causality of the symptoms (i.e., inclusive approach). 2) Generally, the diagnosis of depression requires patients fulfilling the core criterion of depression—depressed mood or

anhedonia. But only depressed mood should be considered as the core feature when evaluating depression in PD because apathy or anhedonia may also occur in PD. 3) Practitioners should evaluate patients during "on-state" since drug-related motor fluctuations are associated with mood changes. 4) To avoid the unreliable results reported by PD patients with cognitive impairment, information from caregivers or individuals who know the patient well should be included.[106] In addition to the recommendations above, routine laboratory tests should be performed to rule out the systemic conditions such as deficiencies of testosterone, vitamin B_{12}, hypoglycemia, or hypothyroidism.[99]

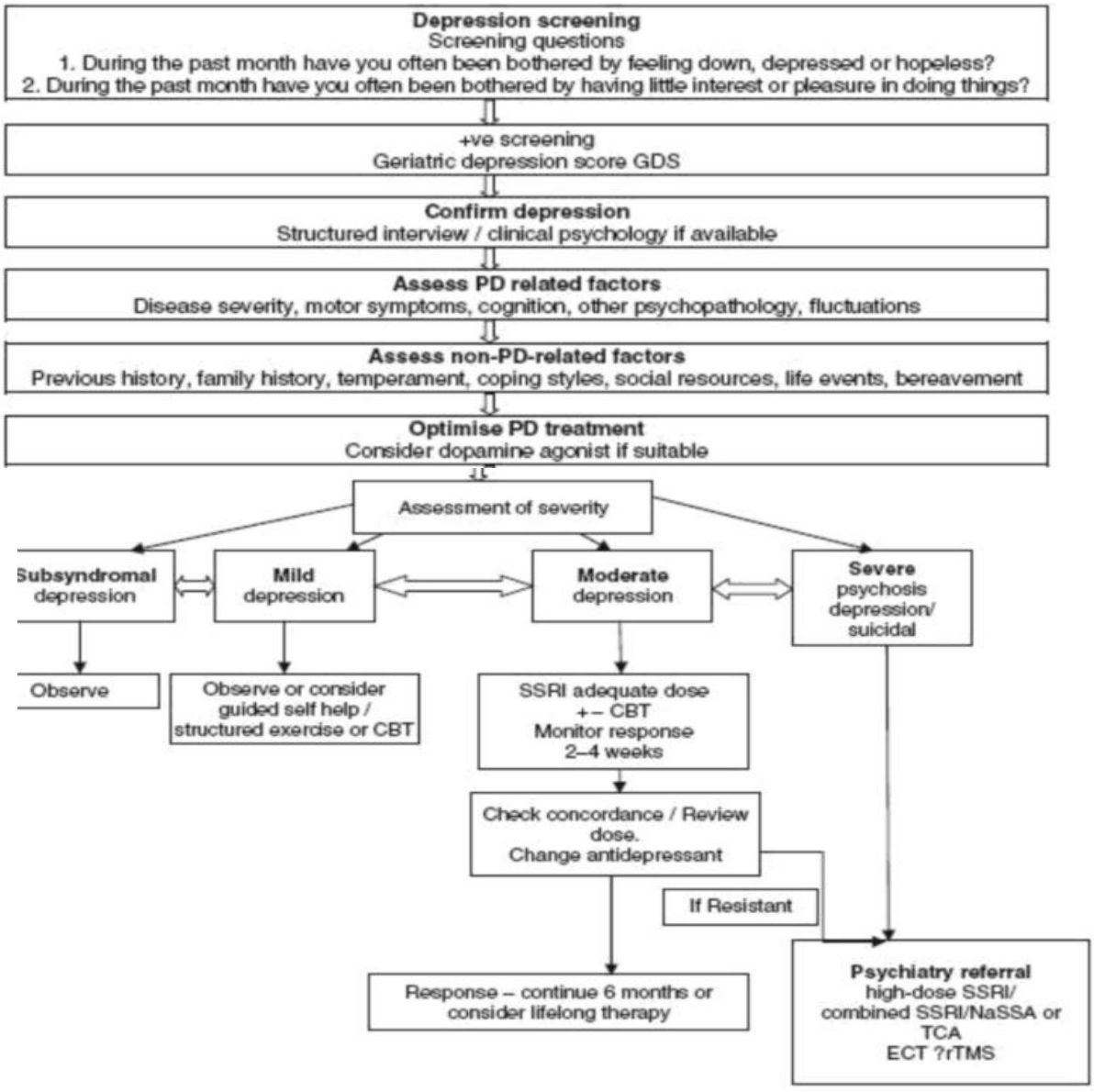
Psychiatric rating scales should also be used to assist in the diagnosis of depression.[107,108] However, because these rating instruments were not specifically designed for PD patients and the overlapping symptoms, the cutoff points might need to be adjusted.[94] Also, the American Academy of Neurology and the Movement Disorders Society Task Force both examined the validity of using these instruments in PD patients and concluded that the Beck Depression Inventory (BDI) and the Hamilton Depression Rating Scale (HAM-D) were valid when screening for depression in PD.[107,108] A recent study reviewed thirteen rating scales used in depression assessment for PD patients. The HAM-D and the Geriatric Depression Scales (GDS) were suitable for screening and evaluating the severity of depression in PD. The Cornell Scale for Depression in Dementia (CSDD) could be considered for patients with comorbid dementia. Several instruments had also shown valid and reliable psychometric properties in PD patients with depression, including the Hospital and Anxiety Depression Scale-Depression subscale (HADS-D), Hamilton Depression Inventory (HDI), the BDI, and the Montgomery–Asberg Depression Rating Scale (MADRS).[109]

1.2.3 Management of Depression in PD

Before treating depression in PD, practitioners should review all medications that a PD patient is taking, then identify and eliminate any adverse influence on mood caused by current medication use.[99] Practitioners should confirm that the antiparkinson medications have been optimized because depressive symptoms may result from the motor "off-and-on" fluctuations.[99] The management of depression in PD depends on the severity of depression. Counseling and cognitive behavioral therapy (CBT) are recommended for PD patients with mild depression while pharmacologic treatment is appropriate for those with moderate to severe depression. Electroconvulsive therapy (ECT) may also be considered when PD patients have severe and medication-resistant depression.[94,99] One meta-analysis examined both pharmacologic and non-pharmacologic intervention to treat depression in PD. The authors concluded that both selective serotonin reuptake inhibitors (SSRIs) and cognitive behavioral therapy (CBT) have shown their efficacy in improving depression among PD patients.[110] The general strategy for treating depression in PD is depicted in Figure 1.3 and

.[99,111] The timing of starting TCAs is different between the two proposed management algorithms. Although there is more evidence for supporting the efficacy of TCAs than SSRIs, TCAs are associated with less tolerability and more side effects. It could be possible that the algorithm from the book — "Principles and Practice of Geriatric Psychiatry"[111] provides more general recommendations based on the common comorbid conditions and potential adverse effects of TCAs for this population, while the algorithm proposed by Chen and Marsh[99] focuses more on the efficacy data based on their reviewed evidence-based medicine (EBM) studies.

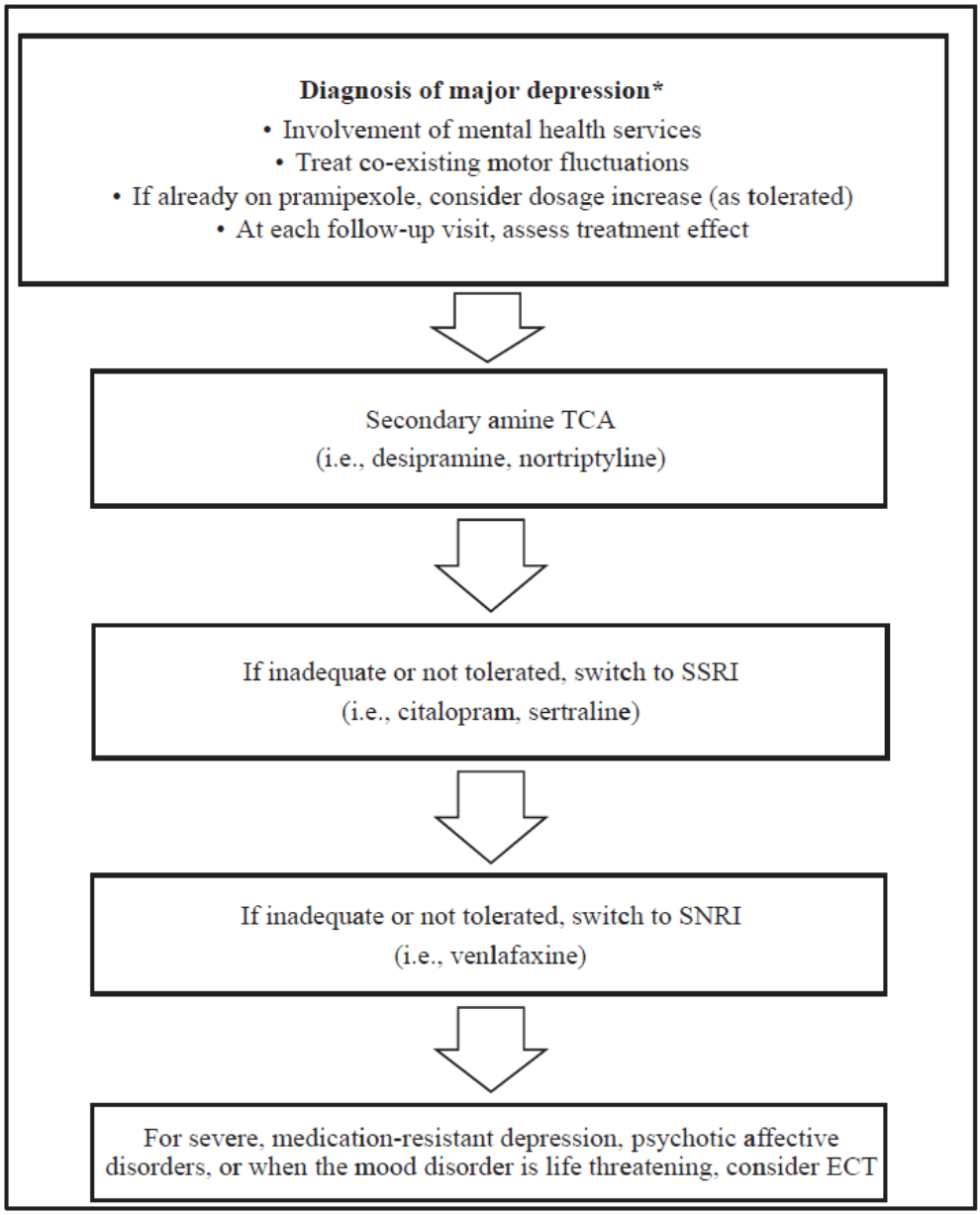
Figure 1.3 Algorithm of managing depression in Parkinson's disease



PD: Parkinson's disease; GDS: Geriatric Depression Scales; CBT: cognitive behavioral therapy; ECT: electroconvulsive therapy; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; NaSSA: noradrenergic and specific serotonergic antidepressants; TCA: tricyclic antidepressant; rTMS: repetitive transcranial magnetic stimulation.

Source: Abou-Saleh MT, Katona C, Kumar A. *Principles and practice of geriatric psychiatry.* John Wiley & Sons; 2011.

Figure 1.4 Management of depression in Parkinson's Disease



*For mild or subsyndromal depression, treatment can be deferred with watchful waiting and ongoing follow-up for symptom worsening. ECT: electroconvulsive therapy; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant.
Source: Chen JJ, Marsh L. Depression in Parkinson's disease: identification and management. *Pharmacotherapy.* Sep 2013;33(9):972-983.

1.2.3.1 Pharmacologic Treatment

A considerable amount of information regarding efficacy and safety of antidepressants can be found in the literature. However, only a few studies examined the efficacy of antidepressants in PD patients with depression. Results from these studies were inconclusive and most of them suffered from methodological difficulties, such as small sample sizes and using open-label trials.[107,112,113] Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) are commonly used in treating depression in PD patients. Other antidepressants commonly used for treating depression in PD include serotonin norepinephrine reuptake inhibitors (SNRIs), pramipexole, bupropion, nefazodone, and trazodone.[94,99] Amitriptyline is recommended by the American Academy of Neurology for treating depression in PD, while pramipexole, nortriptyline, and desipramine are recognized as efficacious or likely efficacious by the Movement Disorders Society.[114,115]

(1) Selective Serotonin Reuptake Inhibitors (SSRIs)

The SSRIs block the reuptake of serotonin (5-HT), resulting in a sustained level of serotonin at the synapse. The SSRIs are commonly prescribed to PD patients because they are well tolerated and have lower side effect profiles. Medications in this class for depression in PD include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline.[99] Inconsistent results have been published with respect to the efficacy of antidepressants in treating depression in PD. Escitalopram, fluoxetine, fluvoxamine, sertraline, citalopram, and paroxetine have shown efficacy in reducing depressive symptoms in PD patients.[98,99] However, two meta-analysis studies compared the efficacy of SSRIs to placebo and reported that SSRIs might be no

more effective than placebo. But after removing one controversial article due to its dosage and definition of major depression, the meta-analysis conducted by Rocha et al. found SSRIs were superior to placebo.[116,117] Despite the lack of consistent empirical evidence regarding their efficacy, SSRIs were still the most commonly prescribed medication for treating depression in PD.[118] This may be because SSRIs are less likely to have adverse events such as drowsiness, constipation, urinary retention, and hypotension compared to other antidepressants.[99] Currently, no one SSRI agent has demonstrated superior efficacy to another.[94,119] But fluoxetine, fluvoxamine, and paroxetine are more likely to cause potential drug interactions through the inhibition of cytochrome P450.[99] There is concern that SSRIs may worsen motor symptoms of PD. Nevertheless, previous studies failed to establish the association between SSRIs and worsening motor function in PD patients.[99,119-121] Although the drug interaction between SSRIs and MAO-B inhibitors (such as selegiline and rasagiline) is very rare, concurrent administration should be avoided.[122]

(2) Tricyclic antidepressants (TCAs)

The TCAs inhibit the reuptake of both norepinephrine and serotonin at the synaptic cleft. Despite their potency of blocking muscarinic, α1 adrenergic, and histamine receptors, TCAs may be prescribed to treat depression in PD patients.[99,118] Several TCAs have shown the efficacy of treating depression in PD, including amitriptyline, imipramine, desipramine, and nortriptyline. The meta-analysis conducted by Rocha et al. concluded that TCAs were more efficacious than SSRIs in depression treatment among PD patients.[116] However, TCAs are not usually recommended as the first-line option for depression in PD because of their unfavorable side

effect profiles. TCAs are associated with the potential risk of exacerbating the pre-existing non-motor symptoms such as orthostatic hypotension, cognitive dysfunction, constipation, and urinary retention. Monitoring of serum levels and electrocardiograms should be performed for patients taking TCAs, due to associated cardiac conduction problems.[99] Currently, there is no evidence suggesting that the efficacy of one TCA agent is superior to another. But tertiary amine TCAs (e.g., amitriptyline and imipramine) are associated with more potent antimuscarinic side effects than secondary amine TCAs (e.g., desipramine and nortriptyline).[99]

(3) Other antidepressants

Bupropion is an antidepressant that inhibits both dopaminergic and norepinephrine reuptake. The efficacy of using bupropion to treat depression in PD has not been confirmed. Serotonin norepinephrine reuptake inhibitors (SNRIs) can also be used for depression in PD. These include desvenlafaxine, duloxetine, milnacipran, and venlafaxine. Previous studies showed that duloxetine and venlafaxine were well tolerated and ameliorated depressive symptoms among PD patients.[123,124] Rocha et al. also concluded that SSRIs and SNRIs might be similarly efficacious in treating depression in PD.[116] Other antidepressants that have been used for treating depression in PD are mirtazapine, moclobemide, selegiline, atomoxetine, reboxetine, nefazodone, trazodone, and vilazodone. Some of these antidepressants have limited evidence of their efficacy in treating depression in PD, therefore further research may be warranted to make definitive conclusions.[99]

(4) Dopamine Agonists

Several studies examined the antidepressant properties of dopamine agonists in PD patients and mixed results were reported.[125-128] Some studies found that pramipexole improved depressive symptoms and was efficacious in treating depression among PD patients.[125,126,128] One RCT even concluded that pramipexole may be an alternative option for treating depression in PD.[127] Another study also reported that a rotigotine transdermal system may improve depressive symptoms in PD.[129] However, some of the efficacy studies did not use DSM or ICD criteria to capture depression diagnosis and the actual improvement of depressive symptoms might not be clinically significant.[127,128] Additionally, other studies did not find the improvement in depression symptoms among PD patients using pramipexole.[130,131]

1.2.3.2 Non-pharmacologic Treatment

Cognitive behavioral therapy (CBT) is a psychosocial intervention that can be used to treat depression in PD patients. A CBT package includes the structural training of behavioral activation, exercise, sleep hygiene, relaxation techniques, cognitive restructuring, and caregiver support.[98] CBT can be used as an adjunctive treatment to pharmacotherapy in treating mild-to-moderate depression in PD, and several studies have shown its efficacy in improving depressive symptoms.[132,133] Electroconvulsive therapy (ECT) is thought to stimulate various neurotransmitters and has shown its efficacy in treating depression among PD patients.[98,99,134] However, due to its main side effect — cognitive impairment and occasional delirium — ECT is usually reserved for patients with severe and medication-resistant depression.[99] Another less invasive intervention than ECT is the repetitive transcranial magnetic stimulation (rTMS).

However, further studies are still needed to evaluate and confirm its efficacy in treating depression in PD.[99]

1.2.4 Impact of Depression on PD

Several studies have reported that depression may adversely affect the course of PD as it may have a negative influence on motor function, cognitive performance, daily functioning, medication compliance, quality of life, healthcare resource utilization, and costs among PD patients.[135-139] Using the Unified Parkinson's Disease Rating Scale (UPDRS), Papapetropoulos et al. observed that depressed PD patients had greater disease severity and poorer motor function than non-depressed counterparts.[135] A subsequent longitudinal study conducted by Ng et al. found similar results. The authors reported that depression might be associated with worse motor and cognitive functions.[138] Pontone et al. examined the impact of depression on disability in PD and concluded that patients with symptomatic depression had greater disability than those without.[140]

Depression can affect medication taking behavior in PD patients. Several studies have identified depression as a predictor of non-compliance to antiparkinson medications. Richy et al. used the US PharMetrics claims database to examine non-compliance (defined as without PD-related medication for > 20% of the follow-up period) among commercially insured population. The authors found that depression was significantly associated with non-compliance in PD patients (No depression diagnosis [reference=depression diagnosed]: OR = 0.79, 95% CI = 0.74-0.85, $p < 0.001$)[28] Another UK observational study defined compliance as the percentage of dose taken compared to the total dose prescribed, and also reported similar results.[75] In addition, one

previous study using a 5% sample of the 2006-2007 Medicare database revealed that depressed PD patients were more likely to have regimen modifications (defined as switching and/or augmentation) of their antiparkinson medications.[84]

Depression has also been linked with lower health-related quality of life (HRQoL) among PD patients. Duncan et al. conducted a prospective longitudinal study and used the Parkinson's Disease Quality of Life Questionnaire (PDQ-39) to measure HRQoL. The authors found depression was associated with lower HRQoL, and among other non-motor symptoms, depression had the greatest negative impact on HRQoL in PD patients.[139] Using the Health Utilities Index Mark 3 (HUI3), Jones reported that the overall HUI3 scores among respondents with depression were lower than those without depression (0.20 vs. 0.49, $p < 0.05$).[141] Shearer et al. analyzed the data from a community-based prospective study and captured HRQoL using the EQ-5D. They observed the health state value among PD patients with depression was reduced by 0.12 (on a scale of 0 to 1), which indicated that depression had a negative impact on HRQoL.[142]

Only a few studies investigated healthcare resource utilization among depressed PD patients in the literature. Chen et al. conducted a cross-sectional study that assessed utilization by male veterans with PD during fiscal year 2002 using the Department of Veterans Affairs (VA) national databases. The authors found that compared with non-depressed PD patients, depressed PD patients had more frequent medical (OR = 1.34, 95% CI = 1.25-1.44, $p < 0.001$) and psychiatric hospitalizations (OR = 2.14, 95% CI = 1.83-2.51, $p < 0.001$), as well as more total outpatient visits (mean number of visits: 27.0 vs. 15.9, $p < 0.001$).[136] Qureshi et al. also used the VA national databases and retrospectively assessed utilization by male PD patients for 12 years. They reported that depressed PD patients were more likely to have outpatient medical/surgical

visits (7.7 vs. 5.0, p = 0.004), mental health visits (1.2 vs. 0.2, p = 0.006), and neurology visits (8.3 vs. 6.1, p = 0.08) than those non-depressed PD patients.[143] In addition, depression has been recognized as one of the cost-driving factors in PD patients. Winter et al. conducted a longitudinal study in Germany. During the 12-month follow-up period, they found that depression was significantly associated with higher out-of-pocket costs among PD patients (b = €420, 95% CI = €34-€1,208, p < 0.05).[144] Another British study evaluated costs among community PD patients and their regression model revealed that depression was a significant predictor of higher costs (b = £257, 90% CI = £33-£482 for each unit increase in the geriatric depression score, p <0.05]).[145] When examining the costs difference between depressed and non-depressed PD patients, one German study analyzed the PD-related medication costs and found that depressed PD patients had lower PD-related medication costs than those who were non-depressed (€6.6/day vs. €7.6/day, p < 0.05).[146] However, the authors did not discuss a possible explanation for the observed lower PD medication costs among depressed PD patients.

1.2.5 Antidepressants Use in PD Patients with Comorbid Depression

There is little information regarding antidepressant use in treating depression among PD patients in "real-world" settings. One early study used a questionnaire to capture antidepressant use in PD and found that 26% of the PD patients received medications for depression.[147] Gony et al. analyzed the data from the French Pharmacovigilance Database and reported that 21.7% of the PD patients received antidepressants.[120] Previous studies also revealed that the majority of depressed PD patients did not receive any antidepressant. Weintraub et al. examined 100 patients in a PD center and observed that 65% of those who met the depression disorder criteria did not

receive any antidepressant.[148] Using a French cross-sectional survey, Nègre-Pagès et al. found among the PD patients with possible/probable depressive symptoms, only 19% of them used antidepressants.[149] Another cross-sectional study also reported that the proportions of PD patients not receiving any antidepressants but having mild or moderate-to-severe depressive symptoms were 83.3% and 75%, respectively.[150] SSRIs were found to be more commonly used than TCAs in treating depression among PD patients. The Gony study found that SSRIs were used most often (51% of the time), followed by TCAs (41% of the time) in France. Chen et al. used VA data in the US to examine the antidepressants use between patients with and without PD. Their results showed that among PD patients with depression, a high proportion of patients received SSRIs (62.9%) while only 7.4% of the patients received TCAs. The most commonly prescribed antidepressant was sertraline (25.9%), followed by citalopram (19.8%) and paroxetine (12.6%).[118] Another study published only in abstract form analyzed the data from the UK General Practice Research Database. The authors reported that among PD patients with depression, 21% of them used amitriptyline, 19% used fluoxetine, 14% used citalopram, 7% used venlafaxine, and 5% used mirtazapine.[151]

1.2.5.1 Summary of Section

The prevalence of depression in PD remains high. Depression is a common non-motor symptom in PD caused by both psychosocial and neurobiological factors. Depression affects not only quality of life and the daily functioning among PD patients, but also the course of PD (motor and cognitive functions) and healthcare resource utilization. TCAs and SSRIs are two main

medications for depression in PD, but little has been reported regarding antidepressant taking behaviors among PD patients.

1.3 Section 3: Study Rationale, Objectives, and Hypotheses

1.3.1 Study Rationale

As mentioned earlier in Section 1 and Section 2, PD is a prevalent neuropsychiatric disease associated with a significant humanistic and economic burden. Depression is a common non-motor symptom in PD. The evidence has shown that psychosocial factors may not be the main determinant in comorbid depression. Neurobiological factors may also play a role. Depression greatly impacts PD. Previous studies have revealed that compared to the non-depressed PD patients, depressed PD patients are more likely to have worse motor function, cognitive impairment, disability, reduced quality of life, and higher healthcare resource utilization and costs. Because of the potential correlation between depression in PD and noradrenergic and serotonergic neuron degeneration, antidepressant use in depressed PD patients is an important consideration due to its potential disease-modifying effects in PD. Several studies have revealed that use of antidepressants can help control depression in PD and even ameliorate motor and cognitive dysfunction in depressed PD patients.[90-93] Adherence to antidepressants may also be associated with the outcomes of the comorbid disease. One previous study reported that depressed patients who were adherent to antidepressants had lower medical costs associated with their other comorbid diseases such as coronary artery disease, dyslipidemia, and diabetes mellitus.[152] Previous studies provide some information regarding the impact of depression on

PD. However, studies on the effects of better adherence to antidepressants and better control of depression on healthcare resource utilization and costs among PD patients are lacking. In addition, there is a gap in the literature concerning antidepressant utilization patterns such as adherence, persistence, as well as regimen modifications, such as switching, and changing to combination therapy, of antidepressants in depressed PD patients.

1.3.2 Purpose of Study

This study aimed to examine antidepressant use patterns (adherence, persistence, regimen modifications — switching and changing to combination therapy) and evaluate the associated healthcare resource utilization and costs in PD patients with comorbid depression.

1.3.3 Objectives and Hypotheses

The study objectives and hypotheses are:

1) To describe baseline demographic and clinical characteristics among PD patients with antidepressant treatment
2) To describe antidepressant use patterns (index antidepressant type, adherence, persistence, switching, combination therapy) among PD patients with depression
3) To identify the factors associated with being adherent to antidepressant (dichotomous variable, Yes/No) among PD patients with depression

   H_{3a}: **Age** is not associated with being adherent to antidepressants after controlling for other covariates

H_{3b}: **Being female** is not associated with being adherent to antidepressants after controlling for other covariates

H_{3c}: **Geographic region** is not associated with being adherent to antidepressants after controlling for other covariates

H_{3d}: **Having anxiety** is not associated with being adherent to antidepressants after controlling for other covariates

H_{3e}: **Having psychosis** is not associated with being adherent to antidepressants after controlling for other covariates

H_{3f}: **Having dementia** is not associated with being adherent to antidepressants after controlling for other covariates

H_{3g}: **The CCI score** is not associated with being adherent to antidepressants after controlling for other covariates

H_{3h}: **Having regimen modification** (switching or combination therapy) of the index antidepressant is not associated with being adherent to antidepressants after controlling for other covariates

H_{3i}: **Pre-index PD-related total costs** are not associated with being adherent to antidepressants after controlling for other covariates

4) To identify the factors associated with antidepressant persistence among PD patients with depression

H_{4a}: **Younger age** is not associated with persistence after controlling for other covariates

H_{4b}: **Being female** is not associated with persistence after controlling for other covariates

H_{04c}: **Geographic region** is not associated with persistence after controlling for other covariates

H_{4d}: **Having anxiety** is not associated with persistence after controlling for other covariates

H_{4e}: **Having psychosis** is not associated with persistence after controlling for other covariates

H_{4f}: **Having dementia** is not associated with persistence after controlling for other covariates

H_{4g}: **The CCI scores** is not associated with persistence after controlling for other covariates

H_{4h}: **Having regimen modification** of the index antidepressant is not associated with persistence after controlling for other covariates

H_{4i}: **The pre-index PD-related total cost** is not associated with persistence after controlling for other covariates

5) To determine if <u>all-cause</u> healthcare resource utilization differs significantly between adherent and non-adherent antidepressants users while controlling for covariates.

H_{05a}: There is no significant difference in **number of outpatient visits** between adherent and non-adherent antidepressants users while controlling for covariates

H_{05b}: There is no significant difference in **number of nursing facility days billed** between adherent and non-adherent antidepressants users while controlling for covariates

H_{05c}: There is no significant difference in **number of inpatient visits** between adherent and non-adherent antidepressants users while controlling for covariates

H_{05d}: There is no significant difference in **number of emergency room (ER) visits** between adherent and non-adherent antidepressants users while controlling for covariates

6) To determine if PD-related healthcare resource utilization rates differs significantly between adherent and non-adherent antidepressants users while controlling for covariates.

   H_{06a}: There is no significant difference in **number of PD-related outpatient visits** between adherent and non-adherent antidepressants users while controlling for covariates

   H_{06b}: There is no significant difference in **PD-related number of nursing facility days billed** between adherent and non-adherent antidepressants users while controlling for covariates

   H_{06c}: There is no significant difference in **number of PD-related inpatient visits** between adherent and non-adherent antidepressants users while controlling for covariates

   H_{06d}: There is no significant difference in **number of PD-related ER visits** between adherent and non-adherent antidepressants users while controlling for covariates

7) To determine if all-cause healthcare costs differ significantly between adherent and non-adherent antidepressants users while controlling for covariates.

