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Dated: _____07/12/2017_____

DISSERTATION

SAFETY OF ATYPICAL ANTIPSYCHOTICS IN THE ELDERLY WITH PARKINSON'S DISEASE

by

FARID CHEKANI

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DISSERTATION SUMMARY

Objectives: According to the 2015 American Geriatrics Society (AGS) Beers criteria, except for aripiprazole, clozapine, and quetiapine, antipsychotic medications are considered generally inappropriate in PD. However, limited data exists regarding safety of atypical antipsychotics in general and inappropriate atypical antipsychotics in specific in patients with PD. This study evaluated the incidence and predictors of inappropriate atypical antipsychotic agents among older patients with PD; and the risks of pneumonia and mortality in older patients with PD using inappropriate atypical antipsychotic agents.

Methods: A retrospective design involving Minimum Data Set (MDS) linked Medicare claims data was used to examine incidence and predictors of inappropriate atypical antipsychotic agents and to evaluate the study hypotheses that there are higher risks of pneumonia and all-cause mortality among older patients with PD using inappropriate atypical antipsychotics when compared to the three selected atypical antipsychotic agents (i.e. aripiprazole, clozapine, and quetiapine). The inappropriate atypical antipsychotics encompassed olanzapine, asenapine, brexpiprazole, iloperidone, lurasidone, paliperidone, risperidone, and ziprasidone. The study sample was selected from a cohort of older adults with depression. Multivariable logistic regression was used to examine various sociodemographic and clinical factors associated with inappropriate antipsychotic use in PD based on Andersen's Behavioral Model. Safety evaluation involved a propensity-matched approach to adjust for the selection bias across antipsychotics within the multivariable context of the Andersen Behavioral Model. Cox proportional hazards regression model stratified on matched pairs was used to evaluate the safety profile of antipsychotics in PD.

Results: There were 13,352 patients aged 65 years or older with PD diagnosis and without schizophrenia/ bipolar disorder who started one atypical antipsychotic agent in 2008-2009. The incidence of atypical antipsychotic use was 17.50% in 2-year follow-up. The most frequently used inappropriate antipsychotics were risperidone (22.95%) and olanzapine (11.25%). The likelihood of inappropriate antipsychotic use was higher for patients who had dementia or Chronic Obstructive Pulmonary Disease (COPD). Conversely, patients who were taking levodopa, dopamine agonists, Catechol-O-methyltransferase (COMT) inhibitors, Monoamine Oxidase (MAO) inhibitors type B, or amantadine were less likely to receive inappropriate antipsychotics. For the second and third objectives, the analysis involved 6-month washout and follow-up periods. There were 12,076 patients in the matched propensity score cohort. The Hazard Ratio (HR) of pneumonia was 1.23 (95% CI: 1.10 – 1.36) and the HR of all-cause-mortality was 1.13 (95% CI: 1.01 - 1.28) for patients who used inappropriate vs. appropriate atypical antipsychotics. There was a significant association between pneumonia and death.

Conclusions: More than one-third of PD patients received inappropriate agents among those who were treated with atypical antipsychotics in this study. Various socio-demographics and clinical factors were associated with inappropriate antipsychotic use among older patients with PD. The risks of pneumonia and all-cause-mortality were significantly higher for inappropriate atypical antipsychotic users in comparison to appropriate antipsychotic group. This study provided a strong evidence base regarding the safety of atypical antipsychotic use in older patients with PD. The study findings can help in optimizing the use of these medications to improve quality of geriatric care in PD.

SPECIFIC AIMS

Parkinson's disease (PD) is a neurodegenerative disorder, associated with significant disability and mortality.[1] In the United States, the prevalence of Parkinson's disease is estimated to be 0.3% in general population, 1% - 5% in the elderly and 5% - 10% in nursing home residents.[2,3] Parkinson's disease symptoms usually begin in the fifth or sixth decade of life, and the disease incidence increases steadily thereafter.[4] Both motor and non-motor symptoms contribute to disability and impaired quality of life of patients with PD. Additionally, numerous complications such as dopaminergic induced psychosis are associated with PD. [5] The combined direct and indirect costs of Parkinson's disease were estimated at $25 billion per year in the United States, while the direct medical costs incurred for patients with PD were $14.4 billion in 2010. [3,6] Despite advances in medical care, the mortality rate in patients with PD remains higher than expected for age.[7] The mortality rate of PD was reported to be 50% in 3 years in a large cohort study of PD patients residing in nursing homes.[2,8] Weintraub et al. 2016 conducted a cohort study and found the mortality rate among Medicare beneficiaries with PD was 64% in 6 years follow-up.[9]

Psychosis is one the most challenging non-motor symptoms that affect both mental and physical functioning in patients with PD.[5] Psychotic symptoms are related to the use of dopaminergic agents such as levodopa. [10] The probability of psychosis was estimated to be 25%–60% in the lifetime course of PD, depending on the type of diagnostic criteria used.[10] Atypical antipsychotics are frequently used (48.2%) for the management of psychotic symptoms in patients with PD.[11] According to previous studies, 15% to 30% of PD patients in long term facilities use antipsychotic agents.[2] The prevalence of antipsychotic use was 50% in a large cohort of veterans with PD psychosis.[11] The efficacy of atypical antipsychotics in the treatment

of PD psychosis has not been evaluated in large clinical trials; however, clozapine has found to be an effective treatment for PD psychosis. [2,12] In spite of effectiveness, clozapine is not commonly used in clinical practice, due to the risk of adverse events and the blood monitoring requirement. [11] There are mixed findings regarding the effect of other atypical antipsychotics on the psychotic features of PD.[2,12] Antipsychotic use is related to adverse events such as pneumonia, in addition to worsening movement PD symptoms.[12,13]

Pneumonia, a potentially preventable complication is the main cause of death among patients with PD.[1] Aspiration pneumonia is related to the impairment of swallow reflex and discoordination of breathing and swallowing which are the clinical features of PD. [14] The impairment of swallow reflex, manifesting as dysphagia can be present in any stage of PD.[14] Antipsychotics potentially aggravate dysphagia by blocking Dopamine receptors type 2, leading to higher risk of aspiration pneumonia in patients with PD.[15] There are other mechanisms related to the risk of pneumonia in antipsychotics users.[13,16] Sedative effect of antipsychotics can suppress cognitive functioning in elderly patients with PD leading to a higher risk of aspiration.[17] Anticholinergic effect of antipsychotics can increase the risk of pneumonia due to reduced sensorium, dry mouth, decreased and thickened mucous secretions, and depressed mucociliary transport.[13] It is not fully understood how antipsychotic agents influence the impaired swallow reflex which is the main mechanism of aspiration in patients with PD.[18] It is plausible that the swallow reflex becomes more dysfunctional when patients with PD use antipsychotics that worsen Parkinsonian symptoms, and it leads to a higher risk of pneumonia for those patients.[18]