   H_{07a}: There is no significant difference in **all-cause outpatient costs** between adherent and non-adherent antidepressants users while controlling for covariates

   H_{07b}: There is no significant difference in **all-cause nursing facility costs** between adherent and non-adherent antidepressants users while controlling for covariates

   H_{07c}: There is no significant difference in **all-cause inpatient costs** between adherent and non-adherent antidepressants users while controlling for covariates

   H_{07d}: There is no significant difference in **all-cause ER costs** between adherent and non-adherent antidepressants users while controlling for covariates

H_{07e}: There is no significant difference in **all-cause pharmacy costs** between adherent and non-adherent antidepressants users while controlling for covariates

H_{07f}: There is no significant difference in **all-cause total costs** between adherent and non-adherent antidepressants users while controlling for covariates

8) To determine if PD-related healthcare costs differ significantly between adherent and non-adherent antidepressant users while controlling for covariates.

H_{08a}: There is no significant difference in **PD-related outpatient costs** between adherent and non-adherent antidepressants users while controlling for covariates

H_{08b}: There is no significant difference in **PD-related nursing facility costs** between adherent and non-adherent antidepressants users while controlling for covariates

H_{08c}: There is no significant difference in **PD-related inpatient costs** between adherent and non-adherent antidepressants users while controlling for covariates

H_{08d}: There is no significant difference in **PD-related ER costs** between adherent and non-adherent antidepressants users while controlling for covariates

H_{08e}: There is no significant difference in **PD-related pharmacy costs** between adherent and non-adherent antidepressants users while controlling for covariates

H_{08f}: There is no significant difference in **PD-related total costs** between adherent and non-adherent antidepressants users while controlling for covariates

CHAPTER 2: METHODOLOGY

2.1 Institutional Review Board (IRB) Approval

The study was submitted and reviewed by the Institutional Review Board (IRB) Board of The University of Texas at Austin. An exempt study with a waiver of informed consent was granted because this study only involved de-identified patient-level data (IRB protocol number: 2016-06-0013).

2.2 Study Design and Data Source

This study was a retrospective cohort study using administrative claims data from the Humana database, for years 2007 to 2010. This database contains medical, pharmacy, enrollment, and partial laboratory results data for fully insured patients with commercial and Medicare health plans. Detailed demographic and enrollment data were available. Information regarding physician office visits, outpatient visits, hospital admissions, procedures, and diagnosis codes were captured from the medical claims database. Information regarding outpatient prescription fills such as quantity of the medication fill, dispense date, and the National Drug Codes (NDCs) was extracted from the pharmacy database. The Humana database includes over 12 million individuals and more than 5 million Medicare Advantage Plan members in the US. It covers all census regions in the US, with predominance in the Midwestern and Southern regions. These data are de-identified and are fully compliant with the Health Insurance Portability and Accountability Act (HIPAA) regulations.

2.3 Inclusion Criteria

Patients who met the following criteria were included in the present study:

a) Table 2.1Received at least two study antidepressant prescriptions listed in Table 2.1 during the study period;[99,118]
b) Had a diagnosis of depression at any time in the medical claims during the study period. In order to be consistent with previous research, the following ICD-9-CM codes were used: mood disorder resulting from a general medical condition (293.83); major depressive disorder (296.2x and 296.3x); mood disorder, not otherwise specified (296.90); dysthymia (300.4); prolonged depressive reaction (309.1); depressive disorder, not otherwise specified (311);[118,153]
c) Had either 1) at least 2 diagnoses of PD (International Classification of Disease, Ninth Revision, Clinical Modification [ICD-9-CM] Code 332.0) on different dates from the 6-month pre-index period to 6 months after the index date, or 2) had one PD-related prescription (i.e., levodopa, carbidopa, dopamine agonist, monoamine oxidase type B inhibitor, or catechol-O-methyltransferase inhibitor, see Table 2.2) plus a diagnosis of PD within the 6-month pre-index period to 6 months after the index date[154];
d) Had continuous enrollment for at least 6 months before and 12 months after the index date;
e) Were covered by a Medicare Advantage plan; and
f) Were aged ≥ 65 years old at the index date

Table 2.1 List of antidepressants for depression in Parkinson's disease

Drug Class	Generic Names
Tricyclic Antidepressants (TCAs)	amitriptyline, imipramine, desipramine, nortriptyline, trimipramine, clomipramine, doxepin
Selective Serotonin Reuptake Inhibitors (SSRIs)	citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)	desvenlafaxine, duloxetine, milnacipran, venlafaxine
Others	bupropion, mirtazapine, nefazodone, trazodone, phenelzine, tranylcypromine

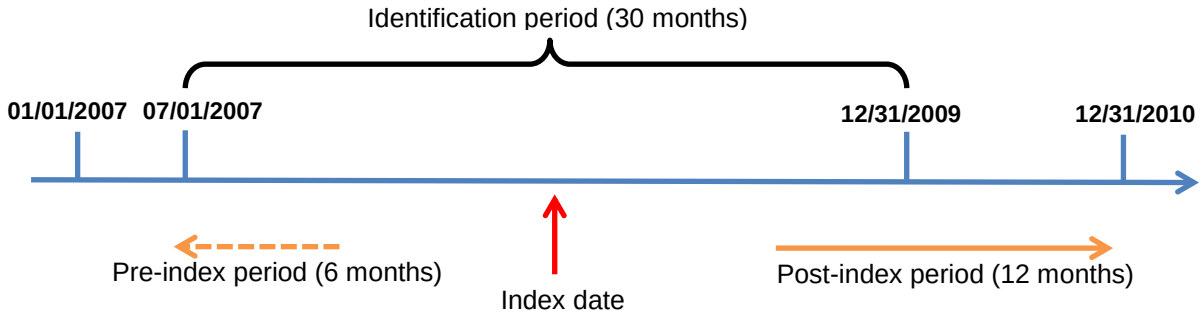
Table 2.2 List of antiparkinson medications

Drug Class	Generic Names
Anticholinergics	benztropine, biperiden, ethopropazine, procyclidine, trihexyphenidyl
Catechol-O-Methyltransferase (COMT) Inhibitors	tolcapone, entacapone
Amantadine	amantadine
Dopamine Agonists (DAs)	bromocriptine, cabergoline, pramipexole, ropinirole
Levodopa	levodopa/ carbidopa, levodopa/carbidopa/entacapone
Monoamine Oxidase B (MAO-B) Inhibitors	rasagiline, selegiline

2.4 Data Collection and Index Date

The Humana data from January 1, 2007 to December 31, 2010 were extracted for the present study. The index date was the date the patient was newly initiated on an antidepressant (AD) prescription (no AD 6 months prior) with a confirmatory diagnosis of depression during the identification period (July 1, 2007 to December 31, 2009; See Figure 2.1). Figure 2.1 provides an illustration of the data extraction and the study design timeline.

Figure 2.1 Data extraction and patient identification period



2.5 Study Variables

2.5.1 Dependent Variables

The dependent variables in the present study were: 1) Treatment patterns (i.e., adherence and persistence), and 2) Healthcare resource utilization and direct medical costs. A detailed description and operational definitions are provided below:

1) Treatment patterns

Medication Adherence to Antidepressants

Medication adherence was evaluated using proportion of days covered (PDC) during the 12-month follow-up period. PDC was defined as ‘‘the number of days with drug on hand divided by the number of days in the specified time interval,’’ which generated a PDC value that falls between 0 and 1.[155] The formula (Figure 2.2) is provided below:[156]

Figure 2.2 Formula of proportion of days covered (PDC)

$$\text{PDC} = \frac{\text{Total days all drug(s) available}}{\text{Days in the follow} - \text{up period}}$$

In our present study, PDC was used to measure adherence to antidepressants and was calculated as the number of days with any antidepressant on hand divided by the number of days in the follow-up period (365 days). Because PD patients might start with only one antidepressant for the comorbid depression (monotherapy) then switch to or add another antidepressant (combination therapy), patients were allowed to switch to or add other antidepressants other than the index antidepressant. For objectives 5 to 8, patients were further categorized into adherent and non-adherent antidepressant users using 0.8 as the cut-off point for PDC as recommended in the literature.[157] PD patients with PDCs $\geq$ 0.8 were considered as adherent, while those with PDCs < 0.8 were considered as non-adherent. Sensitivity analyses using PDC = 0.7 and 0.9 were also performed.

Medication Persistence and Discontinuation of Antidepressants

Medication persistence refers to "the duration of time from initiation to discontinuation of therapy."[71] A permissible gap between an expected next refill and an actual refill is usually assigned. In line with previous studies examining antidepressant persistence, the allowable gap used in the present study was 30 days[158-160] (Sensitivity analyses were also conducted for gaps of 45, 60, and 90 days).[161] Hence, the operational definition of medication persistence was the number of days from the first day any antidepressant was initiated (i.e., the index date) to the

discontinuation of all antidepressants without any 30-day gap. The operational definition of medication discontinuation was a refill gap of more than 30 days following a prescription.

2) Healthcare Resource Utilization (HCRU) and Direct Healthcare Costs

The present study estimated all-cause and PD-related healthcare resource utilization (HCRU) and direct medical costs. All-cause HCRU was assessed as the number of outpatient visits, nursing facility days billed, inpatient visits, and emergency room (ER) visits during the 12-month follow-up period. All-cause direct healthcare costs include costs corresponding to the above healthcare services use and costs of medications (i.e., pharmacy costs). The healthcare service use and costs associated with medical claims containing a PD diagnosis (ICD-9-CM Code 332.0 as primary or secondary diagnosis) were considered as PD-related HCRU and PD-related medical costs. The costs of prescription claims for PD-related medications were considered as PD-related medication costs. All costs were adjusted to 2010 US dollars using the US Consumer Price Index for Medical Care.

Table 2.3 Operational definitions of dependent variables

Dependent Variable	Measurement Level	Operational Definition
Treatment patterns		
Adherence	Continuous	Adherence for AD use in the 12-month follow-up period measured by PDC.
Adherence	Categorical (Dichotomous)	Adherence for AD use in the 12-month follow-up period measured by PDC. 0 = Non-adherent (PDC < 0.8) 1 = Adherent (PDC ≥ 0.8)
Persistence	Continuous	The number of days from the first day that a patient initiated any AD (index-date) to the discontinuation of all ADs without any 30-day gap. Patients who took AD until the end of the 12-month follow-up were censored.
All-cause utilization		
Number of all-cause outpatient (OP) visits	Count	Number of all-cause outpatient (OP) visits during the 12-month follow-up period. It was categorized into OP-office, OP-home, and OP-other visits based on place of services— • OP-office visit: physician office • OP-home visit: location where the patient receives care in a private residence • OP-other visit: assisted living facility, mobile unit, urgent care facility, on campus-outpatient hospital, independent clinic, federally qualified health center, community mental health center, mass immunization center, end-stage renal disease treatment facility, public health clinic, rural health clinic, and independent laboratory
Number of all-cause nursing facility days billed	Count	Number of all-cause nursing facility days billed during the 12-month follow-up period
Number of all-cause inpatient visits	Count	Number of all-cause inpatient visits during the 12-month follow-up period
Number of all-cause emergency room (ER) visits	Count	Number of all-cause ER visits during the 12-month follow-up period
All-cause direct medical costs		
All-cause outpatient (OP) cost	Continuous	All-cause cost of outpatient (OP) visits during the 12-month follow-up period. It was categorized into OP-office, OP-home, and OP-other costs based on place of services— • OP-office visit: physician office • OP-home visit: location where the patient receives care in a private residence • OP-other visit: assisted living facility, mobile unit, urgent care facility, on campus-outpatient hospital, independent clinic, federally qualified health center,

Table 2.3 Operational definitions of dependent variables (continued)

		community mental health center, mass immunization center, end-stage renal disease treatment facility, public health clinic, rural health clinic, and independent laboratory
All-cause nursing facility cost	Continuous	All-cause cost of nursing facility services during the 12-month follow-up period
All-cause inpatient cost	Continuous	All-cause cost of inpatient visits during the 12-month follow-up period
All-cause emergency room (ER) cost	Continuous	All-cause cost of ER visits during the 12-month follow-up period
All-cause pharmacy cost	Continuous	All-cause prescription costs during the 12-month follow-up period
All-cause total cost	Continuous	Sum of all-cause OP, nursing facility, inpatient, ER, and pharmacy costs during the 12-month follow-up period
PD-related utilization		
Number of PD-related outpatient (OP) visits	Count	Number of PD-related (with ICD-9-CM code: 332.0 as primary or secondary diagnosis) outpatient (OP) visits during the 12-month follow-up period. It was categorized into OP-office, OP-home, and OP-other visits based on place of services— • OP-office visit: physician office • OP-home visit: location where the patient receives care in a private residence • OP-other visit: assisted living facility, mobile unit, urgent care facility, on campus-outpatient hospital, independent clinic, federally qualified health center, community mental health center, mass immunization center, end-stage renal disease treatment facility, public health clinic, rural health clinic, and independent laboratory
Number of PD-related nursing facility days billed	Count	Number of PD-related (with ICD-9-CM code: 332.0 as primary or secondary diagnosis) nursing facility days billed during the 12-month follow-up period
Number of PD-related inpatient visit	Count	Number of PD-related (with ICD-9-CM code: 332.0 as primary or secondary diagnosis) inpatient visits during the 12-month follow-up period
Number of PD-related emergency room (ER) services	Count	Number of PD-related (with ICD-9-CM code: 332.0 as primary or secondary diagnosis) ER visits during the 12-month follow-up period
PD-related direct medical costs		
PD-related outpatient (OP) cost	Continuous	PD-related (with ICD-9-CM code: 332.0 as primary or secondary diagnosis) cost of outpatient (OP) visits during the 12-month follow-up period. It was categorized into OP-office, OP-home, and OP-other costs based on place of services— • OP-office visit: physician office • OP-home visit: location where the patient receives care in a private residence

Table 2.3 Operational definitions of dependent variables (continued)

		• OP-other visit: assisted living facility, mobile unit, urgent care facility, on campus-outpatient hospital, independent clinic, federally qualified health center, community mental health center, mass immunization center, end-stage renal disease treatment facility, public health clinic, rural health clinic, and independent laboratory
PD-related nursing facility cost	Continuous	PD-related (with ICD-9-CM code: 332.0 as primary or secondary diagnosis) cost of nursing facility services during the 12-month follow-up period
PD-related inpatient cost	Continuous	PD-related (with ICD-9-CM code: 332.0 as primary or secondary diagnosis) cost of inpatient visits during the 12-month follow-up period
PD-related emergency room (ER) cost	Continuous	PD-related (with ICD-9-CM code: 332.0 as primary or secondary diagnosis) cost of ER visits during the 12-month follow-up period
PD-related pharmacy cost	Continuous	PD-related (with ICD-9-CM code: 332.0 as primary or secondary diagnosis) prescription costs during the 12-month follow-up period
PD-related total cost	Continuous	Sum of PD-related (with ICD-9-CM code: 332.0 as primary or secondary diagnosis) OP, nursing facility, inpatient, ER, and pharmacy costs during the 12-month follow-up period

Note: For some objectives adherence is a dependent variable, but for other objectives it serves as the independent variable. AD= antidepressant

2.5.2 Independent Variable and Covariates

The main independent variable was adherence status to the study antidepressant (Adherent: PDC ≥ 0.80, non-adherent: PDC < 0.80). Covariates controlled in the present study included baseline demographic and clinical characteristics, as well as the pre-index PD-related total costs. Covariates for the demographic characteristics include age, gender, and geographic region. Covariates for the clinical characteristics include the presence/absence of common comorbid neuropsychiatric and cognitive impairment diseases in PD patients (i.e. anxiety, psychosis, and dementia), the Charlson Comorbidity Index (CCI),[162,163] and having regimen modification of an antidepressant. In the present study, regimen modification of an antidepressant was defined as switching or changing to a combination AD therapy. We did not

include dose escalation as regimen modification for the current study because antidepressant treatment involves upward dose titration, thus dose escalation may not be suitable as a predictor or a controlled covariate for our study outcomes. Medication switching was defined as starting a new study antidepressant that was different from the index antidepressant within 30 days after the end of the index medication supply, and without a subsequent refill of the index antidepressant.[164,165] Combination therapy referred to adding a new study antidepressant to the index antidepressant while continuing the refills of the index antidepressant without any 30-day gap.[164-166] We only counted the first regimen change (having switching or changing to combination therapy) in our study. Pre-index PD-related (with PD diagnosis as the primary or secondary diagnosis) total cost (sum of medical services and pharmacy costs) was used as the surrogate marker for PD severity. The assigned weights for the CCI, ICD-9-CM codes for selected comorbid neuropsychiatric and cognitive diseases, as well as the operational definitions for the independent variable and covariates are presented below Table 2.4, Table 2.5, and Table 2.6):[162,167-171]

Table 2.4 Charlson Comorbidity Index (CCI)

Comorbid Conditions	**Weights**	**ICD-9-CM Codes (Deyo Adaptation)**
Myocardial infarction	1	410.xx, 412
Congestive heart failure	1	428.x
Peripheral vascular disease	1	441.x, 443.9, 785.4, V43.4, procedure 38.48
Cerebrovascular disease	1	430-437.x, 438
Dementia	1	290.x
Chronic pulmonary disease	1	490-496, 500-505, 506.4
Connective tissue disease	1	710.0-710.1, 710.4, 714.0-714.2, 714.81, 725
Ulcer disease	1	531.4x-531.7x, 532.4x-532.7x, 533.4x-533.7x, 534.4x-534.7x, 531.0x-531.3x, 532.0x-532.3x, 533.0x-533.3x, 534.0x-534.3x, 531.9, 532.9, 533.9, 534.9
Mild liver disease	1	571.2, 571.4, 571.5, 571.6
Diabetes	1	250.0x-250.3x, 250.7x
Diabetes with end organ damage	2	250.4x-250.6x
Hemiplegia	2	342.x, 344.1
Moderate or severe renal disease	2	582.x, 583.0-583.7, 585, 586, 588.x
Any tumor	2	140.x-172.x, 174.x-195.x, 200.xx-208.xx
Leukemia	2	
Lymphoma	2	
Moderate or severe liver disease	3	572.2-582.8, 456.0-456.2x
Metastatic solid tumor	6	196.x-199.x
AIDS	6	042.x-044.x

Source: Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of chronic diseases.* 1987;40(5):373-383. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *Journal of clinical epidemiology.* Jun 1992;45(6):613-619.

Table 2.5 Diagnosis codes for the common comorbid neuropsychiatric and cognitive impairment diseases

Comorbid Neuropsychiatric and Cognitive Impairment Disease	ICD-9-CM Code
Anxiety	300, 309.24, 293.84
Psychosis	298.0, 298.1, 298.4–298.9 (psychosis), 293.82, 368.16, 780.1 (hallucinations), 293.81, 297.1 (delusions)
Dementia	290.0, 290.1, 290.3, 290.4, 290.8, 290.9, 294.1, 294.8, 294.9, 331.0, 331.1, 331.2, 797

Table 2.6 Operational definition of independent variable and covariates

Variable	Measurement Level	Operational Definition
Main independent variable		
Adherence status	Categorical	0 = Non-adherent (PDC < 0.80) 1 = Adherent (PDC ≥ 0.80)
Covariates		
Demographic characteristics		
Age	Continuous	Age at index date
Gender	Categorical	0 = Male 1 = Female
Geographic region	Categorical	1 = Northeast, 2 = Midwest, 3 = South, 4 = West
Clinical characteristics		
Having anxiety	Categorical	0 = No, 1 = Yes
Having psychosis	Categorical	0 = No, 1 = Yes
Having dementia	Categorical	0 = No, 1 = Yes
Charlson Comorbidity Index (CCI) score (Deyo adaptation)	Continuous	Sum of the corresponding weight for each comorbid disease (See Table 2.4)
Having regimen modification	Categorical	Regimen modification refers to switching or changing to a combination therapy • Switching: starting a new study antidepressant that is different from the index antidepressant within 30 days after the end of the index medication supply; and without a subsequent refill of the index antidepressant • Combination therapy: adding a new study antidepressant to the index antidepressant while continuing the refills of the index antidepressant without any 30-day gap 0 = No, 1 = Yes
Other covariate		
Pre-index PD-related total cost	Continuous	Sum of the medical services and pharmacy costs for pre-index healthcare services use with a PD diagnosis (ICD-9-CM code: 332.0) in the claims

2.6 Statistical Analysis

Statistical Analysis System (SAS) version 9.4 (SAS Institute, Cary, NC, USA) and STATA version 12.1 (StataCorp, College Station, TX, USA) were used to conduct data management and data analyses. All statistical analyses used a two-tailed a priori significance level of α=0.05. Histograms and Shapiro Wilkes-tests were used to assess the data distribution. For objectives 1 and 2, descriptive statistics were provided. The comparisons for the categorical variables were performed using Pearson Chi-square tests, while the comparisons for the continuous variables were carried out using Wilcoxon rank-sum tests. For objective 2, Kaplan-Meier survival analysis was employed to describe and compare persistence among study patients. For objective 3, factors associated with being adherent (using 0.80 as the PDC cut-off value) were identified using logistic regression. For objective 4, factors associated with persistence were examined using Cox proportional hazards regression (sensitivity analyses with 45-, 60-, and 90-day gaps were conducted). Zero-inflated negative binomial (ZINB) or GzLM with negative binomial (NB) distributions and log link functions were used to address the healthcare resource utilization comparisons as appropriate (objectives 5 and 6). The choice of ZINB over NB models was based on the results of Vuong's tests. Two-part models (part 1: logistic regression to predict the likelihood of having observation value greater than zero; part 2: GzLM with gamma distribution and log link function to estimate the value greater than zero) and GzLM with gamma distributions and log link functions were used to address the healthcare costs comparisons as appropriate (objectives 7 and 8). The use of two-part models or GzLMs depended on the data distribution. GzLMs were used to account for the positively skewed cost data, while two-part models were employed for cost data with both a "spike" of zero values and positively skewed cost data. Sensitivity analyses were conducted at PDC cut-off values of 0.70 and 0.90. A summary of the objectives, hypotheses, and the corresponding statistical analyses is provided in Table 2.7:

Table 2.7 Study objectives, hypotheses, and corresponding statistical analyses

Objectives/ Hypotheses	Dependent variable	Measurement Level	Independent Variable	Measurement Level	Statistical Analysis
Objective 1: To describe and compare demographic and clinical characteristics among PD patients with depression	Age	Continuous	Adherence status (Yes/No)	Categorical	Descriptive statistics & Wilcoxon rank sum test
	Gender	Categorical			Descriptive statistics & Pearson Chi-square test
	Geographic region	Categorical			Descriptive statistics & Pearson Chi-square test
	Having anxiety	Categorical			Descriptive statistics & Pearson Chi-square test
	Having psychosis	Categorical			Descriptive statistics & Pearson Chi-square test
	Having dementia	Categorical			Descriptive statistics & Pearson Chi-square test
	Charlson Comorbidity Index (CCI) score	Continuous			Descriptive statistics & Wilcoxon rank sum test
	Pre-index PD-related total cost	Continuous			Descriptive statistics & Wilcoxon rank sum test
Objective 2: To describe antidepressant use patterns (index antidepressant type, adherence, persistence, switching, combination therapy) among PD patients with depression	Adherence	Continuous	--	--	Descriptive statistics
	Adherence	Categorical (1 = Adherent [PDC ≥ 0.8], 0 = Non-dherent [PDC < 0.8])	--	--	Descriptive statistics
	Persistence	Continuous	--	--	Kaplan Meier survival

Table 2.7 Study objectives, hypotheses, and corresponding statistical analyses (continued)

					analysis
	Switching	Categorical	--	--	Descriptive statistics
	Combination therapy	Categorical	--	--	Descriptive statistics
Objective 3: To identify the factors associated with being adherent among PD patients with depression					
$H_{3a\text{-}4i}$: Age, gender, anxiety, psychosis, dementia, CCI score, regimen modification, geographic region, pre-index PD-related total cost are not associated with adherence.	Adherent status (1 = Adherent [PDC ≥ 0.8], 0 = Non-adherent [PDC < 0.8])	Categorical (Dichotomous)	Demographic covariates: Age, Gender, Geographic region; Clinical covariates: Having anxiety, Having psychosis, Having dementia, CCI score, regimen modification; Other covariates: Pre-index PD-related total cost	Continuous and categorical	Logistic regression
Objective 4: To identify the factors associated with persistence among PD patients with depression					
$H_{4a\text{-}4i}$: Age, gender, anxiety, psychosis, dementia, CCI score, regimen modification, geographical region, pre-index PD-related total cost are not associated with	Persistence (number of days)	Continuous	Demographic covariates: Age, Gender, Geographic	Continuous and categorical	Cox proportional hazards regression

Table 2.7 Study objectives, hypotheses, and corresponding statistical analyses (continued)

persistence.			region; Clinical covariates: Having anxiety, Having psychosis, Having dementia, CCI score, regimen modification; Other covariates: Pre-index PD-related total cost		
Objective 5: To determine if all-cause healthcare resource utilization differs significantly between adherent and non-adherent antidepressants users while controlling for covariates					
H_{05a}: There is no significant difference in number of all-cause outpatient visits between adherent and non-adherent antidepressants users while controlling for covariates.	Number of all-cause outpatient visits	Count	Adherence status (Dichotomous: Yes [PDC ≥ 0.8] or No [PDC < 0.8])	Categorical	Zero-inflated negative binomial (ZINB) model / Generalized linear model (GzLM) with negative binomial (NB) distribution and log link function
H_{05b}: There is no significant difference in number of all-cause nursing facility days billed between adherent and non-adherent antidepressants users while controlling for covariates.	Number of all-cause nursing facility days billed	Count	Adherence status (Dichotomous: Yes [PDC ≥ 0.8] or No [PDC < 0.8])	Categorical	Zero-inflated negative binomial (ZINB) model

Table 2.7 Study objectives, hypotheses, and corresponding statistical analyses (continued)

H_{05c}: There is no significant difference in number of all-cause inpatient visits between adherent and non-adherent antidepressants users while controlling for covariates.	Number of all-cause inpatient visits	Count	Adherence status (Dichotomous: Yes [PDC ≥ 0.8] or No [PDC < 0.8])	Categorical	Zero-inflated negative binomial (ZINB) model
H_{05d}: There is no significant difference in number of all-cause emergency room (ER) visits between adherent and non-adherent antidepressants users while controlling for covariates.	Number of all-cause emergency room (ER) visits	Count	Adherence status (Dichotomous: Yes [PDC ≥ 0.8] or No [PDC < 0.8])	Categorical	Zero-inflated negative binomial (ZINB) model
Objective 6: To determine if PD-related healthcare resource utilization differs significantly between adherent and non-adherent antidepressants users while controlling for covariates					
H_{06a}: There is no significant difference in number of PD-related outpatient visits between adherent and non-adherent antidepressants users while controlling for covariates.	Number of PD-related outpatient visits	Count	Adherence status (Dichotomous: Yes [PDC ≥ 0.8] or No [PDC < 0.8])	Categorical	Zero-inflated negative binomial (ZINB) model / Generalized linear model (GzLM) with negative binomial (NB) distribution and log link function
H_{06b}: There is no significant difference in number of PD-related nursing facility days billed between adherent and non-adherent antidepressants users while controlling for covariates.	Number of PD-related nursing facility days billed	Count	Adherence status (Dichotomous: Yes [PDC ≥ 0.8] or No [PDC < 0.8])	Categorical	Zero-inflated negative binomial (ZINB) model
H_{06c}: There is no significant difference in number of PD-related inpatient visits between adherent and non-adherent antidepressants users while controlling for covariates.	Number of PD-related inpatient visits	Count	Adherence status (Dichotomous: Yes [PDC ≥ 0.8] or No [PDC < 0.8])	Categorical	Zero-inflated negative binomial (ZINB) model
H_{06d}: There is no significant difference in	Number of PD-	Count	Adherence	Categorical	Zero-inflated negative

Table 2.7 Study objectives, hypotheses, and corresponding statistical analyses (continued)

number of PD-related emergency room (ER) visits between adherent and non-adherent antidepressants users while controlling for covariates.	related emergency room (ER) visits		status (Dichotomous: Yes [PDC ≥ 0.8] or No [PDC < 0.8])		binomial (ZINB) model
Objective 7: To determine if all-cause healthcare costs differ significantly between adherent and non-adherent antidepressants users while controlling for covariates.					
H_{07a}: There is no significant difference in all-cause outpatient costs between adherent and non-adherent antidepressants users while controlling for covariates.	All-cause outpatient costs	Continuous	Adherence status (Dichotomous: Yes [PDC ≥ 0.8] or No [PDC < 0.8])	Categorical	Two-part model
H_{07b}: There is no significant difference in all-cause nursing facility costs between adherent and non-adherent antidepressants users while controlling for covariates.	All-cause nursing facility costs	Continuous	Adherence status (Dichotomous: Yes [PDC ≥ 0.8] or No [PDC < 0.8])	Categorical	Two-part model
H_{07c}: There is no significant difference in all-cause inpatient costs between adherent and non-adherent antidepressants users while controlling for covariates.	All-cause inpatient costs	Continuous	Adherence status (Dichotomous: Yes [PDC ≥ 0.8] or No [PDC < 0.8])	Categorical	Two-part model
H_{07d}: There is no significant difference in all-cause ER costs between adherent and non-adherent antidepressants users while controlling for covariates.	All-cause ER costs	Continuous	Adherence status (Dichotomous: Yes [PDC ≥ 0.8] or No [PDC < 0.8])	Categorical	Two-part model
H_{07e}: There is no significant difference in all-cause pharmacy costs between adherent	All-cause pharmacy costs	Continuous	Adherence status	Categorical	Generalized linear model (GzLM) with gamma

Table 2.7 Study objectives, hypotheses, and corresponding statistical analyses (continued)

and non-adherent antidepressants users while controlling for covariates.			(Dichotomous: Yes [PDC ≥ 0.8] or No [PDC < 0.8])		distribution and log link function
H_{07f}: There is no significant difference in all-cause total costs between adherent and non-adherent antidepressants users while controlling for covariates.	All-cause total costs	Continuous	Adherence status (Dichotomous: Yes [PDC ≥ 0.8] or No [PDC < 0.8])	Categorical	Generalized linear model (GzLM) with gamma distribution and log link function
Objective 8: To determine if PD-related healthcare costs differ significantly between adherent and non-adherent antidepressants users while controlling for covariates.					
H_{08a}: There is no significant difference in PD-related outpatient costs between adherent and non-adherent antidepressants users while controlling for covariates.	PD-related outpatient costs	Continuous	Adherence status (Dichotomous: Yes [PDC ≥ 0.8] or No [PDC < 0.8])	Categorical	Two-part model
H_{08b}: There is no significant difference in PD-related nursing facility costs between adherent and non-adherent antidepressants users while controlling for covariates.	PD-related nursing facility costs	Continuous	Adherence status (Dichotomous: Yes [PDC ≥ 0.8] or No [PDC < 0.8])	Categorical	Two-part model
H_{08c}: There is no significant difference in PD-related inpatient costs between adherent and non-adherent antidepressants users while controlling for covariates.	PD-related inpatient costs	Continuous	Adherence status (Dichotomous: Yes [PDC ≥ 0.8] or No [PDC < 0.8])	Categorical	Two-part model
H_{08d}: There is no significant difference in PD-related ER costs between adherent and non-adherent antidepressants users while	PD-related ER costs	Continuous	Adherence status (Dichotomous:	Categorical	Two-part model

Table 2.7 Study objectives, hypotheses, and corresponding statistical analyses (continued)

controlling for covariates.			Yes [PDC ≥ 0.8] or No [PDC < 0.8])		
H_{08e}: There is no significant difference in PD-related pharmacy costs between adherent and non-adherent antidepressants users while controlling for covariates.	PD-related pharmacy costs	Continuous	Adherence status (Dichotomous: Yes [PDC ≥ 0.8] or No [PDC < 0.8])	Categorical	Two-part model
H_{08f}: There is no significant difference in PD-related total costs between adherent and non-adherent antidepressants users while controlling for covariates.	PD-related total costs	Continuous	Adherence status (Dichotomous: Yes [PDC ≥ 0.8] or No [PDC < 0.8])	Categorical	Two-part model

2.7 Statistical Tests Assumptions and Sample Size Calculations

This section describes the statistical tests assumptions and the required sample size calculations. Objectives that only involve descriptive statistics and baseline characteristics comparisons were discussed here. All required sample sizes were calculated using G*Power and PASS 14 software, with α set at 0.05 and power at 0.8.