According to the 2015 American Geriatrics Society (AGS) Beers criteria antipsychotics are generally inappropriate medications in Parkinson's disease, because they can potentially worsen Parkinsonian symptoms, except for aripiprazole, quetiapine, and clozapine.[19] However,

limited data exists regarding safety of atypical antipsychotics in general and inappropriate atypical antipsychotics in specific in patients with PD. In addition, no comparative studies have been conducted to evaluate the risk of pneumonia and mortality associated with inappropriate atypical antipsychotics. This study will fill the evidence gap regarding antipsychotic use in PD by:

Aim 1 – evaluating the incidence and predictors of inappropriate antipsychotics among elderly patients with Parkinson disease.

Aim 2 – examining the risk of pneumonia in elderly patients with PD using inappropriate antipsychotic agents vs. other atypical antipsychotics.

Aim 3 - examining the risk of mortality in patients with PD using inappropriate antipsychotic agents vs. other atypical antipsychotics.

A retrospective design involving Minimum Data Set (MDS) linked Medicare claims data was used to examine incidence and predictors of inappropriate atypical antipsychotic agents and to evaluate the study hypotheses that there are higher risks of pneumonia and all-cause mortality among older patients with PD using inappropriate atypical antipsychotics when compared to the three selected atypical antipsychotic agents (i.e. aripiprazole, clozapine, and quetiapine).

BACKGROUND AND SIGNIFICANCE

Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder, associated with significant disability and mortality.[1] In the United States, the prevalence of Parkinson's disease is estimated to be 0.3% in general population, 1% - 5% in the elderly and 5% - 10% in nursing home residents.[2,3] PD symptoms usually begin in the fifth or sixth decade of life, and the disease incidence increases steadily thereafter.[4] Pringsheim et al., 2014 conducted a systematic review and found a significantly higher prevalence of PD in male population aged 50 to 59 years old, compared to the same age female group; however, the PD prevalence by sex was not significantly different in other age groups.[20] The combined direct and indirect costs of PD were estimated at $25 billion per year in the United States, while the direct medical costs incurred for patients with PD were $14.4 billion in 2010. [3,6]

The classic features of PD encompass tremor at rest, rigidity, slowness of movement, postural instability, flexed posture, and freezing. [21] Additionally, the non-motor features such as neurobehavioral symptoms contribute to disability and impaired quality of life of patients with PD. [21] Cognitive deficits ranging from mild cognitive decline to severe dementia can be present in any stages of PD. [22] PD dementia is sometimes accompanied by psychotic features such as visual hallucinations, aggression and agitation. These symptoms are traditionally treated with antipsychotic medications which are contraindicated for patients with PD dementia. [22] Psychotropic medications are also used for treating mood symptoms in PD. The prognosis of PD is related to factors such as postural instability and dementia. In a 10-years follow-up study, the prevalence of postural instability and dementia was 68% and 46% respectively; and 23% of PD patients remained free of these symptoms. [23]

Dysphagia or difficulty swallowing is a non-motor symptom of PD, which is significantly associated with impaired quality of life and increased risk of mortality.[24,25] A systematic review conducted by Takizawa et al., 2016 estimated the prevalence of dysphagia to range from 11% to 81% among PD patients.[25] PD can affect all stages of swallowing that involve lingual, laryngeal and upper esophageal sphincter movements. [26] Impaired lingual and laryngeal movements result in abnormal bolus formation and aspiration respectively.[26] Severe dysphagia mainly occurs in the advanced stages of PD.[24] Although numerous interventions have been described for the treatment of dysphagia, the current evidence supports the application of rehabilitation techniques to improve swallowing process in patients with PD. [26] Dysphagia in some patients with PD responds significantly to levodopa administration.[24] Almirall et al., 2013 performed a case-control study and found a strong association between oropharyngeal dysphagia and community-acquired pneumonia in the elderly population (OR: 11.9, 95% CI: 3.0-46.9), after adjusting for functional status and comorbidities. [27]

Parkinsonian symptoms occur in a number of distinct disorders such as Dementia with Lewy Body (DLB) that potentially lead to misdiagnosis of Parkinson's disease.[28] The prevalence of motor features in DLB is similar to those of patients with PD. [29] Dementia occurs in the both conditions; however, the temporal course of dementia and levodopa responsivity are different for patients with DLB in comparison to PD. [29] Patients with DLB are at risk of severe neuroleptic sensitivity which is characterized by severe Parkinsonism and lack of consciousness after exposure to antipsychotics.[29] Additionally, vascular diseases of brain can mimic both DLB and PD and make the diagnosis more challenging. [29] The differential diagnoses of PD also include Progressive Supranuclear Palsy (PSP), Multiple System Atrophy (MSA), and Cortical-Basal

Ganglionic Degeneration (CBGD). These conditions are known as Parkinson-plus syndromes which indicate the presence of unique clinical features in addition to Parkinsonism. [30]

Pharmacotherapy is the cornerstone of PD treatment. [31] Levodopa is the most effective antiparkinson medication which acts as a replacement for dopamine. [31] Long-term levodopa therapy is associated with the development of disabling motor complications which occur in up to 80% of PD patients receiving levodopa.[12,32] The presence of motor complications such as dyskinesia is an important indicator for the advanced stage of PD. [33,34] There are three strategies for patients who develop motor complications: 1) levodopa dose reduction 2) combination therapy with other antiparkinson medications 3) surgery.[12] Other antiparkinson medications include dopamine agonists, catechol-O-methyl transferase inhibitors (COMTIs), monoamine oxidase type B inhibitors (MAOBIs), amantadine and anticholinergics. These antiparkinson agents can be initiated as monotherapy for the purpose of DOPA-sparing strategy or they can be added as adjuvant therapy to ongoing levodopa treatment. [12,34] The adjuvant antiparkinson therapy allows for levodopa dose reduction that ameliorates dyskinesia and other motor fluctuations.[12,34]

Parkinson's disease Complications

Psychosis is one the most challenging non-motor symptoms that affect both mental and physical functioning in patients with PD.[5] Although psychosis can occur anytime in the course of PD, psychotic symptoms are related to the use of dopaminergic agents such as levodopa. [10] The probability of psychosis was estimated to be 25%–60% in the lifetime course of PD, depending on the type of diagnostic criteria used.[10] The incidence of Parkinson's disease psychosis was estimated to range from 6% to 22% among PD patients who start treatment with dopaminergic

agents based on the findings of randomized controlled trials. [35] The cross-sectional prevalence of psychosis is reported to be 20%-40% among PD patients.[11] Visual hallucination is the most common symptom of PD psychosis, while delusions and systemized hallucinations can occur in severe cases.[10] Atypical antipsychotics are frequently used (48.2%) for the management of psychotic symptoms in patients with PD; however, most of the antipsychotic agents aggravate Parkinsonian symptoms.[11,12,35] Furthermore, antipsychotic use is associated with increased risk of pneumonia in elderly population.[36]

Pneumonia, a potentially preventable complication is the main cause of death among patients with PD.[1] According to a case control study conducted by Vinogradova et al., 2009, the risk of aspiration pneumonia is 1.82 times higher for PD patients when compared to the general population.[37] Gambassi et al., 2010 found that PD was a significant predictor for community-acquired pneumonia among older patients using antipsychotics.[36] Akbar et al., 2015 performed a cohort study and found that in a 5-years follow-up, 4.9% of PD patients developed aspiration pneumonia, while the incidence of pneumonia was 1.7% among non-PD patients. [38] Aspiration pneumonia is related to the impairment of swallow reflex and discoordination of breathing and swallowing which are the clinical features of PD. [14] The impairment of swallow reflex, manifesting as dysphagia can be present in any stage of PD.[14] The aspiration pneumonia occurs when a patient inhales oropharyngeal secretions colonized by pathogenic microorganisms. [39] The aspiration of sterile gastric contents can lead to chemical pneumonitis which does not involve an infectious process. Aspiration pneumonitis is sometimes misdiagnosed as pneumonia, due to some overlap in clinical manifestations.[39]

Despite advances in medical care, the mortality rate in patients with PD remains higher than expected for age.[7] The mortality rate of PD was reported to be 50% in 3 years in a large

cohort study of PD patients residing in nursing homes.[2,8] The mortality rate among Medicare beneficiaries with PD was 64% in 6 years follow-up. There exist disparities in PD related mortality by gender and race, since the survival of patients with PD was lower amongst male and African-American individuals. Infections such as pneumonia and cardiovascular disease were the most common causes of death among Medicare beneficiaries with PD. [9] According to a systematic review by Xu et al., 2014, the risk of all-cause mortality increases by 2.22 fold for patients with PD, in comparison to the general population; and age is the most important determinant of mortality in PD.[1] Most of the studies included in this systematic review reported that pneumonia and cardiovascular disease were the leading causes of death among patients with PD. [1]

Antipsychotic Use in Parkinson's disease

Studies have found that 15% to 30% of PD patients in long term facilities use antipsychotic drugs.[2] The prevalence of antipsychotic use was 50% in a large cohort of veterans with PD psychosis.[11] The efficacy of atypical APs in the treatment of PD psychosis has not been evaluated in large clinical trials; however, clozapine has found to be an effective treatment for PD psychosis. [2,12] In spite of effectiveness, clozapine is not commonly used in clinical practice, due to the risk of adverse events and the blood monitoring requirement. [11] There are mixed findings regarding the effect of other atypical antipsychotics on the psychotic features of PD.[2,12] Previous studies have shown that quetiapine is the most frequently prescribed AP for PD psychosis. [11] A post hoc study conducted by Ballard et al., 2015 shows that the use of antipsychotics for PD psychosis is associated with increased risk of serious adverse events, cognitive decline, and infections including pneumonia.[40] Fernandez et al., 2004 reported the

overall 5-year mortality rate was 44% in a cohort of patients with PD psychosis treated with clozapine.[41]

Antipsychotics target neuro-receptors with various mechanisms of action. [42] Patients with PD are particularly vulnerable to the effect of antipsychotics on Dopamine receptors type 2 (D_2). The loss of dopamine in the brain of patients with PD leads to a hypersensitivity of D_2 receptors which contributes to the adverse effects of APs in the treatment of PD psychosis. [42] Amongst antipsychotics, aripiprazole is exceptionally a partial agonist for D_2 receptors and the other APs are D_2 antagonists. The level of D_2 antagonism is lowest for clozapine and quetiapine, compared to conventional and other atypical APs. [42] The effect of APs on serotonin receptors varies across individual antipsychotics and plays an important role in the treatment of psychotic symptoms. However, serotonin receptor affinity may not be directly related to Parkinsonian symptoms. [43] *Pimavanserin*, a 5HT2A inverse *agonist* has been recently approved by FDA and brought *new hope* to patients with PD psychosis. [44]

Dopamine pathways are involved in swallow reflex and coordination of swallowing-breathing. [45] The dopaminergic neurodegeneration disturbs the coordination of swallowing and respiration that results in dysphagia and aspiration. [45] Antipsychotics potentially aggravate dysphagia by blocking D_2 receptors, leading to higher risk of aspiration pneumonia in patients with PD.[15] There are other mechanisms related to the risk of pneumonia in antipsychotics users.[13,16] Sedative effect of antipsychotics can suppress cognitive functioning in elderly patients with PD leading to a higher risk of aspiration.[17] It is also plausible that the swallow reflex becomes more dysfunctional when patients with PD use antipsychotics that worsen Parkinsonian symptoms, and it leads to a higher risk of pneumonia for those patients.[18] Anticholinergic effect of antipsychotics can increase the risk of pneumonia due to reduced sensorium, dry mouth,

decreased and thickened mucous secretions, and depressed mucociliary transport.[13] To our knowledge, limited data exists regarding the risk of pneumonia related to antipsychotic use in PD patients. In a 4-week clinical trial on ziprasidone (n=6) versus clozapine (n=8) for PD psychosis, only one patient developed pneumonia in the ziprasidone group. [46] In the open label extension of clozapine trial, the incidence of pneumonia was 10% in 12 weeks follow-up among PD patients with psychotic symptoms. [47]

Antipsychotic use is associated with several adverse events such as worsening Parkinsonian symptoms.[12,13] According to the 2015 American Geriatrics Society (AGS) Beers criteria antipsychotics are generally inappropriate medications in PD, because they can potentially worsen Parkinsonian symptoms, except for aripiprazole, quetiapine, and clozapine.[19] Inappropriate antipsychotics include all typical antipsychotics, olanzapine, asenapine, brexpiprazole, iloperidone, lurasidone, paliperidone, risperidone, and ziprasidone. [19,48] Previous studies found that some inappropriate antipsychotics such as risperidone are commonly used in clinical practice for the treatment of PD psychosis. [11] However, limited data exist regarding safety of atypical antipsychotics in general and inappropriate atypical antipsychotics in specific in patients with PD. Only Marras et al., 2012 conducted a nested case-control study and found that PD patients who were exposed to atypical antipsychotics were at a higher risk of death (OR: 2.0, 95% CI: 1.4–2.7), compared to the non-exposed group.[49] No comparative studies have been conducted to evaluate the risk of pneumonia and mortality associated with inappropriate atypical antipsychotics.