2.7.1 Logistic Regression

Logistic regression is a statistical approach to predict a dichotomous variable value from other variables. The key assumptions for logistic regression include: 1) binary outcomes for the dependent variable; and 2) each observation is independent. Based on the calculation using G*Power, the minimum required sample size was 794 (See Table 2.9).

2.7.2 Generalized Linear Model (GzLM)

The generalized linear model (GzLM) is a large class of statistical models that extend the general linear model to allow for response (dependent) variables (Y) with non-normal distributions.[172] A GzLM includes three components: the probability distribution of the response variable, the combination of linear predictors, and a link function. The probability distribution of the response variable can be any member of the exponential (e.g., normal, binomial, gamma, Poisson, inverse-Gaussian distribution), multivariate exponential, (multinomial distribution), non-exponential families (e.g., two-parameter negative binomial distribution), or distribution that is not specified. A combination of linear predictors (η) refers to the explanatory variables (X) in the model (See Figure 2.3). A link function, $g(\cdot)$, specifies the relationship between the expected

value of the response variable and the linear predictor (See Figure 2.4).[172,173] Some commonly used exponential families and the link functions are provided in Table 2.8.

Figure 2.3 A combination of linear predictors

$$\eta_i = \alpha + \beta_1 X_{i1} + \beta_2 X_{i2} + \cdots + \beta_k X_{ik}$$

Figure 2.4 A link function

$$\mu_i \equiv E(Y_i)$$
$$g(\mu_i) = \eta_i = \alpha + \beta_1 X_{i1} + \beta_2 X_{i2} + \cdots + \beta_k X_{ik}$$

Table 2.8 Canonical link and response range for commonly used exponential families

Exponential Family	**Canonical Link**	**Range of Yi**
Gaussian	Identity	$(-\infty,\infty)$
Binomial	Logit	$(0,1,\ldots n_i)/n_i$
Poisson	Log	0,1,2,..
Gamma	Inverse	$(0,\infty)$
Inverse-Gaussian	Inverse-square	$(0,\infty)$

Source: Fox J. *Applied regression analysis and generalized linear models.* Sage Publications; 2015

The assumptions of GzLM include: "1) statistical independence of the observations; 2) correct specification of the variance function; 3) correct specification of the dispersion parameter; 4) correct specification of the link function; 5) correct form for the explanatory variables; and 6) lack of undue influence of individual observations on the fit."[172]

Generalized Linear Models (GzLMs) with Gamma Distribution and Negative Binomial Distribution

Little has been reported in the literature regarding the sample size estimation for GzLMs with gamma distribution or negative binomial (NB) distribution. However, it has been suggested that the required sample size for a multiple regression analysis will be sufficient enough to detect statistical significance for GzLMs with gamma distributions.[174] The sample size for multiple regression analysis for our present study was calculated using G*Power and the final estimated sample size is 822 (assuming power = 0.8; $\alpha = 0.05$; small effect size (f^2) = 0.02; number of predictors = 10), which was used as a proxy for sample size requirement for GzLMs with gamma distributions.

The function of sample size calculation for NB regression is not available in the current commonly used sample size estimation software. Because NB regression is an extension of Poisson regression,[175] the required sample size for Poisson regression calculated by G*Power was used as a proxy. The healthcare resource utilization was assumed to be 5% higher in non-adherent patients than the adherent patients at baseline. The detected difference in healthcare resource utilization was set at 10% or more. The distribution of the main independent variable was assumed to be binomial. The covariates were assumed to have a moderate association with the main predictor (X) and yielded an expected squared multiple correlation (R^2 other X) of 0.3. The 12-month follow-up duration (365 days) was used as the mean exposure time. Based on the above assumptions and the proportion of non-adherent antidepressant users reported in previous studies (44.4 to 76.5%),[176,177] the required minimum sample size was 261.

2.7.3 Cox Proportional Hazards Regression

Cox proportional hazards regression, a semi-parametric procedure to estimate the hazard of an event over time, identifies the relationship between survival time and explanatory variables. Cox proportional hazards regression allows unspecified form or shape of the underlying hazard function (h(t)) and assumes a fixed ratio of the hazards for any two individuals at any time point.[178,179] The basic structure of the Cox proportional hazards regression can be depicted as shown in Figure 2.5.

Figure 2.5 Cox proportional hazards regression

$$\boldsymbol{log_e}\left\{\frac{\boldsymbol{h_i(t)}}{\boldsymbol{h_0(t)}}\right\} = \mathbf{X_1\beta_1 + \ldots\ldots + X_n\beta_n}$$

$h_i(t)$: the hazard at time t

$h_0(t)$: the baseline hazard

X: the independent variable or the covariates in the model

β: the regression coefficient for the corresponding independent variable or the covariates

The required sample size for the Cox proportional hazards regression was estimated using PASS 14 software (Kaysville, Utah). Based on the reported event rates of discontinuing antidepressants (0.42 to 0.63),[176,180] the minimum required sample size was 650.

Table 2.9 Summary of sample sizes for the statistical analytical tests

Statistical Analytical Tests	Logistic regression[a]	Generalized Linear Models with Gamma Distribution[b]	Generalized Linear Models with Negative Binomial Distribution[c]	Cox Proportional Hazards Regression[d]
Required sample size	794	822	261	650

All sample size calculations used $\alpha = 0.05$, power = 0.8

[a] R^2 other X = 0.3, odds ratio = 1.5, $Pr(Y=1|X=1)$ H_O=0.05, assumed a Poisson distribution

[b] Because the required sample size for the multiple regression will be sufficient for generalized linear models with a gamma distribution, the minimum sample size for multiple regression will be used as a proxy

[c] Using the required sample size for a Poisson regression as the proxy with R^2 other X=0.3, base rate $Exp(\beta 0)=0.05$, $Exp(\beta 1)=1.1$, and exposure time=365 days

[d] R^2 other X=0.3, log hazard ratio=1.5, $Pr(Y=1|X=1)$ H_O=0.42, SD of X=0.5

Based on the above sample size calculation (Table 2.9), the required minimum sample size for the present study was 822.

CHAPTER 3: RESULTS

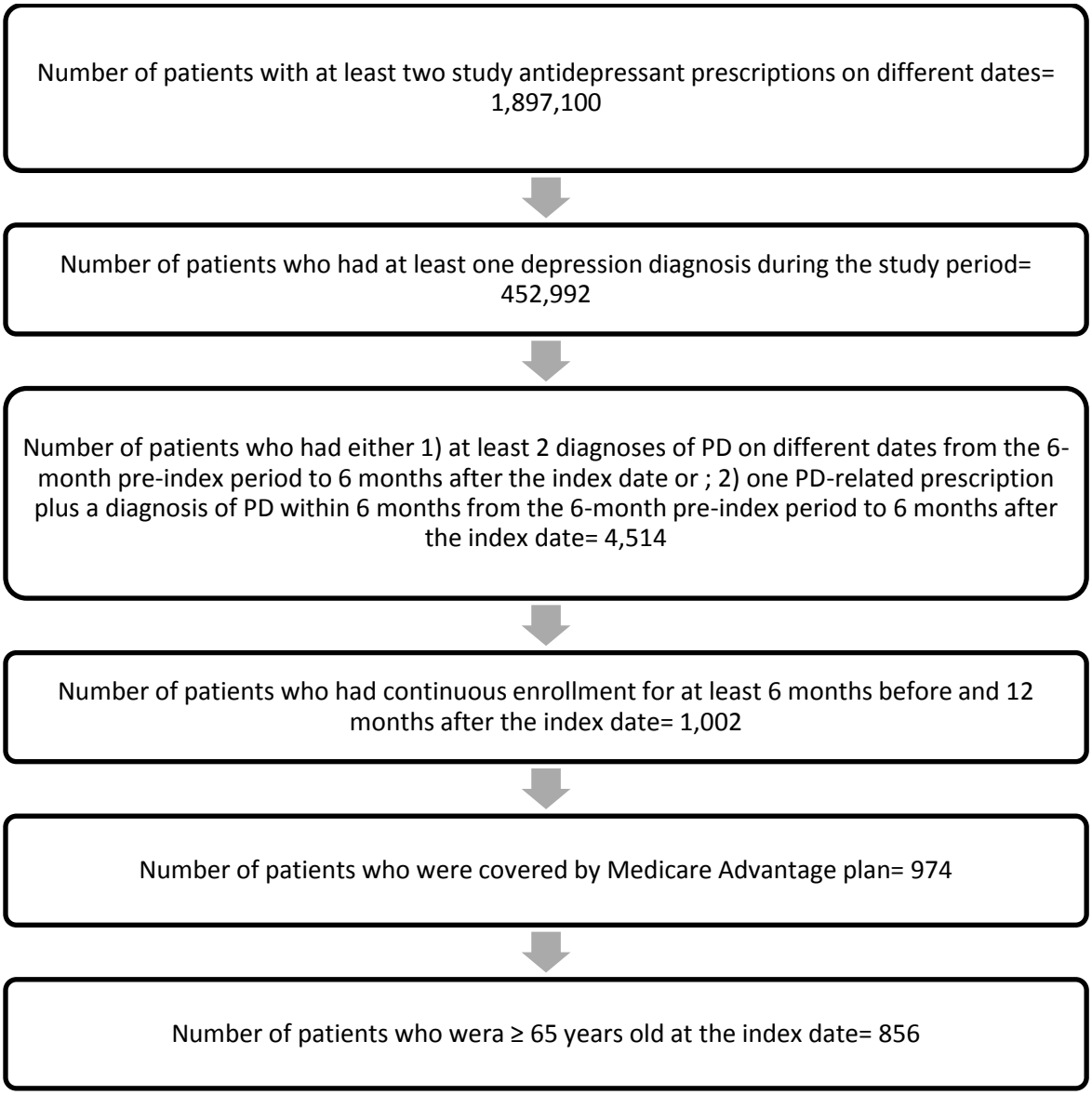
3.1 Chapter Overview

This chapter provides a detailed description of study results. The patient selection process, statistical analyses, and hypothesis tests are presented for each objective.

3.2 Patient Selection

There were 1,897,100 patients with at least two study antidepressant prescriptions on different dates between 01/01/2007 to 12/31/2010. Among them, 452,992 patients had a diagnosis of depression during the study period. After applying the criteria to identify PD patients, the sample size reduced to 4,514. Of those, 856 patients met the inclusion criteria for age, covered by MAPD plan, and sufficient continuous enrollment. A flowchart depicts study inclusion criteria, and the corresponding sample sizes are presented in Figure 3.1.

Figure 3.1 Diagram of patient selection process



3.3 Study Objectives

3.3.1 Objective 1: Demographic and Clinical Characteristics

Objective 1 was to describe and compare demographic and clinical characteristics among adherent and non-adherent antidepressant users. Demographic and clinical characteristics of the study sample are shown in Table 3.1.

The mean age for the study patients was 75.4 (±5.5) years old. Slightly less than half of them were females (47.1%). The majority of the patients resided in the southern US (59.4%). The average CCI was 2.2 (±2.5). More than one-fifth of the patients had anxiety (23.6%) or dementia (27.2%). Only 11% of the patients had a regimen modification. The mean pre-index PD-related total cost was $4,973 (±$11,462). Among the 856 patients, 58.5% (N = 501) of them were non-adherent to their antidepressants (i.e., PDC <0.8).

A significant difference in geographic region between adherent and non-adherent antidepressant (AD) users was observed (p= 0.032). When compared to patients who were non-adherent to AD, patients who were adherent to AD had higher proportions of psychosis (10.4% vs. 4.8%, p= 0.002) and dementia (31.3% vs. 24.4%, p= 0.025). More adherent AD users had regimen modifications than non-adherent AD users (17.2% vs. 6.6%, p <0.001). Additionally, the pre-index PD-related total cost was also higher in adherent AD users relative to non-adherent AD users.

Table 3.1 Demographic and clinical characteristics of adherent versus non-adherent patients

Variable	Overall (N=856)	Non-adherent to AD (N=501)	Adherent to AD (N= 355)	p-value
Age, mean (SD) [a]	75.4 (5.5)	75.2 (5.4)	75.7 (5.6)	0.124
Females (%) [b]	47.1	44.3	51.0	0.054
Region (%) [b]				0.032*
Midwest	28.7	25.6	33.2	
Northeast	3.2	2.6	3.9	
South	59.4	61.9	55.8	
West	8.8	10.0	7.0	
Charlson Comorbidity Index (CCI), mean (SD) [a]	2.2 (2.5)	2.1 (2.3)	2.5 (2.7)	0.055
Having anxiety (%) [b]	23.6	22.8	24.8	0.490
Having psychosis (%) [b]	7.1	4.8	10.4	0.002*
Having dementia (%) [b]	27.2	24.4	31.3	0.025*
Having regimen modification (%) [b]	11.0	6.6	17.2	<0.001*
Preindex PD-related total cost, mean (SD) [a]	$4,973 ($11,462)	$4,203 ($10,634)	$6,059 ($12,472)	0.032*

AD = antidepressant; SD = standard deviation; PD = Parkinson's disease
[a] Wilcoxon rank-sum test
[b] Chi-square test
*Significant at $p < 0.05$

3.3.2 Objective 2: Antidepressant Use Patterns

Objective 2 was to describe antidepressant use patterns (index antidepressant type, adherence, persistence, switching, and combination therapy) among PD patients with depression. Among the type of antidepressants, most of the patients were prescribed SSRIs at the index date (68.1%), followed by other ADs (17.8%), SNRIs (9%), and then TCAs (5.1%). The most common antidepressant prescriptions were for citalopram (38.0%) and sertraline (14.1%). The mean PDC (±SD) for antidepressant medications was 0.63 (± 0.31). When measuring adherence as a dichotomous variable using PDC = 0.8 as the cut-off value, 41.5% of the study sample were adherent (PDC ≥0.8). The mean and median time to discontinuation of any antidepressant treatment were 194.2 and 163.5 days. As shown in Table 3.3, 47.3% of the patients were still

taking antidepressants after six months, and 32.0% of the patients continued their antidepressants for at least one year. Figure 3.2 is the Kaplan-Meier curve showing the percentage of patients who remain persistent on antidepressants during the 1-year follow-up period. Regimen modification occurred in 11% of the patients, 2.1% of them switched from their index antidepressant to another antidepressant, and 8.9% of them changed to a combination therapy for depression treatment.

Table 3.2 Type of index antidepressant prescribed

Index Antidepressants Use	Frequency	%
Amitriptyline	29	3.39
Doxepin	3	0.35
Imipramine	7	0.82
Nortriptyline	5	0.58
Any TCAs	44	5.14
Citalopram	325	37.97
Fluoxetine	80	9.35
Paroxetine	57	6.66
Sertraline	121	14.14
Any SSRIs	583	68.11
Duloxetine	44	5.14
Venlafaxine	33	3.86
Any SNRIs	77	9.00
Bupropion	24	2.80
Mirtazapine	65	7.59
Trazodone	63	7.36
Any other antidepressant	152	17.76

TCAs = tricyclic antidepressants; SSRIs = selective serotonin reuptake inhibitors; SNRIs = serotonin norepinephrine reuptake inhibitors

Table 3.3 Persistence to antidepressants

Variable Description	Time to Discontinuation (Persistence)
Number of patients with discontinuation, N (%)	582 (68.0%)
Time to discontinuation, adjusting for censoring, Mean (days)	194.2
Time to discontinuation, adjusting for censoring, Median (days)	163.5
Percentage of Patients remaining on antidepressant at time points:	
3 months, % (95% CI)	62.3 (58.9, 65.4)
6 months, % (95% CI)	47.3 (43.9, 50.6)
9 months, % (95% CI)	39.4 (36.1, 42.6)
12 months, % (95% CI)	32.0 (28.9, 35.1)

Figure 3.2 Kaplan-Meier survival curve for persistence to antidepressant

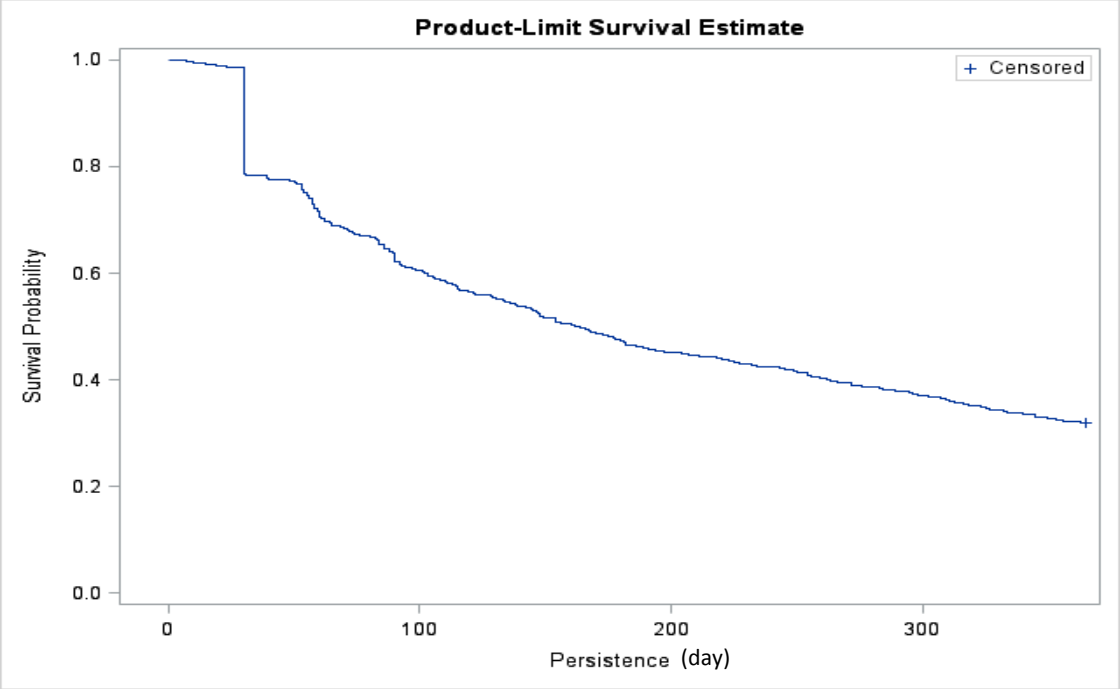
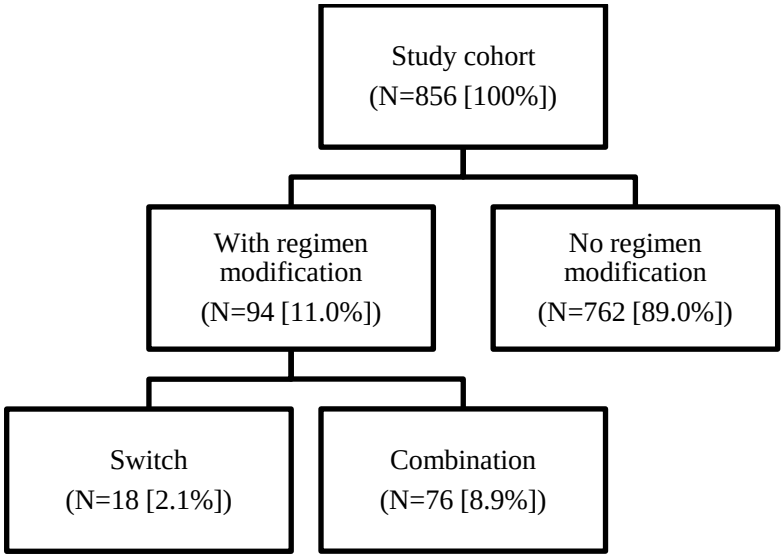


Figure 3.3 Treatment change patterns



3.3.3 Objective 3: Adherence

Objective 3 was to identify the factors associated with being adherent to antidepressant treatment (dichotomous variable, Yes = 'PDC ≥ 0.8', No = 'PDC < 0.8') among PD patients with depression. Logistic regression showed that CCI score and regimen modification were significantly associated with being adherent (Table 3.4). For every one point increase in CCI score, patients were 6% more likely to be adherent to their antidepressant (OR =1.063, 95% CI = [1.003, 1.126], p = 0.039). Patients who had a regimen modification were almost 3 times more likely to be adherent to antidepressant therapy (OR = 2.966, 95% CI = [1.879, 4.682], p < 0.001).

Table 3.4 Logistic regression results to identify factors associated with being adherent to antidepressant treatment

Covariate	Odds Ratio	95% Wald Confidence Limits		Wald Chi-Square	p-value
Age	1.014	0.988	1.041	1.0801	0.299
Female (ref = Male)	1.324	0.996	1.761	3.7228	0.054
Region (ref = Northeast)					
Midwest	0.917	0.402	2.09	0.0427	0.836
South	0.634	0.284	1.417	1.2335	0.267
West	0.535	0.212	1.348	1.7617	0.184
Charlson Comorbidity Index (CCI)	1.063	1.003	1.126	4.2461	0.039*
Having Anxiety	1.117	0.798	1.563	0.4175	0.518
Having Psychosis	1.712	0.962	3.045	3.344	0.067
Having Dementia	1.137	0.816	1.585	0.5792	0.447
Regimen Modification[a]	2.966	1.879	4.682	21.8094	<0.001*
Pre-Index PD-Related Total Cost	1	1	1	1.8395	0.175

Model Fit Statistics: Likelihood ratio = 53.4925, df = 11, $p < 0.001$
*Significant at $p < 0.05$
a: AD switch or combination therapy

H_{3a}: **Age** is not associated with being adherent to antidepressants after controlling for other covariates. **(Not rejected)**

H_{3b}: **Being female** is not associated with being adherent to antidepressants after controlling for other covariates. **(Not rejected)**

H_{3c}: **Geographic region** is not associated with being adherent to antidepressant after controlling for other covariates. (**Not rejected**)

H_{3d}: **Having anxiety** is not associated with being adherent to antidepressants after controlling for other covariates. **(Not rejected)**

H_{3e}: **Having psychosis** is not associated with being adherent to antidepressants after controlling for other covariates. **(Not rejected)**

H_{3f}: **Having dementia** is not associated with being adherent to antidepressants after controlling for other covariates. **(Not rejected)**

H_{3g}: **The CCI score** is not associated with being adherent to antidepressants after controlling for other covariates. **(Rejected)**

H_{3h}: **Having regimen modification of the index antidepressants** is not associated with being adherent to antidepressants after controlling for other covariates. **(Rejected)**

H_{3i}: **The pre-index PD-related total cost** is not associated with being adherent to antidepressants after controlling for other covariates. **(Not rejected)**

3.3.4 Objective 4: Persistence

Objective 4 was to identify the factors associated with antidepressant persistence among PD patients with depression. A Cox proportional hazards regression model with a 30-day gap was used to address this objective (Table 3.5). Sensitivity analyses were conducted using 45-, 60-, and 90-day gaps. The results showed that patients with regimen modification were more persistent to antidepressant (36.9% less likely to discontinue their antidepressant) than those without regimen modification (Hazard ratio = 0.631, 95% CI = [0.474, 0.841], p = 0.0016). Results of the sensitivity analyses remained robust at 45-, 60-, and 90-day gap periods (Table 3.6, Table 3.7, and Table 3.8).