Significance and Innovation

Inappropriate antipsychotics can worsen Parkinsonian symptoms leading to a higher risk of serious adverse events. [5,19] In clinical practice, antipsychotics are commonly used for patients with PD and limited data exists regarding use of inappropriate antipsychotics in PD. This study will identify the incidence and predictors of inappropriate antipsychotics among patients with PD. Knowledge about these factors will help in determining the subpopulations of PD patients who are vulnerable to the adverse effects of antipsychotics due to higher rates of antipsychotic utilization. The study findings can also help in developing better treatment strategies for patients with PD.

Previous studies demonstrated that antipsychotics with higher level of D_2 antagonist activity are commonly prescribed for patients with PD.[11] According to Beers criteria 2015, most antipsychotics including those with higher level of D_2 antagonist activity are inappropriate for patients with PD. [19,42] However, the safety profile of antipsychotics in PD have not been examined based on the neuro-receptors targeted by antipsychotics. Atypical antipsychotics have been implicated for increased risk of pneumonia in general and mortality in specific. The study will evaluate the risks of medication-related morbidity and mortality in older patients with PD using inappropriate atypical antipsychotic agents. Specifically, the research will test hypotheses that there are higher risks of pneumonia and all-cause mortality among older patients with PD using inappropriate atypical antipsychotics when compared to the three selected atypical antipsychotic agents. Clinical trials generally include healthy adults and it limits the understanding of the safety aspect of the antipsychotics among vulnerable patients with PD. To our knowledge, no observational studies have examined the risk of pneumonia related to antipsychotic use in PD patients. This study will provide much needed evidence regarding the

safety of antipsychotics in PD and thereby help providers to select the safer treatment options for PD; as it can identify the high risk antipsychotics for PD patients who are vulnerable to aspiration pneumonia.

This research is innovative for several reasons. Although the Beers criteria specify inappropriate medications for patients with PD, the concept of inappropriate antipsychotics for PD patients has not been examined in previous research. This is the first study aiming to identify the incidence and predictors of inappropriate antipsychotics among patients with PD. The study uses neuro-pharmacological rationale to examine the risks of medication-related morbidity and mortality in older patients with PD using inappropriate atypical antipsychotic agents. Thus, the study findings can provide insight into the clinical manifestations of PD, due to underlying mechanisms of inappropriate antipsychotics. Although previous studies evaluated the safety of antipsychotic in the elderly in general and dementia in specific, very limited research exists regarding antipsychotic safety in PD. Therefore, the study findings will fill much needed evidence gap in this field.

The study involves use of large, linked Medicare involving Parts A, B, and D and National Death Index to conduct comparative safety research involving PD patients.[52,53] With introduction of Part D coverage, the Medicare claims have become a valuable data source for pharmacoepidemiology research. [53] The linked Medicare data sources will have the power and clinical information to address safety issues of medications, specifically adverse effects of antipsychotics. This study will use population-based cohort design to fill the critical evidence gap in this under-researched population. Although randomized trials provide the need efficacy data, large-scale epidemiological designs are the gold standard to obtain long-term safety data because of ethical and cost considerations. The study involves propensity score-matched cohort

study design to account for indication and selection bias within the drug class. [54] The strength of observational studies lies in their ability to estimate treatment effects in real world settings. However, they suffer potential biases due to uncontrolled confounding by unmeasured, unknown, or inadequately measured covariates. [54] This study will address potential confounding and selection bias by using propensity scores as it involves matching of study sample based on observable to address selection bias. This methodological approach is innovative in the context of PD outcomes.

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MANUSCRIPT 1

USE OF ATYPICAL ANTIPSYCHOTICS IN LONG-TERM CARE RESIDENTS WITH PARKINSON'S DISEASE

ABSTRACT

Objectives: According to the 2015 American Geriatrics Society (AGS) Beers criteria, most antipsychotics are inappropriate in Parkinson's disease (PD) patients due to the risk of worsening Parkinsonian symptoms. There is a gap in literature regarding the use of inappropriate atypical antipsychotics in elderly patients with PD. This study examined the incidence and predictors of inappropriate antipsychotic use in PD in nursing homes.

Methods: The study used a retrospective cohort, with a 12-month baseline and a 24-month follow-up. The study utilized 2007-2009 Minimum Data Set (MDS) cross-linked to Chronic Condition Warehouse (CCW) Medicare data files involving patients with depression. Older adults aged over 65 years with a diagnosis of PD were included and patients with bipolar disorders or schizophrenia were excluded. Patients who received atypical antipsychotics in the baseline period were also excluded. Inappropriate atypical antipsychotics comprised of asenapine, brexpiprazole, iloperidone, lurasidone, olanzapine, paliperidone, risperidone, or ziprasidone. As specified in Beers criteria 2015, the use of aripiprazole, clozapine, or quetiapine in PD patients was considered as appropriate in this study. Multivariable logistic regression was used to examine various sociodemographic and clinical factors associated with inappropriate antipsychotic use in PD based on Andersen's Behavioral Model.

Results: The prevalence of atypical antipsychotic use was 36.77% (28,055/76,294) and the incidence rate was 17.50% (13,352/76,294) in a 2-year follow-up of eligible patients with PD. The rate of inappropriate use among atypical antipsychotic users was 36.32%. The most

frequently used inappropriate antipsychotics were risperidone (22.95%) and olanzapine (11.25%). The likelihood of inappropriate antipsychotic use was higher for patients who had dementia (OR=1.22, 95% CI: 1.12-1.33) or Chronic Obstructive Pulmonary Disease ((OR=1.13, 95% CI: 1.03-1.24). Conversely, patients who were taking levodopa (OR=0.62, 95% CI: 0.57-0.67), dopamine agonists (OR=0.90, 95% CI: 0.82-0.98), Catechol-O-methyltransferase (COMT) inhibitors (OR=0.77, 95% CI: 0.68-0.86), Monoamine Oxidase (MAO) inhibitors type B (OR=0.72, 95% CI: 0.60-0.86), or amantadine (OR=0.84, 95% CI: 0.71-0.98) were less likely to receive inappropriate antipsychotics.