Table 3.5 Cox proportional hazards model results to identify factors associated with persistence to antidepressant (with a 30-day gap)

Covariate	Hazard Ratio	95% Hazard Ratio Confidence Limits		Wald Chi-Square	p-value
Age	0.995	0.98	1.01	0.4878	0.485
Female (ref = Male)	0.86	0.729	1.015	3.169	0.075
Region (ref= Northeast)					
Midwest	0.975	0.582	1.634	0.009	0.924
South	1.156	0.699	1.912	0.3194	0.572
West	1.184	0.676	2.073	0.3491	0.555
Charlson Comorbidity Index (CCI)	0.972	0.938	1.007	2.5003	0.114
Having anxiety	0.951	0.779	1.161	0.2417	0.623
Having psychosis	0.736	0.507	1.066	2.6303	0.105
Having dementia	0.938	0.771	1.141	0.4128	0.521
Regimen modification	0.631	0.474	0.841	9.92	0.0016*
Preindex PD-related total cost	1	1	1	0.9483	0.330

Model Fit Statistics: Likelihood ratio = 31.3128, df = 11, p = 0.001
*Significant at $p < 0.05$

Table 3.6 Cox proportional hazards model results to identify factors associated with persistence to antidepressant (with a 45-day gap)

Covariate	Hazard Ratio	95% Hazard Ratio Confidence Limits		Wald Chi-Square	p-value
Age	0.998	0.982	1.014	0.0806	0.777
Female (ref = Male)	0.858	0.72	1.022	2.9459	0.086
Region (ref= Northeast)					
Midwest	0.953	0.549	1.656	0.0288	0.865
South	1.207	0.706	2.065	0.4733	0.492
West	1.201	0.661	2.183	0.36	0.549
Charlson Comorbidity Index (CCI)	0.972	0.936	1.009	2.2753	0.132
Having anxiety	0.882	0.714	1.09	1.3491	0.245
Having psychosis	0.728	0.486	1.089	2.3855	0.123
Having dementia	0.932	0.757	1.148	0.4398	0.507
Regimen modification	0.578	0.421	0.794	11.4823	0.001*
Preindex PD-related total cost	1	1	1	0.6624	0.416

Model Fit Statistics: Likelihood ratio = 35.2394, df = 11, p = 0.0002
*Significant at $p < 0.05$

Table 3.7 Cox proportional hazards model results to identify factors associated with persistence to antidepressant (with a 60-day gap)

Covariate	Hazard Ratio	95% Hazard Ratio Confidence Limits		Wald Chi-Square	p-value
Age	0.994	0.978	1.011	0.4139	0.520
Female (ref = Male)	0.863	0.717	1.038	2.4488	0.118
Region (ref= Northeast)					
Midwest	1.021	0.563	1.852	0.0048	0.945
South	1.297	0.727	2.315	0.7756	0.379
West	1.288	0.679	2.445	0.6012	0.438
Charlson Comorbidity Index (CCI)	0.973	0.935	1.012	1.8496	0.174
Having anxiety	0.891	0.713	1.113	1.0415	0.308
Having psychosis	0.666	0.431	1.029	3.3462	0.067
Having dementia	0.961	0.772	1.197	0.1244	0.724
Regimen modification	0.446	0.308	0.647	18.161	<0.001*
Preindex PD-related total cost	1	1	1	0.3491	0.555

Model Fit Statistics: Likelihood ratio = 43.3627, df = 11, p < 0.0001
*Significant at $p < 0.05$

Table 3.8 Cox proportional hazards model results to identify factors associated with persistence to antidepressant (with a 90-day gap)

Covariate	Hazard Ratio	95% Hazard Ratio Confidence Limits		Wald Chi-Square	p-value
Age	0.997	0.979	1.015	0.0967	0.756
Female (ref = Male)	0.849	0.696	1.036	2.5969	0.107
Region (ref= Northeast)					
Midwest	1.073	0.56	2.056	0.0446	0.833
South	1.284	0.681	2.421	0.5949	0.441
West	1.375	0.686	2.757	0.8044	0.370
Charlson Comorbidity Index (CCI)	0.985	0.945	1.027	0.4977	0.481
Having anxiety	0.871	0.684	1.108	1.2684	0.260
Having psychosis	0.699	0.438	1.115	2.2574	0.133
Having dementia	0.870	0.685	1.105	1.2995	0.254
Regimen modification	0.411	0.272	0.621	17.7793	<0.001*
Preindex PD-related total cost	1	1	1	0.0127	0.910

Model Fit Statistics: Likelihood ratio = 39.1492, df = 11, $p < 0.0001$
*Significant at $p < 0.05$

H_{4a}: **Age** is not associated with persistence after controlling for other covariates. **(Not rejected)**

H_{4b}: **Being female** is not associated with persistence after controlling for other covariates. **(Not rejected)**

H_{04c}: **Geographic region** is not associated with persistence after controlling for other covariates. **(Not rejected)**

H_{4d}: **Having anxiety** is not associated with persistence after controlling for other covariates. **(Not rejected)**

H_{4e}: **Having psychosis** is not associated with persistence after controlling for other covariates. **(Not rejected)**

H_{4f}: **Having dementia** is not associated with persistence after controlling for other covariates. **(Not rejected)**

H_{4g}: **The CCI scores** is not associated with persistence after controlling for other covariates. **(Not rejected)**

H_{4h}: **Having regimen modification of the index antidepressants** is not associated with persistence after controlling for other covariates. **(Rejected)**

H_{4i}: **The pre-index PD-related total cost** is not associated with persistence after controlling for other covariates. **(Not rejected)**

3.3.5 Objective 5: All-cause Healthcare Resource Utilization (HCRU)

All-cause medical claims for depressed PD patients with AD were examined (A summary of number of claims for different utilization was presented in Appendix 1). Objective 5 involved the comparisons between adherent and non-adherent antidepressants (AD) users with regard to all-cause outpatient visits (OP-office, OP-home, and OP-other), nursing facility days billed, inpatient visits, and ER visits.

3.3.5.1 All-cause HCRU comparison (Unadjusted analysis)

The unadjusted numbers of all-cause HCRU comparisons were estimated using Wilcoxon rank-sum tests. No significant differences were found in all-cause HCRU between adherent and non-adherent AD users using the PDC cut-off value of 80% (Table 3.9). For the sensitivity analyses: when the cut-off value for was set at "PDC = 0.70", the unadjusted median numbers of all-cause OP-other visits were higher in adherent AD users than those who were non-adherent (5.00 vs. 6.00, p = 0.034). Although the median numbers for nursing facility days billed were equal, significant difference was found in Wilcoxon rank sum test and adherent AD users had more number of nursing facility days billed than those who were non-adherent (median: 0.00 vs. 0.00, mean rank: 419.94 vs. 442.00, p = 0.029) (Table 3.10). When the cut-off value was set at "PDC = 0.90", the unadjusted median number of all-cause inpatient visits was significantly higher in non-adherent AD users than adherent AD users (1.00 vs. 0.00, p = 0.001) (Table 3.11).

Table 3.9 Unadjusted numbers of all-cause healthcare resource utilization comparisons (Cut-off value for being adherent: PDC = 0.80)

All-cause Medical Service	Overall (N=856)		Non-adherent to AD (N=501)		Adherent to AD (N=355)		Z	p-value
	Median	IQR	Median	IQR	Median	IQR		
# of OP-office visit	14.00	14.00	15.00	16.00	13.00	13.00	-1.395	0.163
# of OP-home visit	1.00	8.50	1.00	9.00	1.00	8.00	-0.354	0.724
# of OP-other visit	6.00	8.00	6.00	8.00	6.00	9.00	1.514	0.130
# of nursing facility days billed	0.00	3.00	0.00	2.00	0.00	4.00	1.645	0.100
# of inpatient visit	1.00	2.00	1.00	2.00	0.00	2.00	-1.736	0.083
# of ER visit	0.00	1.00	0.00	1.00	0.00	1.00	0.815	0.415

Note: Wilcoxon rank-sum tests were used. AD = antidepressant; IQR = interquartile range; OP = outpatient; ER = emergency room

Table 3.10 Unadjusted numbers of all-cause healthcare resource utilization comparisons (Cut-off value for being adherent: PDC = 0.70)

All-cause Medical Service	Non-adherent to AD (N=413)		Adherent to AD (N=443)		Z	p-value
	Median	IQR	Median	IQR		
# of OP-office visit	15.00	16.00	14.00	13.00	1.5401	0.124
# of OP-home visit	1.00	8.00	1.00	9.00	0.0259	0.979
# of OP-other visit	5.00	7.00	6.00	9.00	-2.1259	0.034*
# of nursing facility days billed	0.00	2.00	0.00	5.00	-2.1798	0.029*
# of inpatient visit	1.00	2.00	0.00	2.00	1.1619	0.245
# of ER visit	0.00	1.00	0.00	1.00	-0.4053	0.685

Note: Wilcoxon rank-sum tests were used. AD = antidepressant; IQR = interquartile range; OP = outpatient; ER = emergency room
*Significant at $p < 0.05$

Table 3.11 Unadjusted numbers of all-cause healthcare resource utilization comparisons (Cut-off value for being adherent: PDC = 0.90)

All-cause Medical Service	Non-adherent to AD (N=624)		Adherent to AD (N=232)		Z	p-value
	Median	IQR	Median	IQR		
# of OP-office visit	15.00	14.00	13.00	12.00	-1.4639	0.143
# of OP-home visit	1.00	10.00	0.00	7.00	-1.941	0.052
# of OP-other visit	6.00	9.00	6.00	8.00	0.261	0.794
# of nursing facility days billed	0.00	3.00	0.00	1.50	-0.3028	0.762
# of inpatient visit	1.00	2.00	0.00	1.00	-3.4488	0.001*
# of ER visit	0.00	1.00	0.00	1.00	0.437	0.662

Note: Wilcoxon rank-sum tests were used. AD = antidepressant; IQR = interquartile range; OP = outpatient; ER = emergency room
*Significant at $p < 0.05$

3.3.5.2 All-cause HCRU comparison (Adjusted analysis)

Based on the results from Vuong tests, zero-inflated negative binomial models were used for the comparisons in number of nursing facility days billed, OP-office, OP-home, and inpatient visits; GzLMs with negative binomial distribution and log link function were performed for OP-other and ER visits (Outputs were presented in Appendix 3 to Appendix 8). After adjusting for age, gender, geographical region, presence of specific comorbidities (anxiety, psychosis, and dementia), Charlson Comorbidity Index (CCI), having regimen modification, and pre-index Parkinson's disease-related total cost, no significant difference was found in number of all-cause nursing facility days billed, outpatient (OP-office, OP-home, and OP-other), and ER visits for adherent versus non-adherent AD users. However, the results showed that non-adherent AD users had more frequent all-cause inpatient visits than adherent AD users during the 1-year follow-up period (1.4 vs. 1.0, $p = 0.001$) (Table 3.12). For the sensitivity analyses when the cut-

off value for PDC was set at 0.7, no difference was found in the number of all-cause inpatient visits. Instead, more number of nursing facility days billed in adherent AD users than non-adherent AD users was observed (4.20 vs. 6.23, p = 0.020) (Table 3.13). When a PDC cut-off of 0.9 was used, the result remained the same as the original analysis (using the 0.8 cut-off) (Table 3.14).

Table 3.12 Zero-inflated negative binomial model or GzLM adjusted all-cause healthcare resource utilization comparisons (Cut-off value for being adherent: PDC = 0.80)

All-cause Medical Service	**Non-adherent to AD (N=501)**				**Adherent to AD (N=355)**				**p-value**
	Mean	SE	95% CI		Mean	SE	95% CI		
# of OP-office visit[a]	18.296	0.593	17.134	19.458	17.099	0.693	15.740	18.457	0.193
# of OP-home visit[a]	9.796	1.115	7.610	11.982	9.676	1.150	7.422	11.930	0.933
# of OP-other visit[b]	10.641	0.520	9.622	11.660	9.553	0.513	8.548	10.557	0.137
# of nursing facility days billed[a]	4.629	0.569	3.513	5.745	6.062	0.788	4.518	7.606	0.134
# of inpatient visit[a]	1.439	0.098	1.246	1.631	1.007	0.080	0.849	1.164	0.001*
# of ER visit[b]	0.637	0.050	0.539	0.734	0.543	0.049	0.447	0.640	0.186

Note: GzLM = generalized linear model; AD = antidepressant; SE = standard error; CI = confidence interval; OP = outpatient; ER = emergency room
All models adjusted for age, gender, geographical region, presence of specific comorbidities (anxiety, psychosis, and dementia), Charlson Comorbidity Index (CCI), having regimen modification, and pre-index Parkinson's disease-related total cost.
[a] Zero-inflated negative binomial model
[b] GzLM with negative binomial distribution and a log link function
*Significant at $p < 0.05$

Table 3.13 Zero-inflated negative binomial model or GzLM adjusted all-cause healthcare resource utilization comparisons (Cut-off value for being adherent: PDC = 0.70)

All-cause Medical Service	Non-adherent to AD (N=413)				Adherent to AD (N=443)				p-value
	Mean	SE	95% CI		Mean	SE	95% CI		
# of OP-office visit[a]	18.555	0.692	17.200	19.910	17.047	0.626	15.820	18.273	0.108
# of OP-home visit[a]	9.556	1.167	7.267	11.844	9.903	1.103	7.741	12.065	0.810
# of OP-other visit[b]	10.159	0.536	9.109	11.210	10.132	0.488	9.177	11.088	0.970
# of nursing facility days billed[a]	4.195	0.561	3.096	5.293	6.229	0.725	4.808	7.650	0.020*
# of inpatient visit[a]	1.357	0.099	1.163	1.552	1.139	0.081	0.981	1.298	0.089
# of ER visit[b]	0.648	0.055	0.539	0.757	0.551	0.045	0.463	0.639	0.175

Note: GzLM = generalized linear model; AD = antidepressant; SE = standard error; CI = confidence interval; OP = outpatient; ER = emergency room

All models adjusted for age, gender, geographical region, presence of specific comorbidities (anxiety, psychosis, and dementia), Charlson Comorbidity Index (CCI), having regimen modification, and pre-index Parkinson's disease-related total cost.

[a] Zero-inflated negative binomial model

[b] GzLM with negative binomial distribution and a log link function

*Significant at $p < 0.05$

Table 3.14 Zero-inflated negative binomial model or GzLM adjusted all-cause healthcare resource utilization comparisons (Cut-off value for being adherent: PDC = 0.90)

All-cause Medical Service	Non-adherent to AD (N=624)				Adherent to AD (N=232)				p-value
	Mean	SE	95% CI		Mean	SE	95% CI		
# of OP-office visit[a]	18.153	0.551	17.073	19.232	16.775	0.851	15.106	18.444	0.175
# of OP-home visit[a]	9.957	1.016	7.967	11.948	9.212	1.351	6.563	11.861	0.632
# of OP-other visit[b]	10.446	0.445	9.575	11.318	9.412	0.625	8.187	10.637	0.176
# of nursing facility days billed[a]	5.178	0.554	4.092	6.264	6.123	1.114	3.938	8.307	0.425
# of inpatient visit[a]	1.434	0.084	1.268	1.599	0.791	0.082	0.631	0.951	<0.001*
# of ER visit[b]	0.615	0.043	0.532	0.699	0.545	0.061	0.425	0.665	0.350

Note: GzLM = generalized linear model; AD = antidepressant; SE = standard error; CI = confidence interval; OP = outpatient; ER = emergency room

All models adjusted for age, gender, geographical region, presence of specific comorbidities (anxiety, psychosis, and dementia), Charlson Comorbidity Index (CCI), having regimen modification, and pre-index Parkinson's disease-related total cost.

[a] Zero-inflated negative binomial model

[b] GzLM with negative binomial distribution and a log link function

*Significant at $p < 0.05$

H_{05a}: There is no significant difference in number of **outpatient visits** between adherent and non-adherent antidepressants users while controlling for covariates. **(Not rejected)**

H_{05b}: There is no significant difference in number of **nursing facility days billed** between adherent and non-adherent antidepressants users while controlling for covariates. **(Not rejected)**

H_{05c}: There is no significant difference in number of **inpatient visits** between adherent and non-adherent antidepressants users while controlling for covariates. **(Rejected)**

H_{05d}: There is no significant difference in number of **emergency room (ER) visits** between adherent and non-adherent antidepressants users while controlling for covariates. **(Not rejected)**

3.3.6 Objective 6: PD-related Healthcare Resource Utilization (HCRU)

PD-related medical claims for depressed PD patients with AD were examined (A summary of number of claims for different utilization was presented in Appendix 2). Objective 6 involved the comparisons between adherent and non-adherent antidepressants (AD) users with regard to PD-related nursing facility days billed, outpatient visits (OP-office, OP-home, and OP-other), inpatient visits, and ER visits.

3.3.6.1 PD-related HCRU comparison (Unadjusted analysis)

The unadjusted numbers of PD-related HCRUs were compared using Wilcoxon rank-sum tests (Table 3.15). No statistically significant differences were found in PD-related HCRUs between adherent and non-adherent AD users. When changing the cut-off PDC value to 0.7, adherent AD users had significantly higher number of PD-related nursing facility days billed than non-adherent AD users even though the medians were equal (median: 0.00 vs. 0.00, mean rank: 413.64 vs. 442.35, $p = 0.012$) (Table 3.16). When cut-off value of 0.9 was applied, same median values in non-adherent and adherent AD users were found but non-adherent AD users had significantly higher PD-related inpatient visits than adherent AD users (median: 0.00 vs. 0.00, mean rank: 438.62 vs. 401.29, $p = 0.017$) (Table 3.17).

Table 3.15 Unadjusted numbers of PD-related healthcare resource utilization comparisons (Cut-off value for being adherent: PDC = 0.80)

PD-related Medical Services	Overall (N=856)		Non-adherent to AD (N=501)		Adherent to AD (N=355)		Z	p-value
	Median	IQR	Median	IQR	Median	IQR		
# of OP-office visit	3.00	5.00	3.00	5.00	3.00	5.00	-1.293	0.196
# of OP-home visit	0.00	1.00	0.00	1.00	0.00	1.00	-0.571	0.568
# of OP-other visit	0.00	1.00	0.00	1.00	0.00	1.00	0.474	0.636
# of nursing facility days billed	0.00	0.00	0.00	0.00	0.00	0.00	1.898	0.058
# of inpatient visit	0.00	1.00	0.00	1.00	0.00	1.00	-1.381	0.167
# of ER visit	0.00	0.00	0.00	0.00	0.00	0.00	1.111	0.267

Note: Wilcoxon rank-sum tests were used. AD = antidepressant; IQR = interquartile range; OP = outpatient; ER = emergency room; PD = Parkinson's disease

Table 3.16 Unadjusted numbers of PD-related healthcare resource utilization comparisons (Cut-off value for being adherent: PDC = 0.70)

PD-related Medical Services	Non-adherent to AD (N=413)		Adherent to AD (N=443)		Z	p-value
	Median	IQR	Median	IQR		
# of OP-office visit	3.00	5.00	3.00	5.00	1.4292	0.153
# of OP-home visit	0.00	1.00	0.00	1.00	0.5289	0.597
# of OP-other visit	0.00	1.00	0.00	1.00	-0.2059	0.837
# of nursing facility days billed	0.00	0.00	0.00	0.00	-2.5027	0.012*
# of inpatient visit	0.00	1.00	0.00	1.00	0.8119	0.417
# of ER visit	0.00	0.00	0.00	0.00	-0.8067	0.420

Note: Wilcoxon rank-sum tests were used. AD = antidepressant; IQR = interquartile range; OP = outpatient; ER = emergency room; PD = Parkinson's disease
*Significant at $p < 0.05$

Table 3.17 Unadjusted numbers of PD-related healthcare resource utilization comparisons (Cut-off value for being adherent: PDC = 0.90)

PD-related Medical Services	Non-adherent to AD (N=624)		Adherent to AD (N=232)		Z	p-value
	Median	IQR	Median	IQR		
# of OP-office visit	3.00	5.00	3.00	5.00	-0.8673	0.386
# of OP-home visit	0.00	1.00	0.00	0.50	-1.3938	0.163
# of OP-other visit	0.00	1.00	0.00	1.00	-0.3394	0.734
# of nursing facility days billed	0.00	0.00	0.00	0.00	0.9058	0.365
# of inpatient visit	0.00	1.00	0.00	1.00	-2.3966	0.017*
# of ER visit	0.00	0.00	0.00	0.00	1.7338	0.083

Note: Wilcoxon rank-sum tests were used. AD = antidepressant; IQR = interquartile range; OP = outpatient; ER = emergency room; PD = Parkinson's disease
*Significant at $p < 0.05$

3.3.6.2 PD-related HCRU comparison (Adjusted analysis)

Based on the results from Vuong tests, zero-inflated negative binomial models were used for the comparisons in PD-related nursing facility days billed, OP-office, OP-home, inpatient, and ER visits; while GzLM with negative binomial distribution was used for PD-related OP-other visits (Outputs were presented in Appendix 9 to Appendix 14). After controlling for the covariates, no significant differences were found in number of PD-related nursing facility days billed, outpatient (OP-office, OP-home, and OP-other), and ER visits. The only difference was found in PD-related inpatient visits: non-adherent AD users had more frequent PD-related inpatient visits than adherent antidepressant users during the 1-year follow-up period (0.66 vs. 0.47, $p = 0.015$) (Table 3.18). For the sensitivity analyses, no significant differences were found between the two groups when using a cut-off value of "PDC = 0.70" (Table 3.19). If the cut-off value was changed to "PDC = 0.90", the adjusted PD-related OP-other and inpatient visits for non-adherent AD users were higher than those who were adherent to AD (OP-other: 1.44 vs. 0.99, $p = 0.024$; inpatient: 0.67 vs. 0.35, $p < 0.001$) (Table 3.20).

Table 3.18 Zero-inflated negative binomial model or GzLM adjusted PD-related healthcare resource utilization comparisons (Cut-off value for being adherent: PDC = 0.80)

PD-related Medical Service	Non-adherent to AD (N=501)				Adherent to AD (N=355)				p-value
	Mean	SE	95% CI		Mean	SE	95% CI		
# of OP-office visit[a]	4.535	0.219	4.106	4.963	4.193	0.250	3.702	4.683	0.299
# of OP-home visit[a]	5.775	1.372	3.085	8.465	4.613	0.933	2.785	6.441	0.371
# of OP-other visit[b]	1.316	0.151	1.021	1.611	1.294	0.170	0.962	1.627	0.921
# of nursing facility days billed[a]	1.225	0.204	0.825	1.626	1.591	0.314	0.977	2.206	0.318
# of inpatient visit[a]	0.658	0.057	0.547	0.769	0.469	0.051	0.368	0.570	0.015*
# of ER visit[a]	0.239	0.029	0.182	0.295	0.214	0.029	0.158	0.270	0.548

Note: GzLM = generalized linear model; AD = antidepressant; SE = standard error; CI = confidence interval; OP = outpatient; ER = emergency room. All models adjusted for age, gender, geographical region, presence of specific comorbidities (anxiety, psychosis, and dementia), Charlson Comorbidity Index (CCI), having regimen modification, and pre-index Parkinson's disease-related total cost.

[a] Zero-inflated negative binomial model

[b] GzLM with negative binomial distribution and a log link function

*Significant at $p < 0.05$

Table 3.19 Zero-inflated negative binomial model or GzLM adjusted PD-related healthcare resource utilization comparisons (Cut-off value for being adherent: PDC = 0.70)

PD-related Medical Service	Non-adherent to AD (N=413)				Adherent to AD (N=443)				p-value
	Mean	SE	95% CI		Mean	SE	95% CI		
# of OP-office visit[a]	4.629	0.244	4.150	5.108	4.177	0.223	3.741	4.614	0.169
# of OP-home visit[a]	5.012	1.119	2.819	7.206	4.999	0.969	3.100	6.899	0.992
# of OP-other visit[b]	1.209	0.148	0.920	1.499	1.394	0.161	1.078	1.710	0.365
# of nursing facility days billed[a]	1.063	0.201	0.669	1.458	1.660	0.281	1.110	2.211	0.080
# of inpatient visit[a]	0.586	0.055	0.479	0.693	0.566	0.055	0.459	0.674	0.803
# of ER visit[a]	0.244	0.033	0.179	0.309	0.216	0.028	0.162	0.270	0.505

Note: GzLM = generalized linear model; AD = antidepressant; SE = standard error; CI = confidence interval; OP = outpatient; ER = emergency room. All models adjusted for age, gender, geographical region, presence of specific comorbidities (anxiety, psychosis, and dementia), Charlson Comorbidity Index (CCI), having regimen modification, and pre-index Parkinson's disease-related total cost.

[a] Zero-inflated negative binomial model

[b] GzLM with negative binomial distribution and a log link function

*Significant at $p < 0.05$

Table 3.20 Zero-inflated negative binomial model or GzLM adjusted PD-related healthcare resource utilization comparisons (Cut-off value for being adherent: PDC = 0.90)

PD-related Medical Service	Non-adherent to AD (N=624)				Adherent to AD (N=232)				p-value
	Mean	SE	95% CI		Mean	SE	95% CI		
# of OP-office visit[a]	4.482	0.196	4.098	4.867	4.140	0.300	3.552	4.727	0.334
# of OP-home visit[a]	5.409	1.035	3.381	7.437	4.279	1.028	2.264	6.293	0.358
# of OP-other visit[b]	1.443	0.151	1.147	1.739	0.986	0.154	0.685	1.287	0.024*
# of nursing facility days billed[a]	1.336	0.197	0.950	1.721	1.649	0.424	0.819	2.480	0.491
# of inpatient visit[a]	0.672	0.052	0.571	0.773	0.354	0.050	0.256	0.453	<0.001*
# of ER visit[a]	0.223	0.024	0.175	0.271	0.242	0.039	0.166	0.319	0.668

GzLM = generalized linear model; AD = antidepressant; SE = standard error; CI = confidence interval; OP = outpatient; ER = emergency room. All models adjusted for age, gender, geographical region, presence of specific comorbidities (anxiety, psychosis, and dementia), Charlson Comorbidity Index (CCI), having regimen modification, and pre-index Parkinson's disease-related total cost.

[a] Zero-inflated negative binomial model

[b] GzLM with negative binomial distribution and a log link function

*Significant at $p < 0.05$

H_{06a}: There is no significant difference in number of **PD-related outpatient visits** between adherent and non-adherent antidepressants users while controlling for covariates. **(Not rejected)**

H_{06b}: There is no significant difference in number of **PD-related nursing facility days billed** between adherent and non-adherent antidepressants users while controlling for covariates. **(Not rejected)**

H_{06c}: There is no significant difference in number of **PD-related inpatient visits** between adherent and non-adherent antidepressants users while controlling for covariates. **(Rejected)**

H_{06d}: There is no significant difference in number of **PD-related ER visits** between adherent and non-adherent antidepressants users while controlling for covariates. **(Not rejected)**

3.3.7 Objective 7: All-cause Healthcare Cost

Objective 7 involved the comparisons between adherent and non-adherent AD users with regard to all-cause outpatient costs (OP-office, OP-home, and OP-other), nursing facility service costs, inpatient costs, ER costs, pharmacy costs, and total costs.

3.3.7.1 All-cause Healthcare Cost Comparison (Unadjusted analysis)

The unadjusted costs for all-cause healthcare services for adherent and non-adherent AD users were compared using Wilcoxon rank-sum tests. The detailed results are presented in Table 3.21. There were no significant differences in all-cause outpatient (OP-office, OP-home, and OP-other), inpatient, ER, and total costs between the two groups. Patients who were adherent to antidepressant medications had higher all-cause pharmacy costs than those who were non-adherent to antidepressants ($2,765 vs. $4,260, $p < 0.001$). Sensitivity analyses with different levels as PDC cut-off values were carried out (Table 3.22 and Table 3.23). When a PDC cut-off value of 0.70 was specified, higher all-cause pharmacy cost ($2,673 vs. $3,994, $p < 0.001$) and total cost ($12,654 vs. $ 15,457, $p = 0.034$) were observed in adherent AD users than non-adherent AD users. If the PDC cut-off value was set at 0.90, non-adherent AD users had higher all-cause inpatient costs ($144 vs. $ 0, $p < 0.001$) and lower all-cause pharmacy costs ($3,069 vs. $4,340, $p < 0.001$) compared to adherent AD users.

Table 3.21 Unadjusted all-cause healthcare costs comparisons (Cut-off value for being adherent: PDC = 0.80)

All-cause Cost Category	Overall (N=856)		Non-adherent to AD (N=501)		Adherent to AD (N=355)		Z	p-value
	Median	IQR	Median	IQR	Median	IQR		
OP-office	$1,579	$2,038	$1,610	$1,857	$1,501	$2,187	-0.6759	0.499
OP-home	$95	$2,674	$115	$2,677	$68	$2,651	-0.2188	0.827
OP-other	$699	$2,258	$746	$2,326	$666	$2,103	-0.1535	0.878
Nursing facilities	$0	$1,119	$0	$875	$0	$1,208	0.392	0.695
Inpatient	$11	$10,498	$85	$11,451	$0	$9,040	-1.9285	0.054
ER	$177	$939	$176	$1,030	$178	$860	-0.6773	0.498
Pharmacy	$3,361	$3,408	$2,765	$3,081	$4,260	$3,745	8.1157	<0.001*
Total	$14,225	$26,401	$13,623	$30,255	$14,401	$23,777	1.0275	0.304

Note: Wilcoxon rank-sum tests were used. AD = antidepressant; IQR = interquartile range; OP = outpatient; ER = emergency room
*Significant at $p < 0.05$

Table 3.22 Unadjusted all-cause healthcare costs comparisons (Cut-off value for being adherent: PDC = 0.70)

All-cause Cost Category	Non-adherent to AD (N=413)		Adherent to AD (N=443)		Z	p-value
	Median	IQR	Median	IQR		
OP-office	$1,639	$2,020	$1,467	$2,002	1.3398	0.180
OP-home	$103	$2,658	$92	$2,866	-0.1045	0.917
OP-other	$669	$2,122	$716	$2,410	-0.9518	0.341
Nursing facilities	$0	$386	$0	$1,482	-1.191	0.234
Inpatient	$84	$11,315	$0	$9,849	1.2668	0.205
ER	$177	$1,010	$178	$905	0.563	0.573
Pharmacy	$2,673	$2,944	$3,994	$3,942	-8.4878	<0.001*
Total	$12,654	$24,870	$15,457	$27,791	-2.1155	0.034*

Note: Wilcoxon rank-sum tests were used. AD = antidepressant; IQR = interquartile range; OP = outpatient; ER = emergency room
*Significant at $p < 0.05$

Table 3.23 Unadjusted all-cause healthcare costs comparisons (Cut-off value for being adherent: PDC = 0.90)

All-cause Cost Category	Non-adherent to AD (N=624)		Adherent to AD (N=232)		Z	p-value
	Median	IQR	Median	IQR		
OP-office	$1,613	$2,069	$1,436	$1,934	-1.3378	0.181
OP-home	$128	$3,228	$0	$1,624	-1.8817	0.060
OP-other	$771	$2,279	$535	$2,214	-1.3095	0.190
Nursing facilities	$0	$2,072	$0	$542	-1.7109	0.087
Inpatient	$144	$12,546	$0	$5,498	-4.3478	<0.001*
ER	$179	$1,008	$171	$768	-0.9721	0.331
Pharmacy	$3,069	$3,244	$4,340	$3,606	5.8271	<0.001*
Total	$14,827	$31,902	$12,737	$18,386	-1.6102	0.107

Note: Wilcoxon rank-sum tests were used. AD = antidepressant; IQR = interquartile range; OP = outpatient; ER = emergency room
*Significant at $p < 0.05$

3.3.7.2 All-cause Healthcare Cost Comparison (Adjusted analysis)

GzLMs with gamma distribution and log link function were used for the comparisons in all-cause pharmacy and total costs to account for the right skewed cost data. Two-part models were performed for the comparisons in all-cause OP-office, OP-home, OP-other, nursing facility, inpatient, and ER costs because these cost data were right skewed and many of them were zero (Outputs were presented in Appendix 15 to Appendix 22). The adjusted mean all-cause nursing facility costs ($5,179 vs. $2,351, $p < 0.001$) and inpatient costs ($10,503 vs. $6,254, $p < 0.001$) for non-adherent AD users were approximately two times higher than adherent AD users (Table 3.24.). The all-cause ER cost ($859 vs. $644, $p =0.027$) and total cost ($28,813 vs. $23,290, $p =0.008$) were also significantly higher in non-adherent AD users than adherent AD users. However, the all-cause mean pharmacy cost was higher in adherent AD users than non-adherent

AD users ($3,596 vs. $4,889, p <0.001). The results for all-cause inpatient and pharmacy cost were robust in sensitivity analyses (Table 3.25 and Table 3.26). But all-cause nursing facility, ER, and total costs were no longer significantly different between adherent and non-adherent AD users when cut-off value was 0.70. The adjusted all-cause ER costs did not differ significantly when a cut-off value of 0.90 was applied.