Conclusions: The incidence rate of inappropriate atypical antipsychotic use was relatively high; as more than one-third of PD patients received inappropriate agents among those who were treated with atypical antipsychotics in this study. Various socio-demographics and clinical factors were associated with inappropriate antipsychotic use among older patients with PD. Further research is warranted to evaluate rates and patterns of antipsychotic use after implementation of new guidelines for PD psychosis.

INTRODUCTION

Parkinson's disease (PD) is characterized by loss of dopaminergic neurons and associated with various motor and non-motor symptoms. [1] The prevalence of PD is estimated to be 0.3% and 1% in general population and older adults aged over 65 years respectively. [2,3] PD primarily affects voluntary movements, however lack of dopamine leads to neurobehavioral symptoms and other non-motor features. [1] Both motor and non-motor symptoms contribute to impaired quality of life of patients with PD. [4] Dopaminergic medications act as dopamine replacement (i.e. levodopa) or agonist for dopamine receptors. [5] These medications can alleviate Parkinsonian symptoms; however, the use of antiparkinson agents is associated with adverse events such as dopaminergic psychosis. [6] For patients with PD, the probability of psychosis is between 25% and 60% in their lifetime course, depending on the diagnostic criteria used.[6] The most common symptom of PD psychosis is visual hallucination while delusions and systemized hallucinations are associated with sever psychosis. [6] In addition, psychotic features in PD patients might relate to underlying comorbidities such as dementia. [7]

Although antipsychotics are recommended for the treatment of psychotic symptoms, these medications are implicated for increased risk of adverse events in elderly population and specifically in patients with PD. [8] According to the 2015 American Geriatrics Society (AGS) Beers criteria, most antipsychotics are inappropriate in PD patients due to the risk of worsening Parkinsonian symptoms. [9] Three atypical antipsychotics (i.e. aripiprazole, clozapine, and quetiapine) have been excluded from the list of high risk medications in PD, based on expert review of evidence. [9] The efficacy of antipsychotics in patients with dopaminergic psychosis has been evaluated in small clinical trials. [2,10] These clinical trials provided convincing evidence that

clozapine is effective in the treatment of PD psychosis, while there are mixed findings regarding the efficacy of other atypical antipsychotics. [2,10]

Clozapine is not commonly used in clinical practice due to the risk of adverse events. [11] Previous studies have shown that quetiapine is the most frequently used antipsychotic drug in PD and a relatively high number of patients with PD receive inappropriate antipsychotics such as risperidone for the treatment of psychotic symptoms. [11] A cohort study of Veterans Affairs data found that antipsychotic agents were prescribed for 50% of patients with PD psychosis within one year of follow-up and quetiapine was prescribed for 66% of patients who received antipsychotic agents. [11] Risperidone, an inappropriate medication in PD was prescribed for 17.3% of patients who received antipsychotic treatment. [11] There is a gap in literature regarding the use of inappropriate atypical antipsychotics in elderly patients with PD. This study examined the incidence and the factors associated with inappropriate antipsychotic use in PD in nursing homes. The study can help increase the awareness of inappropriate antipsychotic use in patients with PD, and thus help providers to optimize use of these medications.

METHODS

Data Source

The study utilized 2007-2009 Minimum Data Set (MDS) cross-linked to Chronic Condition Warehouse (CCW) data files involving patients with depression. The MDS and CCW datasets contained Research Identifiable Files obtained from Center for Medicaid and Medicare Services (CMS). The MDS was completed by trained nurses via direct face to face interviews within 7-14 days of admission/readmission and during subsequent evaluations on quarterly basis or when any significant change occurred in the resident health status. [12,13] The MDS involves

individual assessment items covering 17 domains, such as medical diagnosis, behavioral and mood indicators and activities of daily living. [12]

The data files linked to MDS included the Master Beneficiary Summary Files and Medicare Parts A, B, and D files for each of the study years. It also involved using MedPar and outpatient files for hospitalization and physician services, respectively. Additionally, the master beneficiary summary files were used to obtain information on demographic characteristics and enrollment status in Medicare Parts A and B as well as disease-specific variables. The Part D files capture drug information for each prescription filled by Medicare enrollees during the study period. [12] This study was approved under exempt category by the institutional review board for the protection of human subjects at the University of Houston.

Study Design and Sample

The study used a retrospective cohort design with a 12-month baseline and a 24-month follow-up. The diagnosis of PD was defined based on both MDS assessment and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 332.0 in the claims database. For all cohort patients, the diagnosis of PD was confirmed in 2007 which was the baseline period. Older adults aged over 65 years with continuous coverage for Medicare parts A, B, and D were included. Patients with a baseline diagnosis of either bipolar disease or schizophrenia were excluded, since those patients were chronic users of antipsychotic medications. Patients were excluded from the cohort if they used any atypical antipsychotics in the baseline period or they started taking more than one atypical antipsychotics simultaneously in the follow-up period.

Analytical Approach

The initiation of atypical antipsychotics in PD patients was evaluated over a two-year study period i.e., 2008 - 2009. The first prescription of atypical antipsychotics in 2008 – 2009 was considered as the new antipsychotics use. The study outcome was the use of inappropriate antipsychotics, based on AGS Beers criteria 2015. [9] The use of inappropriate antipsychotics was defined as the prescription of asenapine, brexpiprazole, iloperidone, lurasidone, olanzapine, paliperidone, risperidone, or ziprasidone. As specified in Beers criteria 2015, the use of aripiprazole, clozapine, or quetiapine in PD patients was appropriate in this study. These medications were identified using Generic Name - Short Version (GNN) from the Prescription Drug Event Data. The Prescription Service Date (DOS) was used to determine the first prescription of antipsychotics in the study period. [12] Typical antipsychotics users were not excluded from the analysis, rather the baseline use of typical agents was taken into account as a confounding factor.

This study applied Andersen's Behavioral Model (ABM) to explain the relationship between predisposing, enabling and need factors and antipsychotic medication use. Based on the ABM, predisposing factors included age, sex, race, education, marital status and geographical region.[14] The type of insurance coverage was an enabling factor that was applied in the cohort identification process. Need factors encompassed cognitive and functional status, walk assessment, clarity of speech, dyskinesia, dysphagia, abusive behavior, insomnia, depressed mood indicators, along with various comorbidities and co-medications. The MDS assessment contains several measures related to PD severity including cognitive and functional impairment items. These validated measures have been used in previous observational studies involving patients with neurological impairment. The current study utilized MDS-Derived Direct

Cognition Scale (MDS-COG) to control for the severity of cognitive impairment in PD. The MDS-COG ranges from 0 to 9, with higher scores indicating greater severity of cognitive impairment. [15] The Activities of Daily Living were scored using ADL-Long Form (0-28) with higher scores indicating a worse functional status. [16]

Based on the ABM, sociodemographic and clinical characteristics were compared between appropriate and inappropriate atypical antipsychotics users. Multivariable logistic regression was used to examine the relationship between predisposing and need factors and the use of inappropriate atypical antipsychotics in elderly patients with PD. All statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, North Carolina) with a statistical significance level of 0.05.

RESULTS

The number of PD patients aged 65 years or older with continuous eligibility for Medicare parts A, B and D coverage was 88,131 from 2007-2009 MDS-linked Medicare data. Excluding those with bipolar disorder or schizophrenia, 76,294 PD patients remained in the cohort and 28,055 patients were found to receive atypical antipsychotics between 1st Jan 2008 and 31st Dec 2009. As shown in the cohort identification flowchart (Figure 1), 14,611 patients were excluded because they used atypical antipsychotics in washout period and 92 patients were excluded because they started more than one antipsychotic drug at the same time in the study period. In the study cohort, 13,352 patients started only one atypical antipsychotic in 2008 and 2009 and the number of inappropriate antipsychotic users was 4,849. The rate of inappropriate use among atypical antipsychotic users was 36.32%.

Figure 1. Cohort Identification flowchart

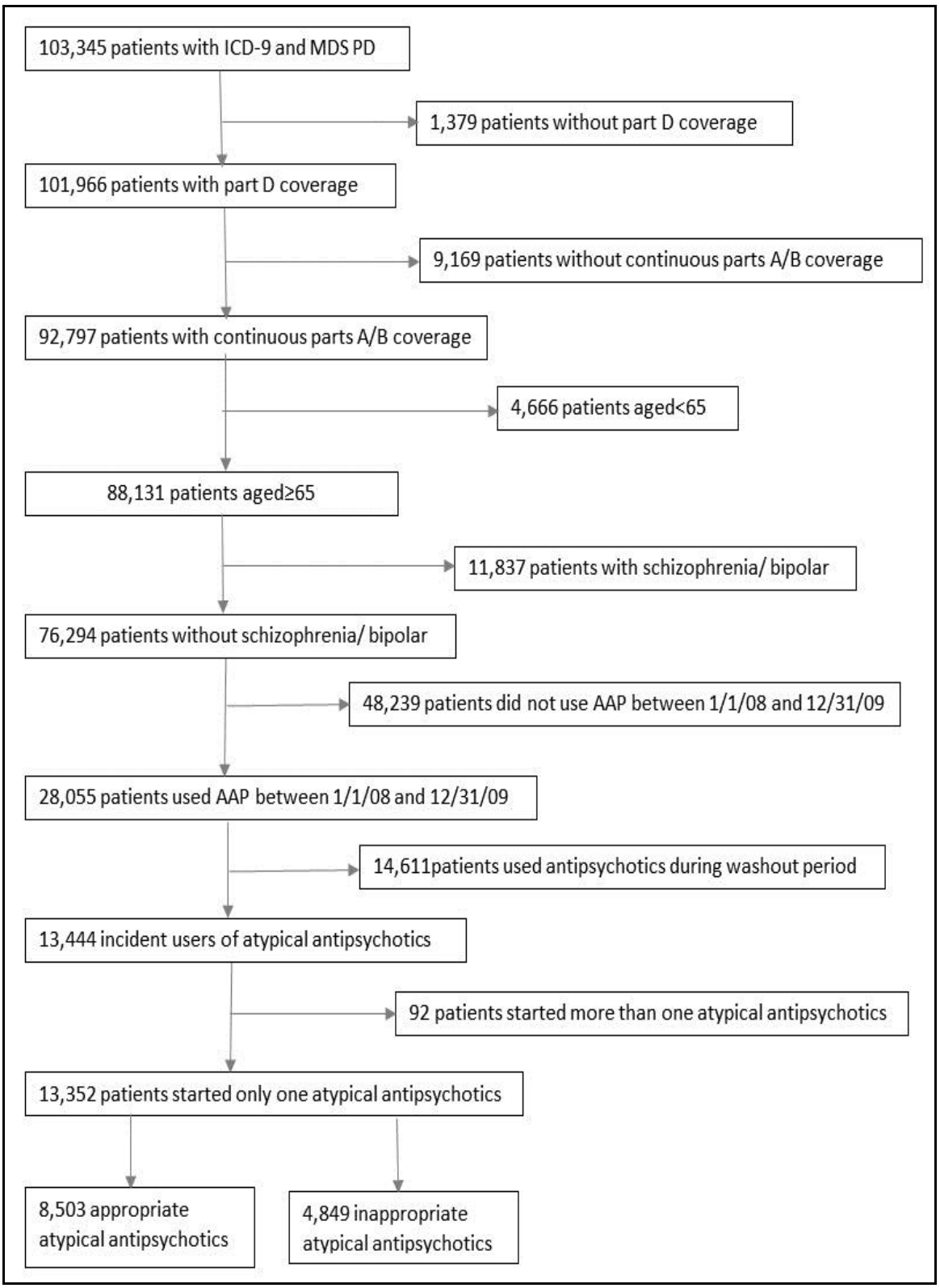

Table 1 presents baseline characteristics of the study cohort. The mean age of the study population was over 80 years in both treatment groups. The percentage of persons with dementia was 28.29% in inappropriate antipsychotic users and 22.05% in the appropriate treatment group. Falls and fractures were the most common comorbidities (>85%) in the study population and hypertension was the second most common comorbidity. The rate of baseline typical antipsychotic use was 6.50% and 7.90% respectively in appropriate and inappropriate antipsychotic groups. Most study patients received levodopa in the baseline period since the rate of levodopa therapy was 73.17% and 59.79% in the appropriate and inappropriate atypical antipsychotic users respectively. As shown in Table 2, the percentages use of quetiapine (55.55%), risperidone (22.95%) and olanzapine (11.25%) were the highest among all atypical antipsychotics.