Table 3.24 Two-part model or GzLM adjusted all-cause healthcare cost comparisons (Cut-off value for being adherent: PDC = 0.80)

All-cause Cost Category	Non-adherent to AD (N=501)				Adherent to AD (N=355)				p-value
	Mean	SE	95% CI		Mean	SE	95% CI		
OP-office[a]	$2,061	$104	$1,857	$2,265	$2,266	$141	$1,990	$2,542	0.239
OP-home[a]	$3,455	$410	$2,652	$4,258	$3,827	$507	$2,832	$4,821	0.536
OP-other[a]	$3,009	$372	$2,280	$3,737	$2,199	$309	$1,594	$2,804	0.084
Nursing facilities[a]	$5,179	$625	$3,954	$6,405	$2,351	$300	$1,763	$2,939	<0.001*
Inpatient[a]	$10,503	$951	$8,639	$12,366	$6,254	$727	$4,829	$7,678	<0.001*
ER[a]	$859	$72	$718	$1,000	$644	$65	$517	$771	0.027*
Pharmacy[b]	$3,596	$137	$3,327	$3,865	$4,889	$213	$4,471	$5,306	<0.001*
Total[b]	$28,813	$1,669	$25,542	$32,084	$23,290	$1,474	$20,401	$26,178	0.008*

Note: GzLM = generalized linear model; AD = antidepressant; SE = standard error; CI = confidence interval; OP = outpatient; ER = emergency room. All models adjusted for age, gender, geographical region, presence of specific comorbidities (anxiety, psychosis, and dementia), Charlson Comorbidity Index (CCI), having regimen modification, and pre-index Parkinson's disease-related total cost.

[a] Two-part model with logistic regression as the first part and GzLM with a gamma regression and a log link as the second part

[b] GzLM with a gamma regression and a log link

*Significant at p < 0.05

Table 3.25 Two-part model or GzLM adjusted all-cause healthcare cost comparisons (Cut-off value for being adherent: PDC = 0.70)

All-cause Cost Category	Non-adherent to AD (N=413)				Adherent to AD (N=443)				p-value
	Mean	SE	95% CI		Mean	SE	95% CI		
OP-office[a]	$2,105	$118	$1,874	$2,336	$2,183	$124	$1,941	$2,425	0.643
OP-home[a]	$3,369	$436	$2,514	$4,224	$3,861	$475	$2,929	$4,793	0.406
OP-other[a]	$2,509	$345	$1,832	$3,186	$2,784	$360	$2,079	$3,489	0.562
Nursing facilities[a]	$4,482	$590	$3,326	$5,638	$3,216	$373	$2,484	$3,947	0.069
Inpatient[a]	$10,115	$1,012	$8,133	$12,098	$7,335	$761	$5,844	$8,826	0.028*
ER[a]	$ 831	$ 76	$681	$ 980	$705	$63	$581	$829	0.205
Pharmacy[b]	$3,437	$145	$3,153	$3,722	$4,786	$189	$4,415	$5,157	<0.001*
Total[b]	$27,080	$1,705	$23,737	$30,422	$25,692	$1,509	$22,734	$28,649	0.514

GzLM = generalized linear model; AD = antidepressant; SE = standard error; CI = confidence interval; OP = outpatient; ER = emergency room. All models adjusted for age, gender, geographical region, presence of specific comorbidities (anxiety, psychosis, and dementia), Charlson Comorbidity Index (CCI), having regimen modification, and pre-index Parkinson's disease-related total cost.

[a] Two-part model with logistic regression as the first part and GzLM with a gamma regression and a log link as the second part

[b] GzLM with a gamma regression and a log link

*Significant at $p < 0.05$

Table 3.26 Two-part model or GzLM adjusted all-cause healthcare cost comparisons (Cut-off value for being adherent: PDC = 0.90)

All-cause Cost Category	Non-adherent to AD (N=624)				Adherent to AD (N=232)				p-value
	Mean	SE	95% CI		Mean	SE	95% CI		
OP-office[a]	$2,139	$100	$1,944	$2,335	$2,156	$170	$1,823	$2,489	0.933
OP-home[a]	$3,489	$355	$2,792	$4,185	$3,977	$658	$2,687	$5,268	0.489
OP-other[a]	$2,798	$315	$2,180	$3,416	$2,284	$408	$1,484	$3,084	0.304
Nursing facilities[a]	$4,871	$481	$3,928	$5,813	$1,296	$223	$859	$1,732	<0.001
Inpatient[a]	$10,573	$873	$8,862	$12,284	$4,049	$629	$2,816	$5,281	<0.001
ER[a]	$817	$62	$696	$938	$635	$80	$479	$792	0.074
Pharmacy[b]	$3,863	$130	$3,607	$4,119	$4,911	$264	$4,393	$5,428	<0.001
Total[b]	$28,980	$1,509	$26,022	$31,939	$19,906	$1,541	$16,886	$22,927	<0.001

GzLM = generalized linear model; AD = antidepressant; SE = standard error; CI = confidence interval; OP = outpatient; ER = emergency room. All models adjusted for age, gender, geographical region, presence of specific comorbidities (anxiety, psychosis, and dementia), Charlson Comorbidity Index (CCI), having regimen modification, and pre-index Parkinson's disease-related total cost.

[a] Two-part model with logistic regression as the first part and GzLM with a gamma regression and a log link as the second part

[b] GzLM with a gamma regression and a log link

*Significant at $p < 0.05$

H_{07a}: There is no significant difference in **all-cause outpatient costs** between adherent and non-adherent antidepressants users while controlling for covariates. **(Not rejected)**

H_{07b}: There is no significant difference in **all-cause nursing facility costs** between adherent and non-adherent antidepressants users while controlling for covariates. **(Rejected)**

H_{07c}: There is no significant difference in **all-cause inpatient costs** between adherent and non-adherent antidepressants users while controlling for covariates. **(Rejected)**

H_{07d}: There is no significant difference in **all-cause ER costs** between adherent and non-adherent antidepressants users while controlling for covariates. **(Rejected)**

H_{07e}: There is no significant difference in **all-cause pharmacy costs** between adherent and non-adherent antidepressants users while controlling for covariates. **(Rejected)**

H_{07f}: There is no significant difference in **all-cause total costs** between adherent and non-adherent antidepressants users while controlling for covariates. **(Rejected)**

3.3.8 Objective 8: PD-related Healthcare Cost

Objective 8 involved the comparisons between adherent and non-adherent antidepressant (AD) users with regard to PD-related outpatient costs (OP-office, OP-home, and OP-other), nursing facility service costs, inpatient costs, ER costs, pharmacy costs, and total costs.

3.3.8.1 PD-related Healthcare Cost Comparison (Unadjusted analysis)

Wilcoxon rank-sum tests were used to assess the PD-related healthcare costs for adherent and non-adherent AD users. The detailed results are shown in Table 3.27. The PD-related outpatient (OP-office, OP-home, and OP-other), nursing facility, inpatient, ER, and total costs of adherent AD users did not significantly differ from non-adherent AD users (all $p > 0.05$). Compared to non-adherent antidepressant users, the pharmacy costs for adherent AD users was \$125 higher (\$340 vs. \$465, $p < 0.001$). The results for PD-related pharmacy costs were robust after conducting sensitivity analyses with PDC cut-off values of 0.70 and 0.90. However, when cut-off value was set at 0.70, adherent AD users had significantly higher PD-related nursing facility costs than non-adherent AD users even though the medians were equal (median: \$0 vs. \$0, mean rank: 414.65 vs. 441.41, $p = 0.019$). If cut-off value equaled to 0.90, non-adherent AD users had significantly higher PD-related inpatient costs than non-adherent AD users despite same median values were observed (median: \$0 vs. \$0, mean rank: 439.95 vs. 397.71, $p = 0.006$). Results for sensitivity analyses are presented in Table 3.28 and Table 3.29.

Table 3.27 Unadjusted PD-related healthcare costs comparisons (Cut-off value for being adherent: PDC = 0.80)

PD-related Cost Category	Overall (N=856)		Non-adherent to AD (N=501)		Adherent to AD (N=355)		Z	p-value
	Median	IQR	Median	IQR	Median	IQR		
OP-Office	$252	$486	$244	$488	$262	$481	-0.7289	0.466
OP-Home	$0	$117	$0	$118	$0	$102	-0.3032	0.762
OP-Other	$0	$115	$0	$123	$0	$108	-0.0155	0.988
Nursing facility	$0	$0	$0	$0	$0	$0	1.6663	0.096
Inpatient	$0	$506	$0	$1,299	$0	$217	-1.6822	0.093
ER	$0	$0	$0	$0	$0	$0	1.0952	0.273
Pharmacy	$393	$983	$340	$843	$465	$1,052	3.8814	<0.001*
Total	$2,500	$9,769	$2,410	$9,781	$2,741	$9,767	1.0562	0.291

Note: Wilcoxon rank-sum tests were used. AD = antidepressant; IQR = interquartile range; OP = outpatient; ER = emergency room; PD = Parkinson's disease
*Significant at $p < 0.05$

Table 3.28 Unadjusted PD-related healthcare costs comparisons (Cut-off value for being adherent: PDC = 0.70)

PD-related Cost Category	Non-adherent to AD (N=413)		Adherent to AD (N=443)		Z	p-value
	Median	IQR	Median	IQR		
OP-Office	$246	$486	$255	$454	1.0226	0.307
OP-Home	$0	$121	$0	$102	0.2527	0.801
OP-Other	$0	$130	$0	$105	0.1807	0.857
Nursing facility	$0	$0	$0	$0	-2.3439	0.019*
Inpatient	$0	$1,021	$0	$309	1.0435	0.297
ER	$0	$0	$0	$0	-0.9938	0.320
Pharmacy	$344	$844	$434	$1,020	-3.0085	0.003*
Total	$2,290	$8,972	$2,750	$10,346	-1.5556	0.120

Note: Wilcoxon rank-sum tests were used. AD = antidepressant; IQR = interquartile range; OP = outpatient; ER = emergency room; PD = Parkinson's disease
*Significant at $p < 0.05$

Table 3.29 Unadjusted PD-related healthcare costs comparisons (Cut-off value for being adherent: PDC = 0.90)

PD-related Cost Category	Non-adherent to AD (N=624)		Adherent to AD (N=232)		Z	p-value
	Median	IQR	Median	IQR		
OP-Office	$252	$497	$251	$462	-0.5756	0.565
OP-Home	$0	$183	$0	$0	-1.3803	0.168
OP-Other	$0	$126	$0	$99	-0.8785	0.380
Nursing facility	$0	$0	$0	$0	0.7343	0.463
Inpatient	$0	$1,533	$0	$0	-2.7261	0.006*
ER	$0	$0	$0	$0	1.3271	0.185
Pharmacy	$366	$890	$465	$1,205	2.8813	0.004*
Total	$2,687	$10,714	$2,290	$6,925	-1.2302	0.219

Note: Wilcoxon rank-sum tests were used. AD = antidepressant; IQR = interquartile range; OP = outpatient; ER = emergency room; PD = Parkinson's disease
*Significant at $p < 0.05$

3.3.8.2 PD-related Healthcare Cost Comparison (Adjusted analysis)

The adjusted mean cost for PD-related healthcare services were estimated using two-part models to account for right skewed distribution and many zero values (Outputs were presented in Appendix 23 to Appendix 30). Table 3.30 shows the results after adjusting for demographic, clinical, and other covariates. There were no significant differences in adjusted PD-related mean outpatient (OP-office, OP-home, and OP-other), nursing facility, inpatient, ER, and total costs between adherent and non-adherent antidepressant users. But the results indicated that adherent antidepressant users had $400 more in PD-related pharmacy costs than non-adherent antidepressant users ($803 vs. $1,203, $p < 0.001$). Sensitivity analyses using different PDC cut-off values were performed and result for PD-related pharmacy costs were robust when the cut-off value was set at 0.70 or 0.90 (Table 3.31 and Table 3.32). However, when cut-off value of 0.90 was used, differences in PD-related OP-other, nursing facility, inpatient, and total mean costs between adherent and non-adherent AD users were found (all $p < 0.05$). The adjusted PD-related

OP-other, nursing facility, and inpatient costs for patients who were not adherent to antidepressant were more than two times higher than those who were adherent (OP-other: $542 vs. $255, p = 0.006; Nursing facility: $1,734 vs. $630, p = 0.001; Inpatient: $3,851 vs. $1,625, p < 0.001). In addition, the PD-related total cost for non-adherent AD users was $3,415 higher than non-adherent AD users when a cut-off value of 0.90 was specified ($11,000 vs. $7,585, p = 0.007) (Table 3.31and Table 3.32).

Table 3.30 Two-part models adjusted PD-related healthcare cost comparisons (Cut-off value for being adherent: PDC = 0.80)

PD-related Cost Category	Non-adherent to AD (N=501)				Adherent to AD (N=355)				p-value
	Mean	SE	95% CI		Mean	SE	95% CI		
OP-Office	$474	$35	$406	$543	$475	$39	$399	$551	0.995
OP-Home	$1,939	$294	$1,363	$2,514	$2,042	$354	$1,349	$2,735	0.814
OP-Other	$518	$88	$345	$691	$369	$71	$230	$507	0.168
Nursing facility	$1,683	$318	$1,059	$2,307	$1,066	$227	$621	$1,510	0.112
Inpatient	$3,709	$511	$2,707	$4,711	$2,499	$456	$1,604	$3,393	0.084
ER	$206	$27	$153	$259	$173	$25	$124	$223	0.38
Pharmacy	$803	$69	$667	$939	$1,203	$113	$982	$1,424	<0.001*
Total	$10,523	$1,505	$7,574	$13,472	$9,010	$1,319	$6,424	$11,596	0.209

Note: Two-part models were used (1st part: Logistic regression, 2nd part: GzLM with a gamma distribution and a log link). AD = antidepressant; SE = standard error; CI = confidence interval; OP = outpatient; ER = emergency room. All models adjusted for age, gender, geographical region, presence of specific comorbidities (anxiety, psychosis, and dementia), Charlson Comorbidity Index (CCI), having regimen modification, and pre-index Parkinson's disease-related total cost.
*Significant at p < 0.05

Table 3.31 Two-part model adjusted PD-related healthcare cost comparisons (Cut-off value for being adherent: PDC = 0.70)

PD-related Cost Category	Non-adherent to AD (N=413)				Adherent to AD (N=443)				p-value
	Mean	SE	95% CI		Mean	SE	95% CI		
OP-Office	$487	$38	$412	$563	$464	$35	$396	$532	0.611
OP-Home	$1,897	$313	$1,285	$2,510	$2,069	$331	$1,422	$2,717	0.693
OP-Other	$465	$83	$301	$628	$443	$80	$287	$599	0.837
Nursing facility	$1,434	$321	$804	$2,063	$1,376	$279	$829	$1,922	0.892
Inpatient	$3,387	$523	$2,362	$4,412	$3,015	$489	$2,055	$3,974	0.613
ER	$198	$29	$141	$256	$186	$25	$137	$235	0.750
Pharmacy	$807	$76	$659	$955	$1,125	$101	$927	$1,322	0.002*
Total	$9,819	$1,423	$7,030	$12,607	$9,840	$1,409	$7,079	$12,601	0.986

Note: Two-part models were used (1st part: Logistic regression, 2nd part: GzLM with a gamma distribution and a log link). AD = antidepressant; SE = standard error; CI = confidence interval; OP = outpatient; ER = emergency room. All models adjusted for age, gender, geographical region, presence of specific comorbidities (anxiety, psychosis, and dementia), Charlson Comorbidity Index (CCI), having regimen modification, and pre-index Parkinson's disease-related total cost.
*Significant at $p < 0.05$

Table 3.32 Two-part model adjusted PD-related healthcare cost comparisons (Cut-off value for being adherent: PDC = 0.90)

PD-related Cost Category	Non-adherent to AD (N=624)				Adherent to AD (N=232)				p-value
	Mean	SE	95% CI		Mean	SE	95% CI		
OP-Office	$483	$33	$418	$547	$456	$44	$370	$542	0.596
OP-Home	$1,912	$243	$1,435	$2,388	$2,195	$479	$1,256	$3,134	0.584
OP-Other	$542	$88	$369	$714	$255	$63	$131	$378	0.006
Nursing facility	$1,734	$285	$1,175	$2,294	$630	$160	$317	$943	0.001
Inpatient	$3,851	$482	$2,908	$4,795	$1,625	$388	$865	$2,386	<0.001
ER	$197	$23	$151	$243	$179	$32	$117	$241	0.657
Pharmacy	$843	$66	$714	$973	$1,299	$139	$1,026	$1,572	0.001
Total	$11,000	$1,605	$7,855	$14,145	$7,585	$1,242	$5,151	$10,020	0.007

Note: Two-part models were used (1st part: Logistic regression, 2nd part: GzLM with a gamma distribution and a log link). AD = antidepressant; SE = standard error; CI = confidence interval; OP = outpatient; ER = emergency room. All models adjusted for age, gender, geographical region, presence of specific comorbidities (anxiety, psychosis, and dementia), Charlson Comorbidity Index (CCI), having regimen modification, and pre-index Parkinson's disease-related total cost.
*Significant at $p < 0.05$

H_{08a}: There is no significant difference in **PD-related outpatient costs** between adherent and non-adherent antidepressants users while controlling for covariates. **(Not rejected)**

H_{08b}: There is no significant difference in **PD-related nursing facility costs** between adherent and non-adherent antidepressants users while controlling for covariates. **(Not rejected)**

H_{08c}: There is no significant difference in **PD-related inpatient costs** between adherent and non-adherent antidepressants users while controlling for covariates. **(Not rejected)**

H_{08d}: There is no significant difference in **PD-related ER costs** between adherent and non-adherent antidepressants users while controlling for covariates. **(Not rejected)**

H_{08e}: There is no significant difference in **PD-related pharmacy costs** between adherent and non-adherent antidepressants users while controlling for covariates. **(Rejected)**

H_{08f}: There is no significant difference in **PD-related total costs** between adherent and non-adherent antidepressants users while controlling for covariates. **(Not rejected)**

3.3.9 Summary of Hypotheses Testing

A summary of hypotheses testing is presented in Table 3.33.

Table 3.33 Results of hypotheses testing

Objectives/Hypotheses	Statistical Analysis	Result
Objective 1: To describe and compare demographic and clinical characteristics among PD patients with depression	Descriptive statistics	--
Objective 2: To describe antidepressants use patterns (index antidepressant type, adherence, persistence, switching, combination therapy) among PD patients with depression	Descriptive statistics	--
Objective 3: To identify the factors associated with being adherent among PD patients with depression		
H_{03a}: **Age** is not associated with being adherent to antidepressants after controlling for other covariates.	Logistic regression	Not rejected
H_{03b}: **Being female** is not associated with being adherent to antidepressants after controlling for other covariates.	Logistic regression	Not rejected
H_{03c}: **Geographic region** is not associated with being adherent to antidepressants after controlling for other covariates.	Logistic regression	Not rejected
H_{03d}: **Having anxiety** is not associated with being adherent to antidepressants after controlling for other covariates.	Logistic regression	Not rejected
H_{03e}: **Having psychosis** is not associated with being adherent to antidepressants after controlling for other covariates.	Logistic regression	Not rejected
H_{03f}: **Having dementia** is not associated with being adherent to antidepressants after controlling for other covariates	Logistic regression	Not rejected
H_{03g}: **The CCI score** is not associated with being adherent to antidepressants after controlling for other covariates.	Logistic regression	Rejected
H_{03h}: Having **regimen modification** of the index antidepressants is not associated with being adherent to antidepressants after controlling for other covariates.	Logistic regression	Rejected
H_{03i}: **The pre-index PD-related total cost** is not associated with being adherent to antidepressants after controlling for other covariates.	Logistic regression	Not rejected
Objective 4: To identify the factors associated with persistence among PD patients with depression		

Table 3.33 Results of hypotheses testing (continued)

H_{04a}: **Age** is not associated with persistence after controlling for other covariates.	Cox proportional hazards model	Not rejected
H_{04b}: **Being female** is not associated with persistence after controlling for other covariates.	Cox proportional hazards model	Rejected
H_{04c}: **Geographic region** is not associated with persistence after controlling for other covariates.	Cox proportional hazards model	Not rejected
H_{04d}: **Having anxiety** is not associated with persistence after controlling for other covariates.	Cox proportional hazards model	Not rejected
H_{04e}: **Having psychosis** is not associated with persistence after controlling for other covariates.	Cox proportional hazards model	Not rejected
H_{04f}: **Having dementia** is not associated with persistence after controlling for other covariates.	Cox proportional hazards model	Not rejected
H_{04g}: **The CCI score** is not associated with persistence after controlling for other covariates.	Cox proportional hazards model	Not rejected
H_{04h}: **Having regimen modification of the index antidepressants** is not associated with persistence after controlling for other covariates.	Cox proportional hazards model	Rejected
H_{04i}: **The pre-index PD-related total cost** is not associated with persistence after controlling for other covariates.	Cox proportional hazards model	Not rejected
Objective 5: To determine if all-cause healthcare resource utilization differs significantly between adherent and non-adherent antidepressants users while controlling for covariates		
H_{05a}: There is no significant difference in number of **outpatient visits** between adherent and non-adherent antidepressants users while controlling for covariates.	ZINB model or GzLM	Not rejected
H_{05b}: There is no significant difference in number of **nursing facility days billed** between adherent and non-adherent antidepressants users while controlling for covariates.	ZINB model	Not rejected
H_{05c}: There is no significant difference in number of **inpatient visits** between adherent and non-adherent antidepressants users while controlling for covariates.	ZINB model	Rejected
H_{05d}: There is no significant difference in number of **emergency room (ER) visits** between adherent and non-adherent antidepressants users while controlling for covariates.	ZINB model	Not rejected
Objective 6: To determine if PD-related healthcare resource utilization differs significantly between adherent and non-adherent antidepressants users while controlling for covariates		

Table 3.33 Results of hypotheses testing (continued)

H_{06a}: There is no significant difference in number of **PD-related outpatient visits** between adherent and non-adherent antidepressants users while controlling for covariates.	ZINB model or GzLM	Not rejected
H_{06b}: There is no significant difference in number of **PD-related nursing facility days billed** between adherent and non-adherent antidepressants users while controlling for covariates.	ZINB model	Not rejected
H_{06c}: There is no significant difference in number of **PD-related inpatient visits** between adherent and non-adherent antidepressants users while controlling for covariates.	ZINB model	Rejected
H_{06d}: There is no significant difference in number of **PD-related ER visits** between adherent and non-adherent antidepressants users while controlling for covariates.	ZINB model	Not rejected
Objective 7: To determine if all-cause healthcare costs differ significantly between adherent and non-adherent antidepressants users while controlling for covariates.		
H_{07a}: There is no significant difference in **all-cause outpatient costs** between adherent and non-adherent antidepressants users while controlling for covariates.	Two-part model	Not rejected
H_{07b}: There is no significant difference in **all-cause nursing facility costs** between adherent and non-adherent antidepressants users while controlling for covariates.	Two-part model	Rejected
H_{07c}: There is no significant difference in **all-cause inpatient costs** between adherent and non-adherent antidepressants users while controlling for covariates.	Two-part model	Rejected
H_{07d}: There is no significant difference in **all-cause ER costs** between adherent and non-adherent antidepressants users while controlling for covariates.	Two-part model	Rejected
H_{07e}: There is no significant difference in **all-cause pharmacy costs** between adherent and non-adherent antidepressants users while controlling for covariates.	GzLM	Rejected
H_{07f}: There is no significant difference in **all-cause total costs** between adherent and non-adherent antidepressants users while controlling for covariates.	GzLM	Rejected
Objective 8: To determine if PD-related healthcare costs differ significantly between adherent and non-adherent antidepressants users while controlling for covariates.		
H_{08a}: There is no significant difference in **PD-related outpatient costs** between adherent and non-adherent antidepressants users while controlling for covariates.	Two-part model	Not rejected
H_{08b}: There is no significant difference in **PD-related nursing facility costs** between adherent and non-adherent antidepressants users while controlling for covariates.	Two-part model	Not rejected
H_{08c}: There is no significant difference in **PD-related inpatient costs** between adherent and non-adherent antidepressants users while controlling for covariates.	Two-part model	Not rejected
H_{08d}: There is no significant difference in **PD-related ER costs** between adherent and non-adherent	Two-part model	Not rejected

Table 3.33 Results of hypotheses testing (continued)

antidepressants users while controlling for covariates.		
H_{08e}: There is no significant difference in **PD-related pharmacy costs** between adherent and non-adherent antidepressants users while controlling for covariates.	Two-part model	Rejected
H_{08f}: There is no significant difference in **PD-related total costs** between adherent and non-adherent antidepressants users while controlling for covariates.	Two-part model	Not rejected

GzLM = generalized linear model; ZINB = zero-inflated negative binomial; ER = emergency room
Covariates include age, gender, geographical region, presence of specific comorbidities (anxiety, psychosis, and dementia), Charlson Comorbidity Index (CCI), having regimen modification, and pre-index Parkinson's disease-related total cost

CHAPTER 4: DISCUSSION AND CONCLUSIONS

4.1 Chapter Overview

This chapter provides a summary of the main findings of our study. Results are compared with previous studies and possible explanations are discussed. Study strengths and limitations, conclusions, and suggestions for future research are covered at the end of this chapter.

4.2 Review of Study Purpose

As discussed in the literature review section, depression is a prevalent comorbidity in PD patients and often starts in the early phase of PD. Previous studies have found that the use of antidepressant may delay the progression of PD and improve motor and cognitive functions of PD patients. However, little has been reported regarding antidepressant use and the related outcomes among depressed PD patients. Therefore, the aims of the present study were to examine antidepressant use patterns and evaluate the associated healthcare resource utilization and costs for depressed PD patients using the Humana database from January 2007 to December 2010.

4.3 Study Objectives

4.3.1 Objective 1: Demographic and Clinical Characteristics

Objective 1 was to describe and compare demographic and clinical characteristics among adherent and non-adherent antidepressant (AD) users. Mean age and gender distribution for our entire study cohort were within the range of the values reported by previous studies for PD

patients (Mean age: 68.9 – 78.4 years old; Female percentage: 39.7% - 60.5%).[23,27,28,79,83,85] As expected, more patients resided in the Southern US in our study than other studies because the Humana database covers a greater proportion of members in the South. The mean CCI for our study cohort (2.2) was higher than the mean CCIs reported for general PD patients in other studies (1.0 – 1.76) .This may indicate that depressed PD patients with antidepressant use had a higher level of overall comorbidity burden than general PD patients.[23,27,79] Compared to non-adherent AD users, adherent AD users had higher pre-index PD-related total costs and greater proportions of the presence of psychosis and dementia. This may suggest that adherent AD users had greater PD severity and more comorbid neuropsychiatric and cognitive impairment diseases than non-adherent AD users at baseline. A greater proportion of adherent AD users had regimen modifications (switching or combination therapy) than non-adherent AD users during the 1-year follow-up. A detailed discussion about the relationship between regimen modification and adherence to AD is presented later in Objective 3 discussion section.

4.3.2 Objective 2: Antidepressant Use Patterns

Objective 2 was to describe antidepressant use patterns (index antidepressant type, adherence, persistence, switching, and combination therapy). In our study, most of the patients were prescribed SSRIs at the index date (68.1%). This was in line with previous findings that the majority of depressed PD patients received SSRIs for their depression treatment.[118,148] Based on the VA data, Chen and his colleagues reported that 62.9% of the patients used SSRIs. Weintraub et al. used a convenience sample from a PD center and found that 69.6% of the patients received SSRIs. This observation also revealed that although some evidence indicated that TCAs may

have greater efficacy for treating depression in PD, SSRIs are still most commonly prescribed in practice.[116] The most commonly prescribed antidepressants in the present study were citalopram (37.97%) and sertraline (14.14%). The proportions of patients using citalopram and sertraline were both 26.1% in the Weintraub study.[148] One previous study also reported that citalopram was more commonly prescribed for depression than sertraline in Medicare beneficiaries with depression.[181] However, the Chen study using VA data and found sertraline use (25.90%) was more common than citalopram (19.76%) use for depressed PD patients with antidepressants.[118] One possible explanation for the proportional differences may be due to the difference in prescription drug coverage under Medicare and the VA system.

Adherence (measured as PDC) to antidepressants among depressed PD patients in our study differed from some of the estimates of adherence to antidepressants for depressed patients in previous studies.[182] In the present study, the mean PDC was 0.63, and 41.5% of the depressed PD patients were considered adherent using a cut-off of PDC=0.8 during the 1-year follow-up. Cantrell et al. used the Impact National Managed Care Benchmark Database to assess the adherence to antidepressant among non-PD patients with depression and/or anxiety and found a mean MPR of 0.43 along with an adherence rate of 43% (MPR ≥0.8) during the 6-month follow-up.[182] Using VA data, Zivin et al. followed depressed patients for six months and reported a mean MPR of 0.66, with 40% being adherent (MPR ≥0.8).[183] Another recent study using the MarketScan Database measured adherence to antidepressants for six months among depressed patients and found a PDC of 0.71.[159] Lin et al. used the Medical Expenditure Panel Survey and observed that 23.5% of the patients were adherent (PDC ≥0.8) during the 1-year follow-up.[177] The differences in adherence may be partially explained by different follow-up periods, different

study population and demographic characteristics in varied databases, and the presence of PD. Rather than using a shorter 6- month follow-up period, we used a 1-year follow-up period to capture adherence, persistence, and annual utilization/costs. For the demographical differences, the samples in the Zivin study were predominantly male (94-95%) while nearly half of the patients in our study were female (47.1%). Previous studies have found that women tend to have lower adherence rate to medications for chronic disease treatment than men, which may partially explain the different adherence results.[184-186] In addition, the study cohorts in the above studies (Zivin study: mean age=52 years; Cantrell study: mean age=37.6 years; Wu study: mean age=41 years; Lin study: less than 10% of the patients older than 65 years) were much younger than our study cohort (mean age=75.4 years). In previous studies, older age and presence of PD were associated with more frequent follow-up medical visits, which may be positively related to better adherence.[187-189] In fact, elderly patients, on average, had better adherence rates than younger patients.[190-192] A published report from the Centers for Medicare & Medicaid Services (CMS) estimated MPR for medications used to treat several chronic diseases and found that most of the patients with chronic conditions had an MPR $\geq$ 0.70 during a 1-year follow-up among those who enrolled in a Medicare prescription drug plan (PDP). The reported MPRs to medications for depression ranged from 0.59 to 0.73.[193] Although we used a relatively conservative approach — PDC instead of MPR- to measure adherence and set our original cut-off at PDC = 0.8 (instead of MPR of .70), our population is similar and our results are comparable to the findings for adherence to depression treatment among depressed Medicare PDP enrollees.

If there is no or minimal response to antidepressants after initial treatment, guidelines recommend 1) increasing the dose, 2) switching ADs, or 3) adding another AD agent. Only a

small proportion of our study cohort experienced regimen modification (11.0%, without examining dose escalation). The proportion of patients with regimen modification in our study (11.0%) was smaller than the result from the Milea study (23.2%) but similar to the proportion for the older patient group from the Sanglier study (10.8%) (Milea et al. and Sanglier et al. did not include dose escalation as one of regimen modification categories either).[194,195] The discrepancy may be due to the age differences. The mean age for our study cohort was 75.4 years, while the mean age among patients in the Milea study was 39.1 years. Sanglier et al. compared the treatment patterns of antidepressants between older (≥65) and younger (25-64 years) patients. The authors reported a mean age of 78.1 for the older patient group. Khandker et al. used the PharMetrics Patient-Centric Database and also found that patients younger than 40 years old were more likely to make an antidepressant switch.[196] It could be possible that physicians may adopt longer antidepressant trials for older patients before they change treatment,[197,198] and thus these patients may be less likely to have regimen modifications during the follow-up period.

In our study patients had higher rates of combination therapy than switching (8.9% vs. 2.1%). However, Milea et al. reported that the proportion of patients with combination therapy was similar to those with antidepressant switching (9.1% vs. 9.5%);[194] and Sanglier et al. observed nearly reversed results of our study (2.8% combination vs. 8.0% switching).[195] The proportional differences of combination therapy and switching among our study and previous studies might indicate that the main reasons for regimen modification were different. Instead of switching to another antidepressant because of intolerable side effects of the initial therapy, the majority of depressed PD patients with regimen modification might have tolerated initial therapy

but had inadequate response to monotherapy. In addition, there may be fewer antidepressant switching options for depressed PD patients. For example, TCAs are not recommended to depressed PD patients because their antimuscarinic side effects (such as constipation and urinary retention) may exacerbate the pre-existing non-motor symptoms of PD.[99] Other antidepressants such as phenelzine and tranylcypromine should also be used with caution because of their potential for causing a hypertensive crisis among PD patients using levodopa.[99]

The persistence to antidepressants of depressed PD patients in our study differed from the persistence results from other studies. Cantrell et al. found that only 44.6% of those patients with depression were still on their antidepressants after six months.[182] Milea et al. reported the median treatment duration was 111 days, and 37.5% of the depressed patients were still using antidepressants at the 6-month follow-up.[194] Milea et al. also reported that at the end of the 1-year follow-up period, the proportion of patients who remained on antidepressant treatment was 22.8%. Compared to the Cantrell study and the Milea study, the study cohort in our analysis had better persistence (median treatment duration: 163.5 days; percentages of patients with antidepressant after six months: 47.3%, after one year: 32.0%). However, patients in our study were less persistent than those patients from the Bao study and the Sanglier study. Bao et al. found the rate of antidepressant disruption among Medicare beneficiaries ranged from 29.3 to 39.3% after six months.[199] Sanglier et al. also investigated the rate of antidepressant disruption using the IMS LifeLink Health Plan Database.[195] The non-persistence rate for the older patient group (aged ≥65 years) from their study was 51%. Age may partially contribute to the varying persistence results. The mean age for our study cohort was 75.4 years, which was greater than the observations in the first two studies described (the Cantrell study: 43 years; the Milea study:

39.1 years), but slightly younger than the observations in the last two studies above (the Bao study: 78.9 and 77.9 years depending on whether they were receiving low-income subsidy; the Sanglier study: 78.1 years). As mentioned above, clinicians tend to extend the antidepressant titration period for elderly patients to evaluate whether patients have adequate response.[197,198] Therefore, older patients may have longer initial antidepressant trial periods and show better persistence results.

A great proportion of patients discontinued antidepressant treatment after the 6-month follow-up (52.7%). However, we do not know the reasons behind early discontinuation. Possible factors associated with suboptimal persistence in this population such as unpleasant side effects of AD, complexity of treatment, and lack of understanding of the disease may be explored in the future. Another possible explanation is that lacked follow-up pharmacologic management to optimize antidepressants treatment effect, which in turn caused early discontinuation due to the poor response to antidepressants. We observed a small proportion of patients with regimen modification (11%). Weintraub et al. used a convenience sample at a PD center and also observed nearly all patients did not receive regimen modification to optimize treatment during the follow-up.[148] One possible explanation for this is the difficulty in understanding whether the clinical presentations were related to "inadequate antidepressant treatment" or PD because depression and PD share common symptoms.[94]

4.3.3 Objectives 3 & 4: Factors Associated with Adherence and Persistence

Objectives 3 and 4 were to identify factors associated with adherence and persistence to antidepressants among depressed PD patients. Our results revealed that depressed PD patients with a greater comorbidity score were more likely to be adherent to antidepressants. Mixed results have been found in the literature for the relationship between comorbidities and adherence to antidepressants. Rivero-Santana et al. conducted a systematic review to analyze the predictors of compliance with antidepressants in depressed patients.[200] In this systematic review, three studies reported that higher levels of comorbidity were significantly associated with better adherence to antidepressants, whereas another three studies observed a negative association between the level of comorbidity and adherence. The authors concluded that the inconsistency might be explained as follows: while the experience of coping with a variety of diseases may positively affect patients' medication management, this relationship may be shifted to a reverse direction after the interaction with other factors such as sociodemographics, health beliefs, and access to follow-up pharmacologic management. This assumption may also be applied to our findings given that PD patients are often older and may live with other chronic diseases. In addition, as commented above, higher levels of comorbidity may also be associated with more frequent physician visits for follow-up care, which may be linked to better adherence.[188]

In the present study, depressed PD patients with regimen modification had better adherence and persistence to antidepressants than those without. A similar trend was also observed in the Milea study.[194] After controlling for demographic and clinical characteristics, Milea et al. found that patients with combination therapy or augmentation were less likely to discontinue their antidepressant than those without (combination, HR = 0.83 [95% CI, 0.81–

0.86]; augmentation, HR = 0.75 [95% CI, 0.73–0.77]). One possible explanation is that regimen modification reflects whether physicians optimize antidepressant treatment and adjust treatment strategy for partially responsive depression or resistant depression.[111] Therefore, patients may benefit from regimen modification and have a better response, which in turn may improve adherence and persistence to antidepressants.

4.3.4 Objectives 5 to 8: Utilization and Costs

All-cause and PD-related utilization and costs were calculated for the entire study cohort, and then differences were compared between adherent and non-adherent AD users. For all-cause utilization, we found that the patients in the current study had a higher number of all-cause ER visits (0.59) than other studies that investigated utilization in PD patients (0.16 and 0.37).[23,25] However, it is difficult to compare other healthcare services use from our findings with previous results because the definitions of many healthcare services vary from study to study.[23-25,79] When comparing our cost results to the costs of PD patients, overall, our study cohort had higher all-cause inpatient ($8,646), outpatient (OP-office: $2,232, OP-home: $3,603, OP-other: $2,637), ER ($763), and total costs ($25,746) than the majority of the different service costs in other studies.[22-25,79] Huse et al. analyzed the MarketScan database and reported the following costs for PD patients: inpatient acute plus non-acute care ($11,155), ER ($29), outpatient ($8,557 - which was similar to the sum of our outpatient costs), pharmacy ($3,366), and total cost ($23,101). Another study used survey data from Medicare beneficiaries to estimate costs for PD patients: inpatient ($4,119), outpatient ($4,082), long-term care ($4,926), short-term facility ($855), home health care ($1,111), and total cost ($18,528). O'Brien et al. also calculated costs for PD patients

under different service categories: physician visits ($571), nursing home ($5,126, which was higher than our nursing facility costs), hospitalization ($1,382), other ($2,645), and total cost ($12,491). Davis et al. only categorized the costs into three categories and observed $8,762 for medical cost, $3,504 for pharmacy cost, and $12,266 for the total cost. The reason why our findings are higher than previous studies may be explained by the fact that patients in our study had comorbid depression and received antidepressants for their depression treatment, while other studies included all PD patients, whether or not they had comorbid depression. Given that depression has been reported as a factor associated with worse outcomes in PD,[135-138] it is understandable that we found higher costs in our study.

Objectives 5 and 6 were to compare all-cause and PD-related utilization between adherent and non-adherent AD users among depressed PD patients. We found that adherent AD users had fewer all-cause and PD-related inpatient visits than non-adherent AD users. If we applied a more restrictive criterion for "being adherent" and used PDC=0.90 as the cut-off value, results for inpatient visits remained the same but adherent AD users also had less PD-related OP-other visits than non-adherent AD users. Objectives 7 and 8 were to compare all-cause and PD-related costs between adherent and non-adherent AD users. We found that there were significant differences in all-cause cost categories between adherent and non-adherent users except for all-cause outpatient costs. Overall, adherent AD users had less all-cause nursing facility, inpatient, and ER costs. Although adherent AD users had a higher all-cause pharmacy cost than non-adherent AD users, the extra cost in pharmacy was offset by reduced costs in other cost categories and generated lower all-cause total cost in adherent AD users. However, although we observed this trend in PD-related costs, the results were no longer significant. But if we applied a

more restrictive cut-off value (PDC=0.90) for being adherent to antidepressants, significant differences were found: adherent AD users had higher PD-related pharmacy costs but lower PD-related OP-other, nursing facility, inpatient, and total costs than non-adherent AD users. The reason why applying a higher PDC cut-off value was associated with more significant differences in outcomes may be that using a higher cut-off value may better reflect the effectiveness of antidepressant treatment in our study cohort. This is supported by the Fortney study.[201] Fortney and his colleagues assessed the correlation between adherence to antidepressant and changes in self-reported depression symptoms. Although the traditional recommended cut-off value for MPR is 0.80, they found that MPR $\geq$ 0.90 could better predict treatment response to antidepressants.

Overall, these findings showed that for this cohort of older depressed PD patients, those who were adherent to antidepressant treatment had fewer all-cause and PD-related healthcare utilization and lower costs for some services than those who were non-adherent. Because of the shared etiologic factors, it has been suggested that depression can be a potential risk factor for developing PD or depression could be an early manifestation of PD.[7,87] Several studies have also reported that use of antidepressants to manage depression in PD may not only control depression but also delay the need for dopaminergic therapy, ameliorate motor function, and improve certain domains of cognitive dysfunction for PD patients.[90,91,93] Our results may give credence to these previous findings: Depressed PD patients who were adherent to antidepressants had less all-cause and PD-related inpatient visits. It could be possible that well-controlled depression may slow the progression of PD, and thus prevent falls in PD patients and reduce inpatient visits. The effects of slowing PD progression and improving cognitive function may result in lower all-

cause and PD-related costs among patients who were adherent to antidepressant than those who were not. Moreover, as discussed in the demographic characteristics comparisons above, these adherent patients in our study had higher pre-index PD-related total costs and higher CCI at baseline. This may suggest that better control of depression may decrease all-cause and PD-related utilization and costs despite the greater PD severity and comorbid disease burden at baseline. In addition to the above potential neurobiological link between depression and PD, depression has also been identified as a determinant associated with non-adherence to antiparkinson medications and higher healthcare costs in PD patients. Taken together, improvement of depression care may be associated with better outcomes and reduced healthcare costs among depressed PD patients. Besides these, previous studies have also reported that depression is a determinant of lower HRQoL among PD patients.[4] Therefore, improvement in control of depression and the potential decrease in inpatient visits may translate into a higher HRQoL for depressed PD patients.

4.4 Study Strengths and Limitations

Although previous studies have examined antidepressant use in depressed PD patients, no study has assessed treatment patterns such as adherence, persistence, and regimen modification among this population. Our study provides the first evidence of compliance and treatment changes, as well as the factors associated with these treatment patterns of antidepressant use in this population. Moreover, the Chen study used VA data with predominantly male elderly veterans and the Weintraub study only used a convenience sample at a PD center.[118,148]

Therefore, our study may have a better generalizability, especially for the population enrolled in a Medicare Advantage Prescription Drug (MAPD) plan

Previous studies have suggested that depression may negatively affect PD, but no study has investigated whether better adherence with antidepressants, and thus expected better control of depression, can improve outcomes in PD patients. Based on our knowledge, our study is the first to address the association between adherence to antidepressant treatment and healthcare outcomes among depressed PD patients.

There are several study limitations. First, because this is an observational study, causal relationships cannot be established. This means it cannot be concluded that better adherence to antidepressants caused reduced utilization and costs among depressed PD patients, just that there is an association. Second, due to the lack of clinical data, we were unable to control for disease severity of PD in our present study. Healthcare resource utilization and costs are closely related to the severity of PD. In addition, patients with a PD diagnosis may not receive antiparkinson medication until the motor symptoms affect their daily function.[202] Since depression can occur before or after the onset of motor symptoms,[87,203,204] patients with different PD severity levels were included, which in turn may lead to bias in the outcomes. In addition, although it was expected that pre-index adherence to PD-related medications would be correlated with AD adherence, over 100 patients did not have any PD-related medications before the index AD. Clinically, this occurs because practitioners may wait until symptoms of PD are intensified before prescribing PD-related medications.[202] Third, due to the lack of data, we were not able to examine those factors (e.g., race, laboratory values, education level, marital status, income, and health behavior) that may be relevant to our outcomes. Fourth, the original purpose of

administrative claims databases are for reimbursement rather than research. Therefore, the potential errors of disease misclassification or miscoding could be possible. Fifth, by using a prescription claims database, the outcomes we observed were specifically based on "prescription fill patterns" rather than actual "medication taking patterns". Although high concordance between using prescription fill data and pill count were reported in a previous study,[205] the prescription fill data may not exactly reflect true medication use behavior. Sixth, although all of our AD users were with depression diagnoses, it could still be possible that some of them also used ADs to treat other comorbidities. Lastly, because this study was conducted in patients with Medicare Advantage Prescription Drug (MAPD) Plan, and a majority resided in the southern US regions, this study may have limited generalizability beyond this population.

Although we identified factors associated with adherence and persistence to antidepressants, the reasons for discontinuation or non-adherence are not known. Future research could conduct interviews with focus groups to understand the reasons behind treatment interruption and suboptimal adherence. It would also be interesting to know the association between antidepressant dosing escalation and the corresponding adherence changes. Because we found our results changed with different PDC cut-off values, future studies may also explore the most optimal PDC cut-off value for assessing treatment response and outcomes for depressed PD patients.

4.5 Conclusions

In conclusion, regimen modifications of antidepressants (switching or combination therapy) were associated with better adherence and persistence among depressed PD patients. Less frequent all-cause and PD-related inpatient visits as well as lower all-cause and PD-related direct medical costs were found in adherent AD users compared to non-adherent AD users among depressed PD patients. Our results also have clinical implications. Depression has a negative impact on PD and improved adherence to antidepressant may partially reverse this impact. Given the fact that depression is often under-diagnosed and untreated,[206] it is important to screen for depression in PD and prescribe and monitor antidepressant treatment for those who are identified as depressed PD patients.

Appendix 1 Number of claims for different all-cause healthcare utilization

Category	Place of Service	Frequency	Percent
OP-office	Office	29,196	22.89
OP-home	Home	17,807	13.96
OP-other	Assisted Living Facility	28	0.02
	Urgent Care Facility	17	0.01
	On Campus-Outpatient Hospital	15,062	11.81
	Ambulatory Surgical Center	566	0.44
	Mass Immunization Center	4	0
	End-Stage Renal Disease Treatment Facility	1,509	1.18
	Rural Health Clinic	17	0.01
	Independent Laboratory	11,799	9.25
Inpatient	Inpatient Hospital	24,805	19.45
	Inpatient Psychiatric Facility	2	0
	Psychiatric Facility-Partial Hospitalization	268	0.21
	Comprehensive Inpatient Rehabilitation Facility	143	0.11
ER	Emergency Room – Hospital	9,966	7.82
Nursing facility	Skilled Nursing Facility	5,666	4.44
	Nursing Facility	8,299	6.51
	Custodial Care Facility	12	0.01
Others	Ambulance - Land	2,324	1.82
	Other Place of Service	32	0.03

Note: OP=outpatient; ER=emergency room

Appendix 2 Number of claims for different PD-related healthcare utilization

Category	Place of Service	Frequency	Percent
OP-office	Office	5,401	17.08
OP-home	Home	8,793	27.81
OP-other	Assisted Living Facility	1	0
	Urgent Care Facility	2	0.01
	On Campus-Outpatient Hospital	2,280	7.21
	Ambulatory Surgical Center	17	0.05
	Independent Laboratory	859	2.72
Inpatient	Inpatient Hospital	6,818	21.56
	Psychiatric Facility-Partial Hospitalization	7	0.02
	Comprehensive Inpatient Rehabilitation Facility	24	0.08
ER	Emergency Room – Hospital	2,726	8.62
Nursing facility	Skilled Nursing Facility	1,857	5.87
	Nursing Facility	2,723	8.61
	Custodial Care Facility	2	0.01
Others	Ambulance - Land	106	0.34
	Other Place of Service	1	0

Note: OP=outpatient; ER=emergency room

Appendix 3 Zero-inflated negative binomial model for number of all-cause outpatient office (OP-office) visits

Variable	Coefficient	SE	z	p-value	95% CI	
Being adherent to AD	-0.045	0.052	-0.87	0.386	-0.147	0.057
Age	0.001	0.005	0.13	0.895	-0.008	0.010
Female (Ref=Male)	0.043	0.050	0.85	0.394	-0.056	0.141
Region (Ref=Northeast)						
Midwest	-0.465	0.143	-3.25	0.001	-0.745	-0.184
South	-0.292	0.139	-2.11	0.035	-0.564	-0.020
West	-0.418	0.159	-2.62	0.009	-0.730	-0.105
Having anxiety	0.043	0.059	0.74	0.460	-0.072	0.158
Having psychosis	-0.341	0.107	-3.19	0.001	-0.551	-0.132
Having dementia	-0.174	0.059	-2.93	0.003	-0.290	-0.057
CCI	0.049	0.010	4.86	<0.001	0.029	0.069
Having regimen modification	-0.118	0.081	-1.46	0.146	-0.278	0.041
Pre-index PD-related cost	2.8E-06	<0.001	1.27	0.203	-1.5E-06	7.2E-06
Intercept	3.116	0.376	8.29	<0.001	2.379	3.853
Inflate						
Being adherent to AD	1.995	1.148	1.74	0.082	-0.255	4.244
Age	0.071	0.063	1.14	0.256	-0.052	0.194
Female (Ref=Male)	-0.002	0.638	0	0.997	-1.253	1.249
Region (Ref=Northeast)						
Midwest	16.793	4921.002	0	0.997	-9628.193	9661.780
South	15.786	4921.002	0	0.997	-9629.200	9660.773
West	16.658	4921.002	0	0.997	-9628.328	9661.645
Having anxiety	-1.547	1.751	-0.88	0.377	-4.979	1.886
Having psychosis	1.303	0.712	1.83	0.067	-0.091	2.698
Having dementia	1.238	0.707	1.75	0.080	-0.147	2.624
CCI	-0.266	0.159	-1.67	0.095	-0.578	0.047
Having regimen modification	0.187	0.914	0.2	0.838	-1.604	1.978
Pre-index PD-related cost	1.26E-05	2.12E-05	0.59	0.553	-2.9E-05	5.4E-05
Intercept	-27.249	4921.004	-0.01	0.996	-9672.240	9617.743
ln alpha	-0.809	0.058	-13.95	<0.001	-0.922	-0.695
Alpha	0.445	0.026	--	--	0.398	0.499

Note: Inflation model = logit; LR chi^2 = 72.23; Log likelihood = -3225.927; Vuong test: z = 2.34, p = 0.010; AD=antidepressant; SE=standard error; CI=confidence interval; CCI=Charlson comorbidity index

Appendix 4 Zero-inflated negative binomial model for number of all-cause outpatient home (OP-home) visits

Variable	Coefficient	SE	z	p-value	95% CI	
Being adherent to AD	0.001	0.152	0	0.996	-0.297	0.298
Age	0.020	0.014	1.41	0.159	-0.008	0.048
Female (Ref=Male)	0.054	0.150	0.36	0.717	-0.240	0.348
Region (Ref=Northeast)						
Midwest	0.781	0.489	1.6	0.11	-0.177	1.740
South	1.352	0.470	2.88	0.004	0.431	2.274
West	1.077	0.523	2.06	0.039	0.052	2.102
Having anxiety	-0.088	0.191	-0.46	0.643	-0.463	0.286
Having psychosis	0.083	0.301	0.28	0.783	-0.508	0.674
Having dementia	0.112	0.177	0.63	0.527	-0.234	0.458
CCI	0.110	0.031	3.54	<0.001	0.049	0.170
Having regimen modification	0.355	0.235	1.51	0.131	-0.106	0.815
Pre-index PD-related cost	2.5E-05	7.8E-06	3.21	0.001	9.7E-06	4.0E-05
Intercept	-0.856	1.258	-0.68	0.496	-3.322	1.611
Inflate						
Being adherent to AD	0.161	0.406	0.4	0.691	-0.635	0.958
Age	-0.122	0.049	-2.49	0.013	-0.218	-0.026
Female (Ref=Male)	0.153	0.403	0.38	0.704	-0.637	0.944
Region (Ref=Northeast)						
Midwest	-0.512	1.430	-0.36	0.721	-3.315	2.292
South	0.023	1.281	0.02	0.985	-2.488	2.535
West	0.277	1.336	0.21	0.836	-2.341	2.894
Having anxiety	0.863	0.526	1.64	0.101	-0.168	1.894
Having psychosis	0.425	1.050	0.4	0.686	-1.633	2.483
Having dementia	0.168	0.654	0.26	0.798	-1.114	1.450
CCI	-0.848	0.404	-2.1	0.036	-1.639	-0.057
Having regimen modification	-0.457	0.704	-0.65	0.517	-1.836	0.923
Pre-index PD-related cost	-2.8E-04	1.0E-04	-2.29	0.022	-5.2E-04	-4.1E-05
Intercept	8.816	3.906	2.26	0.024	1.160	16.471
ln alpha	1.196	0.102	11.75	<0.001	0.996	1.395
Alpha	3.306	0.336	--	--	2.708	4.035

Note: Inflation model = logit; LR $chi^2 = 56.54$; Log likelihood = -2194.553; Vuong test: $z = 4.12$, $p < 0.001$; AD=antidepressant; SE=standard error; CI=confidence interval; CCI=Charlson comorbidity index

Appendix 5 GzLM with negative binomial distribution and log link for number of all-cause outpatient other (OP-other) visits

Variable	Coefficient	SE	z	p-value	95% CI	
Being adherent to AD	-0.108	0.073	-1.48	0.138	-0.250	0.035
Age	0.005	0.006	0.88	0.379	-0.007	0.017
Female (Ref=Male)	0.114	0.068	1.67	0.095	-0.020	0.247
Region (Ref=Northeast)						
Midwest	0.135	0.199	0.68	0.497	-0.254	0.524
South	-0.195	0.194	-1	0.315	-0.575	0.185
West	0.063	0.219	0.29	0.774	-0.367	0.493
Having anxiety	-0.219	0.081	-2.71	0.007	-0.378	-0.061
Having psychosis	-0.083	0.134	-0.62	0.538	-0.345	0.180
Having dementia	0.047	0.080	0.59	0.557	-0.110	0.204
CCI	0.098	0.014	6.91	<0.001	0.070	0.125
Having regimen modification	0.301	0.111	2.7	0.007	0.083	0.519
Pre-index PD-related cost	9.7E-06	3.0E-06	3.28	0.001	3.9E-06	1.2E-05
Intercept	1.652	0.501	3.29	0.001	0.669	2.634
ln alpha	-0.163	0.052	--	--	-0.265	-0.062
Alpha	0.849	0.044	--	--	0.767	0.940

Note: LR chi^2 = 99.47; Log likelihood = -2824.5443; $p < 0.001$; GzLM=generalized linear model; AD=antidepressant; SE=standard error; CI=confidence interval; CCI=Charlson comorbidity index

Appendix 6 Zero-inflated negative binomial model for number of all-cause nursing facility days billed

Variable	Coefficient	SE	z	p-value	95% CI	
Being adherent to AD	0.427	0.171	2.5	0.012	0.092	0.761
Age	0.006	0.015	0.39	0.698	-0.023	0.034
Female (Ref=Male)	-0.048	0.166	-0.29	0.772	-0.373	0.277
Region (Ref=Northeast)						
Midwest	0.815	0.394	2.07	0.039	0.043	1.587
South	0.367	0.398	0.92	0.357	-0.414	1.148
West	0.662	0.473	1.4	0.161	-0.265	1.590
Having anxiety	-0.143	0.191	-0.75	0.452	-0.517	0.230
Having psychosis	0.172	0.243	0.71	0.479	-0.304	0.647
Having dementia	0.274	0.173	1.58	0.113	-0.065	0.613
CCI	-0.011	0.031	-0.35	0.729	-0.072	0.051
Having regimen modification	0.373	0.236	1.58	0.114	-0.089	0.836
Pre-index PD-related cost	1.2E-05	6.7E-06	1.77	0.077	-1.3E-06	2.5E-05
Intercept	1.238	1.195	1.04	0.301	-1.105	3.581
Inflate						
Being adherent to AD	0.346	0.202	1.71	0.087	-0.050	0.741
Age	-0.092	0.018	-5.1	<0.001	-0.128	-0.057
Female (Ref=Male)	-0.043	0.189	-0.23	0.820	-0.414	0.328
Region (Ref=Northeast)						
Midwest	-0.086	0.572	-0.15	0.880	-1.207	1.035
South	0.842	0.563	1.5	0.135	-0.261	1.944
West	0.929	0.636	1.46	0.144	-0.318	2.177
Having anxiety	-0.042	0.226	-0.19	0.851	-0.485	0.400
Having psychosis	-0.612	0.396	-1.54	0.122	-1.389	0.165
Having dementia	-0.974	0.213	-4.57	<0.001	-1.391	-0.556
CCI	-0.176	0.046	-3.84	<0.001	-0.265	-0.086
Having regimen modification	-0.493	0.300	-1.65	0.100	-1.080	0.094
Pre-index PD-related cost	-1.9E-05	9.0E-06	-2.11	0.034	-3.7E-05	-1.4E-06
Intercept	7.833	1.476	5.31	<0.001	4.939	10.727
ln alpha	0.418	0.161	2.59	0.010	0.101	0.735
alpha	1.519	0.245	--	--	1.107	2.085