Table 1. Characteristics of PD patients residing in nursing homes with incident use of appropriate and inappropriate atypical antipsychotics (AAP)

Characteristic	Appropriate AAP (n= 8,503)	Inappropriate AAP (n= 4,849)	P-Value
Age (mean ± SD)	80.85 ± 6.99	81.85 ± 7.06	<0.01*
Female, n (%)	4,761 (55.99)	2,891 (59.62)	<0.01*
White, n (%)	7,756 (91.21)	4,346 (89.63)	<0.01*
College education, n (%)	1,790 (21.05)	737 (15.20)	<0.01*
Married, n (%)	3,343 (39.32)	1,666 (34.36)	<0.01*
Region, n (%)			
Midwest	2,299 (27.04)	1,388 (28.62)	<0.01*
Northeast	1,811 (21.30)	870 (17.94)	
West	354 (4.16)	203 (4.19)	
South	4,039 (47.50)	2,388 (49.25)	
ADL Score (mean ± SD)	13.11 ± 7.03	12.96 ± 7.22	0.25
MDS Cognitive Score (mean ± SD)	4.69 ± 1.16	4.67 ± 1.17	0.26
Impaired Walking	4,580 (53.86)	2,519 (51.95)	0.03*
Unclear Speech, n (%)	1,394 (16.39)	797 (16.44)	0.95
Dyskinesia, n (%)	184 (2.16)	80 (1.65)	0.04*
Dysphagia, n (%)	3,220 (37.87)	1,735 (35.78)	0.02*
Insomnia, n (%)	1,135 (13.35)	577 (11.90)	0.02*
Abusive Behavior, n (%)	944 (11.10)	584 (12.04)	0.1
Depressed Mood Indicators, n (%)	2,564 (30.15)	1,394 (28.75)	0.09
Depressive Type Psychosis, n (%)	71 (0.83)	43 (0.89)	0.75
Anxiety, n (%)	3,437 (40.42)	2,100 (43.31)	<0.01*
Dementia, n (%)	1,875 (22.05)	1,372 (28.29)	<0.01*
Stroke, n (%)	1,805 (21.23)	1,180 (24.33)	<0.01*
Falls and Fractures, n (%)	7,310 (85.97)	4,136 (85.30)	0.28
Coronary Artery Disease, n (%)	1,782 (20.96)	1,116 (23.02)	<0.01*
Congestive Heart Failure, n (%)	1,985 (23.34)	1,289 (26.58)	<0.01*
Dysrhythmia, n (%)	1,675 (19.70)	1,014 (20.91)	0.09
Hypertension, n (%)	6,474 (76.14)	3,857 (79.54)	<0.01*
Diabetes Mellitus, n (%)	2,539 (29.86)	1,618 (33.37)	<0.01*
Osteoarthritis, n (%)	3,565 (41.93)	2,168 (44.71)	<0.01*
Cancer, n (%)	888 (10.44)	465 (9.59)	<0.11
Pneumonia history, n (%)	2,759 (32.45)	1,665 (34.34)	0.03*
Asthma, n (%)	402 (4.73)	253 (5.22)	0.21
COPD, n (%)	1,673 (19.68)	1,129 (23.28)	<0.01*
Charlson Comorbidity Index (mean ± SD)	5.45 ± 3.42	5.68 ± 3.45	<0.01*
Typical antipsychotics, n (%)	553 (6.50)	383 (7.90)	<0.01*

SSRI/ SNRI, n (%)	5,918 (69.60)	3,462 (71.40)	0.03*
Levodopa, n (%)	6,222 (73.17)	2,899 (59.79)	<0.01*
Dopamine Agonists, n (%)	2,320 (27.28)	1,050 (21.65)	<0.01*
COMT Inhibitors, n (%)	1,441 (16.95)	474 (9.78)	<0.01*
MAO Inhibitors Type B, n (%)	583 (6.86)	172 (3.55)	<0.01*
Amantadine, n (%)	649 (7.63)	244 (5.03)	<0.01*
Anticholinergics, n (%)	396 (4.66)	226 (4.66)	0.99

* Indicate p value <0.05

Table 2. Proportion of atypical antipsychotic agents initiated for elderly nursing home patients with PD (n=13,352)

Antipsychotics	Frequency	Percent
Aripiprazole	1,036	7.76
Clozapine	50	0.37
Olanzapine	1,502	11.25
Paliperidone	23	0.17
Quetiapine	7,417	55.55
Risperidone	3,064	22.95
Ziprasidone	260	1.95

The odds of receiving inappropriate vs. appropriate antipsychotics are presented in Table 3. Among predisposing factors, patient's age was associated with higher likelihood of receiving inappropriate antipsychotics with adjusted Odds Ratio (OR): 1.01 (1.01-1.02). Patients were less likely to use inappropriate antipsychotics, if they were highly educated [OR=0.76, 95% Confidence Interval (CI): 0.69-0.84], married (OR=0.91, 95% CI: 0.84-0.99) or lived in northeast (OR=0.83, 95% CI: 0.75-0.92). Several need factors including clinical characteristics were associated with inappropriate antipsychotic use among elderly patients with PD. The likelihood of inappropriate antipsychotic use was higher for patients who had dementia (OR=1.22, 95% CI: 1.12-1.33), Chronic Obstructive Pulmonary Disease (COPD) (OR=1.13, 95% CI: 1.03-1.24), or those who received Selective Serotonin Reuptake Inhibitor (SSRI) or Serotonin–Norepinephrine Reuptake Inhibitor (SNRI) (OR=1.14, 95% CI: 1.06-1.24). On the contrary, patients who were taking levodopa (OR=0.62, 95% CI: 0.57-0.67), dopamine agonists (OR=0.90, 95% CI: 0.82-0.98), Catechol-O-methyltransferase (COMT) inhibitors (OR=0.77, 95% CI: 0.68-0.86), Monoamine Oxidase (MAO) inhibitors type B (OR=0.72, 95% CI: 0.60-0.86), or amantadine (OR=0.84, 95% CI: 0.71-0.98) were less likely to receive inappropriate antipsychotics.