Note: Inflation model = logit; LR chi^2 = 30.40; Log likelihood = -1430.849; Vuong test: z = 6.32, p = 0.010; AD=antidepressant; SE=standard error; CI=confidence interval; CCI=Charlson comorbidity index

Appendix 7 Zero-inflated negative binomial model for number of all-cause inpatient visits

Variable	Coefficient	SE	z	p-value	95% CI	
Being adherent to AD	-0.332	0.123	-2.7	0.007	-0.573	-0.091
Age	-0.008	0.010	-0.79	0.427	-0.028	0.012
Female (Ref=Male)	-0.013	0.113	-0.11	0.909	-0.234	0.208
Region (Ref=Northeast)						
Midwest	0.165	0.347	0.48	0.634	-0.515	0.846
South	0.181	0.343	0.53	0.598	-0.491	0.852
West	0.210	0.387	0.54	0.587	-0.549	0.969
Having anxiety	-0.055	0.143	-0.39	0.7	-0.335	0.225
Having psychosis	0.416	0.192	2.16	0.031	0.039	0.793
Having dementia	-0.003	0.130	-0.02	0.981	-0.259	0.253
CCI	0.085	0.021	4.16	<0.001	0.045	0.125
Having regimen modification	0.426	0.191	2.23	0.026	0.051	0.800
Pre-index PD-related cost	6.7E-06	4.3E-06	1.57	0.117	-1.7E-06	1.5E-05
Intercept	0.618	0.876	0.71	0.48	-1.098	2.335
Inflate						
Being adherent to AD	0.242	0.593	0.41	0.683	-0.920	1.404
Age	-0.137	0.046	-3.01	0.003	-0.226	-0.048
Female (Ref=Male)	-0.573	0.572	-1.00	0.316	-1.695	0.549
Region (Ref=Northeast)						
Midwest	-1.668	1.291	-1.29	0.196	-4.198	0.863
South	-0.605	1.049	-0.58	0.564	-2.661	1.452
West	-0.452	1.209	-0.37	0.708	-2.822	1.918
Having anxiety	0.955	0.632	1.51	0.131	-0.284	2.195
Having psychosis	-0.069	1.390	-0.05	0.960	-2.794	2.656
Having dementia	-0.437	0.878	-0.50	0.619	-2.159	1.284
CCI	-0.497	0.210	-2.37	0.018	-0.908	-0.086
Having regimen modification	0.509	0.827	0.62	0.538	-1.111	2.130
Pre-index PD-related cost	-4.5E-04	2.0E-04	-2.29	0.022	-0.001	-6E-04
Intercept	10.622	3.605	2.95	0.003	3.556	17.688
ln alpha	-0.100	0.137	-0.73	0.463	-0.369	0.168
alpha	0.904	0.124	--	--	0.691	1.183

Note: Inflation model = logit; LR chi^2 = 36.74; Log likelihood = -1251.198; Vuong test: z = 2.95, p = 0.002; AD=antidepressant; SE=standard error; CI=confidence interval; CCI=Charlson comorbidity index

Appendix 8 GzLM with negative binomial distribution and log link for number of all-cause ER visits

Variable	Coefficient	SE	z	p-value	95% CI	
Being adherent to AD	-0.158	0.120	-1.32	0.188	-0.395	0.078
Age	0.004	0.011	0.37	0.713	-0.017	0.025
Female (Ref=Male)	0.289	0.118	2.46	0.014	0.058	0.520
Region (Ref=Northeast)						
Midwest	0.244	0.343	0.71	0.478	-0.429	0.917
South	-0.034	0.336	-0.1	0.919	-0.694	0.625
West	-0.116	0.387	-0.3	0.764	-0.875	0.643
Having anxiety	-0.049	0.140	-0.35	0.726	-0.324	0.226
Having psychosis	0.028	0.220	0.13	0.898	-0.403	0.460
Having dementia	0.153	0.132	1.16	0.246	-0.106	0.413
CCI	0.042	0.024	1.78	0.076	-0.004	0.089
Having regimen modification	0.294	0.176	1.67	0.095	-0.051	0.639
Pre-index PD-related cost	1.2E-05	5.0E-06	2.4	0.016	2.2E-06	2.2E-05
Intercept	-1.190	0.880	-1.35	0.177	-2.915	0.536
ln alpha	0.088	0.157	--	--	-0.220	0.397
Alpha	1.093	0.172	--	--	0.803	1.487

Note: LR chi^2 =26.45; Log likelihood = -885.48097; p =0.009; GzLM=generalized linear model; AD=antidepressant; SE=standard error; CI=confidence interval; CCI=Charlson comorbidity index; ER=emergency room

Appendix 9 Zero-inflated negative binomial model for number of PD-related outpatient office (OP-office) visits

Variable	Coefficient	SE	z	p-value	95% CI	
Being adherent to AD	-0.060	0.080	-0.75	0.453	-0.216	0.096
Age	-0.001	0.007	-0.18	0.857	-0.016	0.013
Female (Ref=Male)	0.086	0.079	1.09	0.276	-0.068	0.240
Region (Ref=Northeast)						
Midwest	-0.976	0.207	-4.73	<0.001	-1.381	-0.571
South	-0.862	0.194	-4.44	<0.001	-1.242	-0.481
West	-0.907	0.233	-3.9	<0.001	-1.363	-0.452
Having anxiety	-0.005	0.091	-0.05	0.958	-0.184	0.174
Having psychosis	-0.465	0.188	-2.47	0.013	-0.833	-0.097
Having dementia	-0.233	0.096	-2.43	0.015	-0.421	-0.045
CCI	-0.029	0.018	-1.64	0.101	-0.063	0.006
Having regimen modification	0.013	0.118	0.11	0.915	-0.219	0.244
Pre-index PD-related cost	1.8E-5	3.6E-6	4.97	<0.001	1.1E-5	2.5E-5
Intercept	2.535	0.591	4.29	<0.001	1.376	3.693
Inflate						
Being adherent to AD	0.269	0.481	0.56	0.577	-0.675	1.212
Age	0.045	0.051	0.89	0.375	-0.054	0.144
Female (Ref=Male)	0.208	0.497	0.42	0.676	-0.766	1.181
Region (Ref=Northeast)						
Midwest	1.491	1.526	0.98	0.328	-1.499	4.481
South	0.420	1.439	0.29	0.770	-2.401	3.242
West	0.750	1.726	0.43	0.664	-2.633	4.133
Having anxiety	-0.401	0.698	-0.57	0.565	-1.769	0.966
Having psychosis	-0.556	1.066	-0.52	0.602	-2.645	1.534
Having dementia	0.920	0.476	1.93	0.053	-0.012	1.853
CCI	0.212	0.074	2.88	0.004	0.068	0.357
Having regimen modification	-0.362	0.754	-0.48	0.631	-1.840	1.115
Pre-index PD-related cost	1.7E-05	1.2E-05	1.41	0.158	-6.5E-06	4.0E-05
Intercept	-7.812	4.450	-1.76	0.079	-16.534	0.911
ln alpha	-0.317	0.093	-3.4	0.001	-0.500	-0.134
alpha	0.728	0.068	--	--	0.606	0.874

Note: Inflation model = logit; LR chi^2 = 79.03; Log likelihood = -2156.948; Vuong test: z = 2.20, p = 0.014; PD=Parkinson's disease; AD=antidepressant; SE=standard error; CI=confidence interval; CCI=Charlson comorbidity index

Appendix 10 Zero-inflated negative binomial model for number of PD-related outpatient home (OP-home) visits

Variables	Coefficient	SE	z	p-value	95% CI	
Being adherent to AD	-0.249	0.253	-0.98	0.325	-0.744	0.247
Age	0.064	0.023	2.81	0.005	0.019	0.109
Female	-0.494	0.248	-2	0.046	-0.979	-0.009
Region						
Midwest	1.797	0.675	2.66	0.008	0.475	3.120
South	2.075	0.629	3.3	0.001	0.842	3.308
West	1.428	0.741	1.93	0.054	-0.025	2.881
Having anxiety	0.450	0.326	1.38	0.168	-0.190	1.089
Having psychosis	0.392	0.501	0.78	0.434	-0.590	1.374
Having dementia	-0.481	0.297	-1.62	0.106	-1.064	0.102
CCI	0.130	0.057	2.29	0.022	0.018	0.241
Having regimen modification	0.509	0.369	1.38	0.168	-0.215	1.233
Pre-index PD-related cost	2.7E-05	1.1E-05	2.38	0.017	4.7E-06	4.8E-05
Intercept	-5.174	1.934	-2.68	0.007	-8.964	-1.384
Inflate						
Being adherent to AD	-0.163	0.471	-0.35	0.729	-1.087	0.760
Age	-0.038	0.038	-1.01	0.314	-0.112	0.036
Female	-1.205	0.690	-1.75	0.081	-2.557	0.148
Region						
Midwest	2.269	2.402	0.94	0.345	-2.439	6.976
South	2.243	2.372	0.95	0.344	-2.406	6.893
West	2.738	2.486	1.1	0.271	-2.134	7.610
Having anxiety	1.774	0.740	2.4	0.017	0.323	3.225
Having psychosis	3.745	1.553	2.41	0.016	0.701	6.789
Having dementia	0.040	0.620	0.06	0.949	-1.176	1.256
CCI	0.056	0.085	0.66	0.507	-0.110	0.222
Having regimen modification	-0.002	0.668	0	0.997	-1.312	1.307
Pre-index PD-related cost	-0.001	0.001	-2.05	0.040	-0.003	-6.5E-05
Intercept	1.043	3.778	0.28	0.783	-6.361	8.447
ln alpha	1.833	0.131	14.03	<0.001	1.577	2.089
alpha	6.251	0.816	--	--	4.839	8.074

Note: Inflation model = logit; LR $chi^2 = 34.58$; Log likelihood = -1300.138; Vuong test: $z = 4.96$, $p < 0.001$; PD=Parkinson's disease; AD=antidepressant; SE=standard error; CI=confidence interval; CCI=Charlson comorbidity index

Appendix 11 GzLM with negative binomial distribution and log link for number of PD-related outpatient other (OP-other) visits

Variable	Coefficient	SE	z	p-value	95% CI	
Being adherent to AD	-0.016	0.166	-0.1	0.921	-0.342	0.309
Age	-0.042	0.014	-2.96	0.003	-0.070	-0.014
Female (Ref=Male)	-0.331	0.153	-2.17	0.030	-0.631	-0.032
Region (Ref=Northeast)						
Midwest	-0.747	0.418	-1.79	0.074	-1.566	0.073
South	-1.179	0.407	-2.9	0.004	-1.978	-0.381
West	-0.288	0.465	-0.62	0.535	-1.199	0.623
Having anxiety	-0.233	0.186	-1.25	0.210	-0.597	0.131
Having psychosis	-0.038	0.322	-0.12	0.905	-0.670	0.594
Having dementia	-0.413	0.193	-2.14	0.033	-0.791	-0.034
CCI	-0.116	0.031	-3.72	<0.001	-0.177	-0.055
Having regimen modification	0.478	0.256	1.87	0.062	-0.023	0.979
Pre-index PD-related cost	1.9E-05	7.1E-06	2.66	0.008	5.0E-06	3.3E-05
Intercept	4.592	1.118	4.11	<0.001	2.400	6.784
ln alpha	1.309	0.085	--	--	1.143	1.475
alpha	3.702	0.314	--	--	3.135	4.371

Note: LR chi^2 = 69.80; Log likelihood = -1129.661; $p < 0.001$; GzLM=generalized linear model; PD=Parkinson's disease; AD=antidepressant; SE=standard error; CI=confidence interval; CCI=Charlson comorbidity index

Appendix 12 Zero-inflated negative binomial model for number of PD-related nursing facility days billed

Variable	Coefficient	SE	z	p-value	95% CI	
Being adherent to AD	0.509	0.267	1.9	0.057	-0.015	1.033
Age	-0.036	0.027	-1.3	0.195	-0.089	0.018
Female	-0.149	0.297	-0.5	0.614	-0.731	0.432
Region						
Midwest	0.138	0.779	0.18	0.859	-1.388	1.665
South	0.393	0.811	0.49	0.627	-1.195	1.982
West	-0.282	0.925	-0.3	0.760	-2.095	1.531
Having anxiety	0.005	0.326	0.02	0.987	-0.634	0.645
Having psychosis	-0.361	0.419	-0.86	0.388	-1.183	0.460
Having dementia	0.411	0.305	1.35	0.178	-0.187	1.010
CCI	-0.085	0.065	-1.31	0.191	-0.213	0.043
Having regimen modification	0.131	0.362	0.36	0.718	-0.579	0.840
Pre-index PD-related cost	1.2E-05	8.4E-06	1.38	0.166	-4.8E-06	2.8E-05
Intercept	3.529	2.294	1.54	0.124	-0.968	8.025
Inflate						
Being adherent to AD	0.667	0.380	1.76	0.079	-0.078	1.412
Age	-0.137	0.032	-4.22	<0.001	-0.200	-0.073
Female	0.110	0.356	0.31	0.758	-0.588	0.808
Region						
Midwest	-1.300	0.979	-1.33	0.184	-3.219	0.618
South	0.483	0.923	0.52	0.600	-1.325	2.291
West	0.681	1.132	0.6	0.548	-1.538	2.899
Having anxiety	0.300	0.408	0.73	0.463	-0.501	1.100
Having psychosis	-1.651	0.995	-1.66	0.097	-3.601	0.298
Having dementia	-1.098	0.415	-2.65	0.008	-1.911	-0.285
CCI	-0.092	0.101	-0.91	0.362	-0.291	0.106
Having regimen modification	-1.104	0.544	-2.03	0.042	-2.170	-0.037
Pre-index PD-related cost	-1.1E-04	5.1E-05	-2.15	0.031	-2.1E-04	-9.9E-06
Intercept	11.729	2.580	4.55	0	6.672	16.785
Ln alpha	1.362	0.227	6.01	0	0.918	1.807
Alpha	3.905	0.886	--	--	2.503	6.091

Note: Inflation model = logit; LR chi^2 = 16.44; Log likelihood = -803.994; Vuong test: z = 5.26, p < 0.001; PD=Parkinson's disease; AD=antidepressant; SE=standard error; CI=confidence interval; CCI=Charlson comorbidity index

Appendix 13 Zero-inflated negative binomial model for number of PD-related inpatient visits

Variable	Coefficient	SE	z	p-value	95% CI	
Being adherent to AD	-0.221	0.176	-1.26	0.209	-0.566	0.124
Age	-0.005	0.015	-0.34	0.735	-0.034	0.024
Female	-0.017	0.171	-0.1	0.922	-0.352	0.318
Region						
Midwest	0.505	0.546	0.92	0.355	-0.565	1.575
South	0.281	0.538	0.52	0.601	-0.773	1.336
West	0.573	0.583	0.98	0.326	-0.570	1.715
Having anxiety	-0.180	0.203	-0.88	0.377	-0.578	0.219
Having psychosis	0.016	0.287	0.05	0.956	-0.547	0.578
Having dementia	0.186	0.192	0.97	0.331	-0.189	0.562
CCI	-0.008	0.028	-0.27	0.788	-0.063	0.048
Having regimen modification	0.261	0.277	0.94	0.347	-0.282	0.805
Pre-index PD-related cost	7.1E-06	5.5E-06	1.29	0.197	-3.7E-06	1.8E-05
Intercept	-0.197	1.281	-0.15	0.878	-2.708	2.314
Inflate						
Being adherent to AD	0.558	0.533	1.05	0.295	-0.487	1.603
Age	-0.070	0.043	-1.61	0.107	-0.155	0.015
Female	-0.066	0.534	-0.12	0.902	-1.113	0.981
Region						
Midwest	-0.468	1.561	-0.3	0.764	-3.528	2.592
South	0.042	1.509	0.03	0.978	-2.916	2.999
West	0.488	1.597	0.31	0.76	-2.642	3.618
Having anxiety	0.086	0.602	0.14	0.887	-1.094	1.265
Having psychosis	-0.182	1.082	-0.17	0.867	-2.302	1.939
Having dementia	0.798	0.561	1.42	0.155	-0.301	1.897
CCI	-0.208	0.129	-1.61	0.108	-0.462	0.046
Having regimen modification	0.516	0.687	0.75	0.452	-0.830	1.862
Pre-index PD-related cost	-0.001	3.9E-04	-2.18	0.029	-0.002	-8.6E-05
Intercept	5.174	3.668	1.41	0.158	-2.016	12.364
ln alpha	0.131	0.200	0.66	0.511	-0.260	0.522
Alpha	1.140	0.228	--	--	0.771	1.686

Note: Inflation model = logit; LR chi^2 = 9.74; Log likelihood = -840.1256; Vuong test: z = 2.95, p = 0.002; PD=Parkinson's disease; AD=antidepressant; SE=standard error; CI=confidence interval; CCI=Charlson comorbidity index

Appendix 14 Zero-inflated negative binomial model for number of PD-related ER visits

Variable	Coefficient	SE	z	p-value	95% CI	
Being adherent to AD	-0.348	0.249	-1.4	0.161	-0.836	0.139
Age	0.004	0.020	0.2	0.843	-0.036	0.044
Female	-0.023	0.241	-0.1	0.923	-0.495	0.449
Region						
Midwest	0.893	0.533	1.67	0.094	-0.153	1.938
South	0.637	0.532	1.2	0.231	-0.405	1.679
West	1.029	0.599	1.72	0.086	-0.145	2.202
Having anxiety	-0.047	0.329	-0.14	0.885	-0.692	0.597
Having psychosis	-0.005	0.376	-0.01	0.990	-0.742	0.733
Having dementia	-0.217	0.286	-0.76	0.449	-0.777	0.344
CCI	-0.072	0.061	-1.19	0.235	-0.191	0.047
Having regimen modification	0.151	0.349	0.43	0.665	-0.533	0.835
Pre-index PD-related cost	1.3E-07	8.2E-06	0.02	0.987	-1.6E-05	1.6E-05
Intercept	-1.560	1.635	-0.95	0.340	-4.764	1.645
Inflate						
Being adherent to AD	-0.753	0.618	-1.22	0.223	-1.964	0.458
Age	-0.022	0.045	-0.49	0.626	-0.109	0.066
Female	-0.290	0.547	-0.53	0.596	-1.363	0.782
Region						
Midwest	13.171	682.152	0.02	0.985	-1323.823	1350.165
South	13.486	682.152	0.02	0.984	-1323.507	1350.478
West	13.569	682.152	0.02	0.984	-1323.424	1350.563
Having anxiety	0.433	0.770	0.56	0.574	-1.076	1.941
Having psychosis	-0.148	1.268	-0.12	0.907	-2.633	2.337
Having dementia	-0.032	0.737	-0.04	0.966	-1.476	1.412
CCI	-0.166	0.237	-0.7	0.484	-0.631	0.299
Having regimen modification	-1.224	1.178	-1.04	0.299	-3.534	1.085
Pre-index PD-related cost	-5.0E-04	3.2E-04	-1.57	0.116	-0.001	1.2E-04
Intercept	-10.303	682.164	-0.02	0.988	-1347.319	1326.714
ln alpha	-0.309	0.459	-0.67	0.501	-1.210	0.591
Alpha	0.734	0.337	--	--	0.298	1.806

Note: Inflation model = logit; LR chi^2 =8.65; Log likelihood = -469.7431; Vuong test: z = 2.63, p = 0.004; PD=Parkinson's disease; ER=emergency room; AD=antidepressant; SE=standard error; CI=confidence interval; CCI=Charlson comorbidity index

Appendix 15 Two part model for all-cause outpatient office (OP-office) cost

Variable	Coefficient	SE	z	p-value	95% CI	
Logit						
Being adherent to AD	-1.530	0.528	-2.9	0.004	-2.565	-0.496
Age	-0.048	0.043	-1.12	0.262	-0.133	0.036
Female (Ref=Male)	0.156	0.457	0.34	0.733	-0.739	1.051
Region (Ref=Northeast)						
Midwest	-0.221	0.810	-0.27	0.784	-1.808	1.365
South	0.481	0.820	0.59	0.557	-1.125	2.087
Having anxiety	0.687	0.654	1.05	0.294	-0.595	1.969
Having psychosis	-0.874	0.551	-1.59	0.113	-1.953	0.206
Having dementia	-1.198	0.479	-2.5	0.012	-2.136	-0.259
CCI	0.254	0.123	2.06	0.039	0.013	0.496
Having regimen modification	0.082	0.657	0.12	0.901	-1.207	1.370
Pre-index PD-related cost	-1.9E-05	1.3E-05	-1.52	0.129	-4.4E-05	5.5E-06
Intercept	8.116	3.309	2.45	0.014	1.630	14.602
GzLM						
Being adherent to antidepressant	0.125	0.079	1.59	0.111	-0.029	0.280
Age	4.5E-04	0.007	0.06	0.949	-0.013	0.014
Female (Ref=Male)	-0.036	0.076	-0.47	0.637	-0.184	0.113
Region (Ref=Northeast)						
Midwest	-0.742	0.224	-3.31	0.001	-1.181	-0.303
South	-0.612	0.219	-2.79	0.005	-1.042	-0.183
West	-0.706	0.247	-2.86	0.004	-1.190	-0.222
Having anxiety	0.084	0.089	0.94	0.345	-0.090	0.259
Having psychosis	-0.275	0.158	-1.75	0.081	-0.584	0.034
Having dementia	-0.280	0.089	-3.14	0.002	-0.454	-0.105
CCI	0.065	0.016	4.05	<0.001	0.034	0.097
Having regimen modification	-0.150	0.122	-1.23	0.218	-0.388	0.088
Pre-index PD-related cost	5.6E-06	3.4E-06	1.68	0.093	-9.4E-07	1.2E-05
Intercept	8.170	0.578	14.14	<0.001	7.037	9.302

Note: Log pseudolikelihood = -7321.945; Region category—West was omitted in logit model because of collinearity; AD=antidepressant; SE=standard error; CI=confidence interval; CCI=Charlson comorbidity index; GzLM=generalized linear model

Appendix 16 Two part model for all-cause outpatient home (OP-home) cost

Variable	Coefficient	SE	z	p-value	95% CI	
Logit						
Being adherent to AD	-0.240	0.150	-1.59	0.111	-0.534	0.055
Age	0.038	0.013	2.84	0.005	0.012	0.064
Female (Ref=Male)	0.101	0.145	0.7	0.487	-0.184	0.386
Region (Ref=Northeast)						
Midwest	0.071	0.431	0.16	0.87	-0.775	0.916
South	0.150	0.421	0.36	0.722	-0.675	0.975
West	0.074	0.477	0.16	0.876	-0.861	1.010
Having anxiety	-0.278	0.172	-1.62	0.105	-0.614	0.058
Having psychosis	-0.425	0.300	-1.42	0.157	-1.014	0.163
Having dementia	0.252	0.172	1.47	0.143	-0.085	0.589
CCI	0.158	0.032	4.85	<0.001	0.094	0.221
Having regimen modification	0.268	0.236	1.14	0.255	-0.193	0.730
Pre-index PD-related cost	3.3E-05	8.2E-06	4.03	<0.001	1.7E-05	4.9E-05
Intercept	-3.305	1.105	-2.99	0.003	-5.470	-1.140
GzLM						
Being adherent to AD	0.190	0.155	1.23	0.221	-0.114	0.493
Age	0.014	0.014	0.96	0.337	-0.014	0.041
Female (Ref=Male)	0.196	0.148	1.32	0.188	-0.095	0.487
Region (Ref=Northeast)						
Midwest	0.307	0.443	0.69	0.488	-0.561	1.175
South	0.366	0.429	0.85	0.393	-0.474	1.206
West	0.489	0.491	1	0.319	-0.473	1.451
Having anxiety	-0.045	0.191	-0.24	0.813	-0.419	0.329
Having psychosis	0.082	0.296	0.28	0.781	-0.498	0.663
Having dementia	0.183	0.167	1.09	0.275	-0.145	0.511
CCI	0.071	0.032	2.24	0.025	0.009	0.133
Having regimen modification	0.093	0.228	0.41	0.684	-0.354	0.540
Pre-index PD-related cost	2.2E-05	7.4E-06	3.03	0.002	7.9E-06	3.7E-05
Intercept	6.762	1.166	5.8	<0.001	4.477	9.046

Note: Log pseudolikelihood = -4955.016; AD=antidepressant; SE=standard error; CI=confidence interval; CCI=Charlson comorbidity index; GzLM=generalized linear model

Appendix 17 Two part model for all-cause outpatient other (OP-other) cost

Variable	Coefficient	SE	z	p-value	95% CI	
logit						
Being adherent to AD	0.064	0.367	0.17	0.861	-0.655	0.783
Age	-0.014	0.033	-0.41	0.681	-0.078	0.051
Female (Ref=Male)	0.360	0.362	0.99	0.320	-0.350	1.069
Region (Ref=Northeast)						
Midwest	0.393	0.630	0.62	0.533	-0.843	1.628
South	-0.058	0.573	-0.1	0.919	-1.182	1.065
Having anxiety	0.062	0.426	0.15	0.884	-0.772	0.897
Having psychosis	-0.418	0.609	-0.69	0.493	-1.611	0.776
Having dementia	-0.611	0.394	-1.55	0.121	-1.383	0.161
CCI	0.412	0.130	3.16	0.002	0.157	0.668
Having regimen modification	0.052	0.561	0.09	0.926	-1.046	1.151
Pre-index PD-related cost	-1.6E-05	1.2E-05	-1.4	0.162	-3.9E-05	6.5E-06
Intercept	3.555	2.491	1.43	0.153	-1.327	8.437
GzLM						
Being adherent to AD	-0.315	0.181	-1.74	0.081	-0.670	0.039
Age	-0.027	0.015	-1.79	0.074	-0.056	0.003
Female (Ref=Male)	0.011	0.167	0.07	0.947	-0.317	0.339
Region (Ref=Northeast)						
Midwest	0.251	0.521	0.48	0.630	-0.771	1.273
South	-0.212	0.514	-0.41	0.681	-1.219	0.796
West	-0.192	0.574	-0.34	0.738	-1.318	0.933
Having anxiety	-0.206	0.203	-1.02	0.310	-0.603	0.192
Having psychosis	-0.244	0.356	-0.69	0.493	-0.942	0.454
Having dementia	-0.208	0.199	-1.05	0.294	-0.598	0.181
CCI	0.126	0.037	3.39	0.001	0.053	0.198
Having regimen modification	0.240	0.284	0.84	0.399	-0.318	0.797
Pre-index PD-related cost	4.4E-06	6.5E-06	0.67	0.500	-8.4E-06	1.7E-05
Intercept	9.805	1.247	7.87	<0.001	7.362	12.248

Note: Log pseudolikelihood = -7377.381; Region category—West was omitted in logit model because of collinearity; AD=antidepressant; SE=standard error; CI=confidence interval; CCI=Charlson comorbidity index; GzLM=generalized linear model

Appendix 18 Two part model for all-cause nursing facility cost

Variable	Coefficient	SE	z	p-value	95% CI	
Logit						
Being adherent to AD	-0.194	0.171	-1.13	0.258	-0.530	0.142
Age	0.084	0.016	5.3	0	0.053	0.115
Female (Ref=Male)	0.026	0.167	0.15	0.877	-0.301	0.352
Region (Ref=Northeast)						
Midwest	0.194	0.454	0.43	0.67	-0.696	1.084
South	-0.681	0.445	-1.53	0.126	-1.553	0.190
West	-0.773	0.524	-1.48	0.14	-1.801	0.254
Having anxiety	0.016	0.198	0.08	0.936	-0.372	0.404
Having psychosis	0.480	0.308	1.56	0.119	-0.124	1.084
Having dementia	0.902	0.179	5.05	<0.001	0.552	1.253
CCI	0.137	0.033	4.16	<0.001	0.073	0.202
Having regimen modification	0.402	0.255	1.57	0.115	-0.098	0.903
Pre-index PD-related cost	1.9E-05	7.0E-06	2.75	0.006	5.5E-06	3.3E-05
Intercept	-7.553	1.300	-5.81	<0.001	-10.101	-5.005
GzLM						
Being adherent to AD	-0.685	0.149	-4.6	<0.001	-0.977	-0.393
Age	-0.002	0.013	-0.14	0.887	-0.028	0.024
Female (Ref=Male)	0.081	0.147	0.55	0.584	-0.208	0.369
Region (Ref=Northeast)						
Midwest	0.246	0.349	0.71	0.480	-0.438	0.930
South	-0.114	0.348	-0.33	0.744	-0.796	0.569
West	-0.218	0.431	-0.51	0.612	-1.063	0.626
Having anxiety	-0.190	0.170	-1.12	0.263	-0.524	0.143
Having psychosis	-0.024	0.226	-0.11	0.914	-0.467	0.418
Having dementia	0.230	0.154	1.5	0.135	-0.071	0.531
CCI	-0.030	0.025	-1.19	0.233	-0.079	0.019
Having regimen modification	0.127	0.211	0.6	0.547	-0.286	0.540
Pre-index PD-related cost	1.1E-05	5.8E-06	1.83	0.067	-7.5E-07	2.2E-05
Intercept	9.663	1.080	8.94	<0.001	7.545	11.780

Note: Log pseudolikelihood = -3143.230; AD=antidepressant; SE=standard error; CI=confidence interval; CCI=Charlson comorbidity index; GzLM=generalized linear model

Appendix 19 Two part model for all-cause inpatient cost

Variable	Coefficient	SE	z	p-value	95% CI	
Logit						
Being adherent to AD	-0.473	0.151	-3.13	0.002	-0.770	-0.177
Age	0.028	0.013	2.12	0.034	0.002	0.055
Female (Ref=Male)	0.076	0.145	0.52	0.602	-0.209	0.360
Region (Ref=Northeast)						
Midwest	0.298	0.432	0.69	0.490	-0.549	1.144
South	0.150	0.421	0.36	0.722	-0.675	0.976
West	0.195	0.477	0.41	0.683	-0.740	1.130
Having anxiety	-0.222	0.171	-1.29	0.196	-0.558	0.114
Having psychosis	0.448	0.309	1.45	0.148	-0.159	1.054
Having dementia	0.159	0.171	0.93	0.351	-0.175	0.494
CCI	0.165	0.033	5.07	<0.001	0.101	0.229
Having regimen modification	0.327	0.235	1.39	0.163	-0.133	0.788
Pre-index PD-related cost	2.6E-05	7.7E-06	3.42	0.001	1.1E-05	4.1E-05
Intercept	-2.694	1.105	-2.44	0.015	-4.861	-0.528
GzLM						
Being adherent to AD	-0.310	0.132	-2.34	0.019	-0.570	-0.051
Age	-0.007	0.011	-0.65	0.517	-0.030	0.015
Female (Ref=Male)	0.004	0.128	0.03	0.974	-0.247	0.255
Region (Ref=Northeast)						
Midwest	0.714	0.379	1.89	0.059	-0.028	1.457
South	0.577	0.370	1.56	0.119	-0.148	1.302
West	0.733	0.419	1.75	0.080	-0.088	1.555
Having anxiety	0.190	0.155	1.23	0.218	-0.113	0.493
Having psychosis	0.193	0.222	0.87	0.384	-0.241	0.628
Having dementia	-0.044	0.142	-0.31	0.759	-0.323	0.235
CCI	0.063	0.024	2.59	0.010	0.015	0.110
Having regimen modification	-0.155	0.200	-0.78	0.437	-0.546	0.236
Pre-index PD-related cost	2.0E-06	5.4E-06	0.36	0.716	-8.6E-06	1.3E-05
Intercept	9.561	0.980	9.75	<0.001	7.639	11.482

Note: Log pseudolikelihood = -5193.728; AD=antidepressant; SE=standard error; CI=confidence interval; CCI=Charlson comorbidity index; GzLM=generalized linear model

Appendix 20 Two part model for all-cause ER cost

Variable	Coefficient	SE	z	p-value	95% CI	
Logit						
Being adherent to AD	-0.283	0.150	-1.89	0.059	-0.578	0.011
Age	0.042	0.013	3.14	0.002	0.016	0.068
Female (Ref=Male)	0.359	0.145	2.47	0.014	0.074	0.644
Region (Ref=Northeast)						
Midwest	-0.145	0.446	-0.32	0.745	-1.018	0.729
South	-0.540	0.435	-1.24	0.214	-1.392	0.312
West	-0.401	0.489	-0.82	0.413	-1.360	0.558
Having anxiety	-0.034	0.171	-0.2	0.843	-0.369	0.302
Having psychosis	0.119	0.308	0.39	0.699	-0.485	0.723
Having dementia	0.219	0.172	1.27	0.204	-0.119	0.556
CCI	0.140	0.032	4.32	<0.001	0.077	0.204
Having regimen modification	0.438	0.237	1.85	0.064	-0.026	0.903
Pre-index PD-related cost	1.5E-05	7.1E-06	2.13	0.033	1.2E-06	2.9E-05
Intercept	-3.085	1.107	-2.79	0.005	-5.255	-0.915
GzLM						
Being adherent to AD	-0.172	0.116	-1.48	0.140	-0.399	0.056
Age	-0.009	0.010	-0.87	0.383	-0.029	0.011
Female (Ref=Male)	-0.190	0.113	-1.69	0.091	-0.411	0.030
Region (Ref=Northeast)						
Midwest	0.527	0.302	1.75	0.081	-0.064	1.119
South	0.437	0.296	1.48	0.139	-0.142	1.016
West	0.133	0.341	0.39	0.697	-0.536	0.802
Having anxiety	0.312	0.134	2.33	0.020	0.049	0.575
Having psychosis	0.165	0.206	0.8	0.422	-0.238	0.568
Having dementia	-0.125	0.123	-1.02	0.308	-0.367	0.116
CCI	0.041	0.023	1.8	0.072	-0.004	0.086
Having regimen modification	0.160	0.170	0.94	0.346	-0.173	0.493
Pre-index PD-related cost	2.7E-06	5.4E-06	0.5	0.618	-7.9E-06	1.3E-05
Intercept	7.419	0.842	8.81	<0.001	5.768	9.070

Note: Log pseudolikelihood = -4442.048; ER=emergency room; AD=antidepressant; SE=standard error; CI=confidence interval; CCI=Charlson comorbidity index; GzLM=generalized linear model

Appendix 21 GzLM for all-cause pharmacy cost

Variable	Coefficient	SE	z	p-value	95% CI	
Being adherent to AD	0.307	0.058	5.33	<0.001	0.194	0.420
Age	-0.010	0.005	-1.95	0.052	-0.020	0.000
Female (Ref=Male)	0.022	0.057	0.39	0.696	-0.089	0.133
Region (Ref=Northeast)						
Midwest	0.104	0.166	0.63	0.531	-0.221	0.429
South	0.042	0.161	0.26	0.796	-0.274	0.358
West	0.148	0.183	0.81	0.419	-0.211	0.507
Having anxiety	-0.084	0.067	-1.25	0.211	-0.216	0.048
Having psychosis	0.068	0.114	0.6	0.549	-0.155	0.291
Having dementia	0.240	0.066	3.62	<0.001	0.110	0.370
CCI	0.054	0.012	4.5	<0.001	0.030	0.077
Having regimen modification	0.181	0.090	2.01	0.045	0.004	0.358
Pre-index PD-related cost	9.0E-06	2.8E-06	3.24	0.001	3.6E-06	1.4E-05
Intercept	8.604	0.424	20.28	<0.001	7.772	9.436

Note: Log likelihood = -7946.961; GzLM=generalized linear model; AD=antidepressant; SE=standard error; CI=confidence interval; CCI=Charlson comorbidity index

Appendix 22 GzLM for all-cause total cost

Variable	Coefficient	SE	z	p-value	95% CI	
Being adherent to AD	-0.213	0.080	-2.65	0.008	-0.370	-0.055
Age	0.010	0.007	1.42	0.157	-0.004	0.024
Female (Ref=Male)	0.049	0.079	0.63	0.530	-0.105	0.203
Region (Ref=Northeast)						
Midwest	0.368	0.229	1.6	0.109	-0.082	0.818
South	0.099	0.224	0.44	0.658	-0.339	0.537
West	0.149	0.254	0.59	0.557	-0.348	0.646
Having anxiety	-0.035	0.093	-0.38	0.707	-0.217	0.147
Having psychosis	0.183	0.156	1.17	0.242	-0.123	0.488
Having dementia	0.134	0.091	1.48	0.140	-0.044	0.313
CCI	0.115	0.017	6.66	<0.001	0.081	0.148
Having regimen modification	0.104	0.125	0.83	0.406	-0.141	0.349
Pre-index PD-related cost	1.5E-05	4.0E-06	3.77	<0.001	7.2E-06	2.3E-05
Intercept	8.831	0.584	15.13	<0.001	7.687	9.975

Note: Log likelihood = -9483.912; GzLM=generalized linear model; AD=antidepressant; SE=standard error; CI=confidence interval; CCI=Charlson comorbidity index

Appendix 23 Two-part model for PD-related outpatient office (OP-office) cost

Variable	Coefficient	SE	z	p-value	95% CI	
Logit						
Being adherent to AD	-0.147	0.182	-0.81	0.420	-0.503	0.210
Age	-0.011	0.016	-0.68	0.495	-0.044	0.021
Female (Ref=Male)	-0.105	0.179	-0.59	0.558	-0.456	0.246
Region (Ref=Northeast)						
Midwest	-1.331	0.653	-2.04	0.042	-2.611	-0.050
South	-0.858	0.647	-1.33	0.185	-2.127	0.411
West	-1.026	0.704	-1.46	0.145	-2.405	0.354
Having anxiety	0.142	0.216	0.66	0.511	-0.281	0.566
Having psychosis	-0.238	0.313	-0.76	0.447	-0.851	0.375
Having dementia	-0.743	0.192	-3.87	<0.001	-1.119	-0.367
CCI	-0.132	0.033	-3.98	<0.001	-0.197	-0.067
Having regimen modification	0.337	0.301	1.12	0.263	-0.253	0.926
Pre-index PD-related cost	-2.7E-06	7.3E-06	-0.37	0.712	-1.7E-05	1.2E-05
Intercept	3.858	1.424	2.71	0.007	1.067	6.648
GzLM						
Being adherent to AD	0.028	0.093	0.3	0.767	-0.155	0.210
Age	-0.008	0.008	-0.9	0.368	-0.024	0.009
Female (Ref=Male)	0.131	0.090	1.45	0.148	-0.046	0.308
Region (Ref=Northeast)						
Midwest	-1.474	0.264	-5.59	<0.001	-1.991	-0.957
South	-1.519	0.256	-5.94	<0.001	-2.021	-1.018
West	-1.470	0.286	-5.14	<0.001	-2.030	-0.910
Having anxiety	-0.035	0.105	-0.33	0.742	-0.241	0.171
Having psychosis	-0.071	0.202	-0.35	0.725	-0.466	0.325
Having dementia	-0.256	0.107	-2.39	0.017	-0.467	-0.046
CCI	-3.3E-04	0.021	-0.02	0.987	-0.041	0.040
Having regimen modification	-0.063	0.139	-0.45	0.652	-0.336	0.210
Pre-index PD-related cost	2.6E-05	4.6E-06	5.72	<0.001	1.7E-05	3.5E-05
Intercept	8.162	0.695	11.75	<0.001	6.800	9.524

Note: Log pseudolikelihood = -5345.004; PD=Parkinson's disease; AD=antidepressant; SE=standard error; CI=confidence interval; CCI=Charlson comorbidity index; GzLM=generalized linear model

Appendix 24 Two-part model for PD-related outpatient home (OP-home) cost

Variable	Coefficient	SE	z	p-value	95% CI	
Logit						
Being adherent to AD	-0.158	0.166	-0.95	0.343	-0.484	0.168
Age	0.038	0.015	2.56	0.010	0.009	0.068
Female (Ref=Male)	0.090	0.160	0.56	0.575	-0.224	0.405
Region (Ref=Northeast)						
Midwest	0.155	0.480	0.32	0.747	-0.787	1.096
South	0.175	0.469	0.37	0.710	-0.745	1.094
West	-0.255	0.543	-0.47	0.638	-1.319	0.809
Having anxiety	-0.160	0.193	-0.83	0.408	-0.538	0.218
Having psychosis	-0.441	0.347	-1.27	0.204	-1.121	0.240
Having dementia	-0.103	0.189	-0.55	0.583	-0.473	0.266
CCI	-0.004	0.033	-0.11	0.915	-0.068	0.061
Having regimen modification	0.064	0.256	0.25	0.802	-0.438	0.566
Pre-index PD-related cost	3.9E-05	7.2E-06	5.45	<0.001	2.5E-05	5.3E-05
Intercept	-4.125	1.243	-3.32	0.001	-6.561	-1.689
GzLM						
Being adherent to AD	0.151	0.195	0.78	0.438	-0.230	0.532
Age	0.021	0.018	1.16	0.245	-0.014	0.055
Female (Ref=Male)	0.098	0.185	0.53	0.596	-0.265	0.462
Region (Ref=Northeast)						
Midwest	0.965	0.549	1.76	0.079	-0.112	2.042
South	0.730	0.530	1.38	0.168	-0.308	1.768
West	1.031	0.619	1.67	0.095	-0.181	2.244
Having anxiety	0.116	0.236	0.49	0.621	-0.345	0.578
Having psychosis	-0.059	0.379	-0.16	0.875	-0.802	0.683
Having dementia	-0.012	0.219	-0.06	0.955	-0.441	0.416
CCI	0.054	0.044	1.25	0.212	-0.031	0.140
Having regimen modification	0.266	0.279	0.95	0.340	-0.281	0.814
Pre-index PD-related cost	1.8E-05	7.6E-06	2.33	0.020	2.8E-06	3.3E-05
Intercept	5.985	1.478	4.05	<0.001	3.089	8.881

Note: Log pseudolikelihood = -2760.934; PD=Parkinson's disease; AD=antidepressant; SE=standard error; CI=confidence interval; CCI=Charlson comorbidity index; GzLM=generalized linear model

Appendix 25 Two-part model for PD-related outpatient other (OP-other) cost

Variable	Coefficient	SE	z	p-value	95% CI	
Logit						
Being adherent to AD	0.081	0.152	0.53	0.593	-0.217	0.380
Age	-0.030	0.014	-2.18	0.029	-0.056	-0.003
Female (Ref=Male)	-0.281	0.148	-1.89	0.058	-0.571	0.010
Region (Ref=Northeast)						
Midwest	0.330	0.435	0.76	0.448	-0.522	1.182
South	-0.093	0.426	-0.22	0.826	-0.929	0.742
West	0.362	0.479	0.76	0.450	-0.577	1.300
Having anxiety	0.142	0.173	0.82	0.413	-0.198	0.482
Having psychosis	0.316	0.296	1.07	0.286	-0.265	0.897
Having dementia	-0.347	0.178	-1.95	0.051	-0.696	0.002
CCI	-0.070	0.031	-2.22	0.027	-0.131	-0.008
Having regimen modification	-0.139	0.239	-0.58	0.561	-0.607	0.329
Pre-index PD-related cost	1.2E-05	6.5E-06	1.86	0.063	-6.5E-07	2.5E-05
Intercept	1.813	1.113	1.63	0.103	-0.369	3.994
GzLM						
Being adherent to AD	-0.387	0.229	-1.69	0.091	-0.837	0.062
Age	-0.055	0.020	-2.81	0.005	-0.094	-0.017
Female (Ref=Male)	-0.301	0.209	-1.44	0.151	-0.711	0.110
Region (Ref=Northeast)						
Midwest	-0.673	0.748	-0.9	0.368	-2.139	0.793
South	-1.653	0.744	-2.22	0.026	-3.112	-0.194
West	-1.129	0.775	-1.46	0.145	-2.649	0.390
Having anxiety	-0.218	0.250	-0.87	0.383	-0.708	0.272
Having psychosis	-0.056	0.455	-0.12	0.901	-0.949	0.836
Having dementia	-0.594	0.292	-2.03	0.042	-1.167	-0.021
CCI	0.050	0.040	1.25	0.212	-0.028	0.128
Having regimen modification	0.727	0.378	1.92	0.054	-0.013	1.467
Pre-index PD-related cost	-9.4E-07	8.7E-06	-0.11	0.914	-1.8E-05	1.6E-05
Intercept	12.544	1.538	8.16	<0.001	9.530	15.558

Note: Log pseudolikelihood = -2978.204; PD=Parkinson's disease; AD=antidepressant; SE=standard error; CI=confidence interval; CCI=Charlson comorbidity index; GzLM=generalized linear model

Appendix 26 Two-part model for PD-related nursing facility cost

Variable	Coefficient	SE	z	p-value	95% CI	
Logit						
Being adherent to AD	-0.041	0.198	-0.21	0.837	-0.428	0.347
Age	0.077	0.019	4.15	<0.001	0.041	0.113
Female (Ref=Male)	-0.138	0.195	-0.71	0.478	-0.519	0.243
Region (Ref=Northeast)						
Midwest	0.620	0.522	1.19	0.235	-0.404	1.644
South	-0.249	0.518	-0.48	0.630	-1.264	0.765
West	-0.437	0.621	-0.7	0.482	-1.654	0.780
Having anxiety	0.098	0.229	0.43	0.669	-0.351	0.548
Having psychosis	0.441	0.319	1.38	0.167	-0.184	1.065
Having dementia	0.771	0.203	3.79	<0.001	0.372	1.169
CCI	0.036	0.037	0.98	0.328	-0.036	0.108
Having regimen modification	0.688	0.272	2.53	0.012	0.154	1.221
Pre-index PD-related cost	2.9E-05	7.3E-06	4	<0.001	1.5E-05	4.4E-05
Intercept	-8.003	1.532	-5.23	<0.001	-11.005	-5.001
GzLM						
Being adherent to AD	-0.429	0.248	-1.73	0.083	-0.914	0.057
Age	-0.022	0.024	-0.92	0.359	-0.069	0.025
Female (Ref=Male)	0.117	0.249	0.47	0.637	-0.370	0.605
Region (Ref=Northeast)						
Midwest	0.165	0.623	0.26	0.792	-1.056	1.385
South	-0.015	0.617	-0.02	0.981	-1.224	1.194
West	-0.059	0.766	-0.08	0.938	-1.561	1.443
Having anxiety	-0.191	0.287	-0.67	0.504	-0.754	0.371
Having psychosis	-0.555	0.393	-1.41	0.158	-1.326	0.216
Having dementia	-0.148	0.250	-0.59	0.555	-0.639	0.343
CCI	-0.024	0.042	-0.56	0.573	-0.106	0.059
Having regimen modification	-0.004	0.324	-0.01	0.990	-0.640	0.631
Pre-index PD-related cost	1.3E-05	7.9E-06	1.64	0.101	-2.5E-06	2.9E-05
Intercept	10.766	1.930	5.58	<0.001	6.983	14.550

Note: Log pseudolikelihood = -1901.472; PD=Parkinson's disease; AD=antidepressant; SE=standard error; CI=confidence interval; CCI=Charlson comorbidity index; GzLM=generalized linear model

Appendix 27 Two-part model for PD-related inpatient cost

Variable	Coefficient	SE	z	p-value	95% CI	
Logit						
Being adherent to AD	-0.374	0.162	-2.3	0.021	-0.692	-0.055
Age	0.014	0.014	1.01	0.312	-0.014	0.042
Female (Ref=Male)	-0.029	0.155	-0.19	0.852	-0.332	0.275
Region (Ref=Northeast)						
Midwest	0.768	0.500	1.54	0.125	-0.212	1.749
South	0.405	0.492	0.82	0.411	-0.560	1.370
West	0.562	0.545	1.03	0.303	-0.507	1.630
Having anxiety	0.045	0.183	0.25	0.806	-0.313	0.403
Having psychosis	0.010	0.311	0.03	0.975	-0.600	0.619
Having dementia	-0.104	0.182	-0.57	0.566	-0.461	0.252
CCI	0.051	0.031	1.67	0.096	-0.009	0.111
Having regimen modification	-0.114	0.256	-0.44	0.657	-0.615	0.388
Pre-index PD-related cost	3.3E-05	7.1E-06	4.65	<0.001	1.9E-05	4.7E-05
Intercept	-2.532	1.196	-2.12	0.034	-4.877	-0.187
GzLM						
Being adherent to AD	-0.148	0.208	-0.71	0.477	-0.556	0.260
Age	1.4E-04	0.018	0.01	0.994	-0.036	0.036
Female (Ref=Male)	0.002	0.202	0.01	0.993	-0.395	0.398
Region (Ref=Northeast)						
Midwest	0.363	0.647	0.56	0.575	-0.906	1.632
South	-0.023	0.631	-0.04	0.971	-1.260	1.214
West	0.312	0.698	0.45	0.655	-1.056	1.680
Having anxiety	-0.095	0.233	-0.41	0.685	-0.551	0.362
Having psychosis	-0.553	0.366	-1.51	0.131	-1.271	0.164
Having dementia	-0.045	0.233	-0.19	0.846	-0.502	0.411
CCI	0.027	0.038	0.7	0.485	-0.049	0.102
Having regimen modification	0.065	0.327	0.2	0.844	-0.577	0.706
Pre-index PD-related cost	2.1E-07	7.0E-06	0.03	0.976	-1.4E-05	1.4E-05
Intercept	9.136	1.609	5.68	<0.001	5.982	12.290

Note: Log pseudolikelihood = -3175.4793; PD=Parkinson's disease; AD=antidepressant; SE=standard error; CI=confidence interval; CCI=Charlson comorbidity index; GzLM=generalized linear model

Appendix 28 Two-part model for PD-related ER cost

Variable	Coefficient	SE	z	p-value	95% CI	
Logit						
Being adherent to AD	0.061	0.181	0.34	0.736	-0.293	0.415
Age	0.032	0.016	1.95	0.051	0.000	0.064
Female (Ref=Male)	0.022	0.176	0.13	0.899	-0.323	0.368
Region (Ref=Northeast)						
Midwest	-0.019	0.471	-0.04	0.967	-0.942	0.904
South	-0.520	0.464	-1.12	0.262	-1.429	0.389
West	0.032	0.524	0.06	0.951	-0.994	1.058
Having anxiety	-0.092	0.212	-0.43	0.666	-0.508	0.324
Having psychosis	0.160	0.335	0.48	0.633	-0.497	0.818
Having dementia	-0.219	0.208	-1.05	0.293	-0.628	0.189
CCI	-0.025	0.037	-0.7	0.487	-0.097	0.046
Having regimen modification	0.593	0.253	2.34	0.019	0.097	1.089
Pre-index PD-related cost	2.1E-05	6.8E-06	3.1	0.002	7.7E-06	3.4E-05
Intercept	-3.609	1.336	-2.7	0.007	-6.228	-0.990
GzLM						
Being adherent to AD	-0.221	0.142	-1.56	0.120	-0.499	0.057
Age	0.004	0.012	0.35	0.727	-0.020	0.028
Female (Ref=Male)	-0.018	0.138	-0.13	0.895	-0.289	0.253
Region (Ref=Northeast)						
Midwest	0.813	0.363	2.24	0.025	0.102	1.524
South	0.786	0.358	2.19	0.028	0.084	1.488
West	0.759	0.403	1.88	0.060	-0.031	1.549
Having anxiety	-0.182	0.181	-1.01	0.314	-0.537	0.172
Having psychosis	0.036	0.251	0.14	0.886	-0.456	0.529
Having dementia	-0.402	0.170	-2.37	0.018	-0.736	-0.069
CCI	0.016	0.033	0.5	0.614	-0.047	0.080
Having regimen modification	0.006	0.188	0.03	0.973	-0.363	0.375
Pre-index PD-related cost	-1.8E-06	6.4E-06	-0.28	0.777	-1.4E-05	1.1E-05
Intercept	5.961	0.987	6.04	<0.001	4.027	7.895

Note: Log pseudolikelihood = -1776.685; PD=Parkinson's disease; ER=emergency room; AD=antidepressant; SE=standard error; CI=confidence interval; CCI=Charlson comorbidity index; GzLM=generalized linear model

Appendix 29 Two-part model for PD-related pharmacy cost

Variable	Coefficient	SE	z	p-value	95% CI	
Logit						
Being adherent to AD	0.398	0.197	2.02	0.044	0.011	0.785
Age	0.019	0.017	1.09	0.274	-0.015	0.052
Female (Ref=Male)	0.028	0.187	0.15	0.879	-0.337	0.394
Region (Ref=Northeast)						
Midwest	0.036	0.536	0.07	0.947	-1.015	1.087
South	-0.042	0.522	-0.08	0.935	-1.066	0.981
West	0.130	0.602	0.22	0.830	-1.051	1.310
Having anxiety	0.016	0.220	0.07	0.941	-0.415	0.447
Having psychosis	-0.510	0.330	-1.55	0.121	-1.156	0.135
Having dementia	-0.567	0.206	-2.75	0.006	-0.971	-0.163
CCI	-0.088	0.035	-2.53	0.011	-0.157	-0.020
Having regimen modification	0.584	0.356	1.64	0.101	-0.113	1.281
Pre-index PD-related cost	8.9E-06	9.0E-06	0.99	0.323	-8.8E-06	2.7E-05
Intercept	0.311	1.400	0.22	0.824	-2.433	3.054
GzLM						
Being adherent to AD	0.345	0.101	3.41	0.001	0.147	0.544
Age	-0.034	0.009	-3.75	<0.001	-0.052	-0.016
Female (Ref=Male)	-0.034	0.099	-0.34	0.732	-0.229	0.161
Region (Ref=Northeast)						
Midwest	-0.117	0.297	-0.39	0.693	-0.700	0.465
South	-0.047	0.291	-0.16	0.870	-0.617	0.522
West	-0.102	0.325	-0.31	0.755	-0.739	0.536
Having anxiety	-0.085	0.120	-0.71	0.480	-0.320	0.150
Having psychosis	-0.199	0.215	-0.93	0.353	-0.620	0.221
Having dementia	-0.189	0.120	-1.57	0.116	-0.425	0.047
CCI	-0.097	0.021	-4.59	<0.001	-0.138	-0.056
Having regimen modification	0.121	0.153	0.79	0.430	-0.179	0.421
Pre-index PD-related cost	3.0E-05	5.6E-06	5.29	<0.001	1.9E-05	4.1E-05
Intercept	9.562	0.733	13.05	<0.001	8.126	10.998

Note: Log pseudolikelihood = -5969.268; PD=Parkinson's disease; AD=antidepressant; SE=standard error; CI=confidence interval; CCI=Charlson comorbidity index; GzLM=generalized linear model

Appendix 30 Two-part model for PD-related total cost

Variable	Coefficient	SE	z	p-value	95% CI	
Logit						
Being adherent to AD	0.464	0.403	1.15	0.249	-0.325	1.253
Age	-0.002	0.035	-0.06	0.951	-0.072	0.067
Female	-0.441	0.384	-1.15	0.250	-1.193	0.311
Region						
Midwest	0.404	0.836	0.48	0.629	-1.235	2.043
South	0.489	0.812	0.6	0.547	-1.103	2.081
West	0.854	1.062	0.8	0.421	-1.227	2.934
Having anxiety	-0.073	0.436	-0.17	0.867	-0.927	0.781
Having psychosis	-0.721	0.533	-1.35	0.176	-1.765	0.323
Having dementia	-1.082	0.402	-2.69	0.007	-1.871	-0.294
CCI	-0.090	0.062	-1.45	0.147	-0.212	0.032
Having regimen modification	1.335	1.034	1.29	0.196	-0.691	3.361
Pre-index PD-related cost	2.8E-06	1.7E-05	0.17	0.866	-3.0E-05	3.6E-05
Intercept	3.700	2.835	1.31	0.192	-1.856	9.255
GzLM						
Being adherent to AD	-0.171	0.122	-1.41	0.160	-0.409	0.067
Age	0.016	0.011	1.44	0.149	-0.006	0.037
Female	-0.026	0.118	-0.22	0.826	-0.258	0.206
Region						
Midwest	0.272	0.353	0.77	0.440	-0.419	0.964
South	-0.285	0.343	-0.83	0.406	-0.957	0.387
West	-0.111	0.388	-0.29	0.775	-0.872	0.650
Having anxiety	-0.115	0.141	-0.82	0.414	-0.392	0.162
Having psychosis	-0.313	0.243	-1.29	0.198	-0.790	0.164
Having dementia	-0.067	0.140	-0.48	0.632	-0.342	0.208
CCI	0.026	0.025	1.02	0.308	-0.024	0.075
Having regimen modification	0.195	0.185	1.05	0.292	-0.168	0.558
Pre-index PD-related cost	3.8E-05	7.0E-06	5.38	<0.001	2.4E-05	5.1E-05
Intercept	7.784	0.899	8.65	<0.001	6.021	9.547

Note: Log pseudolikelihood = -8356.364; PD=Parkinson's disease; AD=antidepressant; SE=standard error; CI=confidence interval; CCI=Charlson comorbidity index; GzLM=generalized linear model

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