Table 3. Factors associated with use of inappropriate vs. appropriate atypical antipsychotics in elderly nursing home patients with PD

Characteristic	Unadjusted OR (%95 OR)	Adjusted OR (%95 OR)
Age	1.02 (1.02-1.03)	1.01 (1.01-1.02)
Female vs. Male	1.16 (1.08-1.25)	1.04 (0.96-1.13)
White vs. Others	0.83 (0.74-0.94)	0.88 (0.77-1.00)
College vs. Lower education	0.67 (0.61-0.74)	0.76 (0.69-0.84)
Married vs. Unmarried	0.81 (0.75-0.87)	0.91 (0.84-0.99)
Region		
Midwest	1.02 (0.94-1.11)	1.07 (0.98-1.17)
Northeast	0.81 (0.74-0.89)	0.83 (0.75-0.92)
West	0.97 (0.81-1.16)	1.11 (0.93-1.34)
South	Ref	Ref
ADL Score	1.00 (0.99-1.00)	1.00 (0.99-1.00)
MDS Cognitive Score	0.98 (0.96-1.01)	0.98 (0.95-1.02)
Impaired Walking (Yes vs. No)	0.93 (0.86-0.99)	1.00 (0.93-1.08)
Unclear Speech (Yes vs. No)	1.00 (0.91-1.10)	1.07 (0.96-1.18)
Dyskinesia, n (%)	0.76 (0.58-0.99)	0.96 (0.73-1.26)
Dysphagia, n (%)	0.91 (0.85-0.98)	0.93 (0.86-1.00)
Abusive Behavior (Yes vs. No)	1.10 (0.98-1.22)	1.12 (0.99-1.25)
Insomnia (Yes vs. No)	0.88 (0.79-0.98)	0.90 (0.80-1.00)
Depressed Mood Indicators (Present vs. Absent)	0.94 (0.87-1.01)	0.93 (0.86-1.01)
Depressive Type Psychosis (Yes vs. No)	1.06 (0.73-1.56)	1.06 (0.72-1.56)
Anxiety (Yes vs. No)	1.13 (1.05-1.21)	1.08 (1.00-1.17)
Dementia (Yes vs. No)	1.40 (1.29-1.51)	1.22 (1.12-1.33)
Stroke (Yes vs. No)	1.19 (1.10-1.30)	1.09 (1.00-1.19)
Falls and Fractures (Yes vs. No)	0.95 (0.86-1.05)	0.92 (0.83-1.02)
Coronary Artery Disease (Yes vs. No)	1.13 (1.04-1.23)	1.04 (0.95-1.14)
Congestive Heart Failure (Yes vs. No)	1.19 (1.10-1.29)	1.02 (0.93-1.11)
Dysrhythmia (Yes vs. No)	1.08 (0.99-1.18)	1.00 (0.91-1.09)
Hypertension (Yes vs. No)	1.22 (1.12-1.33)	1.05 (0.96-1.15)
Diabetes Mellitus (Yes vs. No)	1.18 (1.09-1.27)	1.06 (0.98-1.15)
Osteoarthritis (Yes vs. No)	1.12 (1.04-1.20)	1.02 (0.94-1.10)
Cancer (Yes vs. No)	0.91 (0.81-1.02)	0.88 (0.78-0.99)
Pneumonia history (Yes vs. No)	1.01 (1.01-1.17)	1.01 (0.93-1.10)
Asthma (Yes vs. No)	1.11 (0.94-1.30)	1.00 (0.84-1.18)
COPD (Yes vs. No)	1.24 (1.14-1.35)	1.13 (1.03-1.24)
Charlson Comorbidity Index	1.02 (1.01-1.03)	1.01 (1.00-1.02)
Typical antipsychotics, n (%)	1.23 (1.08-1.41)	1.09 (0.95-1.25)
SSRI/ SNRI (Used vs. Not Used)	1.09 (1.01-1.18)	1.14 (1.06-1.24)
Levodopa (Used vs. Not Used)	0.55 (0.51-0.59)	0.62 (0.57-0.67)
Dopamine Agonists (Used vs. Not Used)	0.74 (0.68-0.80)	0.90 (0.82-0.98)
COMT Inhibitors (Used vs. Not Used)	0.53 (0.48-0.59)	0.77 (0.68-0.86)
MAO Inhibitors Type B (Used vs. Not	0.50 (0.42-0.59)	0.72 (0.60-0.86)

Used)		
Amantadine (Used vs. Not Used)	0.64 (0.55-0.75)	0.84 (0.71-0.98)
Anticholinergics (Used vs. Not Used)	1.00 (0.85-1.18)	1.08 (0.91-1.28)

DISCUSSION

In this study, the prevalence of atypical antipsychotic use in a cohort of older patients with PD and depression was 36.77% and the incidence rate was 17.50% in a 2-year follow-up. These prevalence and incidence rates are not directly comparable to previous estimates of antipsychotic use in PD due to the clinical setting and comorbid depression.[17] The prevalence and incidence rates of antipsychotic use are possibly high as the study population was nursing home residents with comorbid depression diagnosis. The high rate of inappropriate atypical antipsychotic use could partly be due to the fact that current recommendations for antipsychotic use might not have been implemented in previous guidelines when the study data were collected.[18]

Although clozapine is an effective treatment in PD psychosis, only 0.37% of patients with PD were treated with this atypical antipsychotic which is consistent with previous studies on antipsychotic use in PD. [11] This is possibly due to the adverse side effect profile of clozapine. Quetiapine was the most frequent appropriate antipsychotic (55.55%) and risperidone was the most commonly used inappropriate antipsychotic (22.95%) in this study. The use of quetiapine was consistently higher than other antipsychotics in previous studies of elderly patients with PD, possibly because quetiapine was considered to be safer than other antipsychotics for those patients. [19] Risperidone is an effective treatment for delirium and other neurobehavioral conditions that might justify these findings. [20]

Multivariable logistic regression was used to examine various predisposing and need factors associated with inappropriate antipsychotic use in PD. Older age was associated with

higher use of inappropriate antipsychotics, which could be related to higher rates of behavioral symptoms due to their comorbidities.[21] Therefore, antipsychotics might be prescribed for reasons other than dopaminergic psychosis, and it increases the risk of inappropriate antipsychotic use in very old patients. The likelihood of receiving inappropriate antipsychotics was lower for college educated and married patients in comparison to others. This indicates that treatment of PD psychosis might vary across different sociodemographic groups. The study found that inappropriate antipsychotics were less prescribed in the Northeast geographical region in comparison to the South, indicating potentially important regional variations in the quality of care.

Amongst clinical characteristics dementia and COPD were associated with higher risk of inappropriate antipsychotics use. Antipsychotics might be administrated for behavioral symptoms in dementia or for treating delirium in COPD. [22] These clinical conditions are not associated with dopaminergic medication use, thus providers might be using these agents to treat the behavioral symptoms of dementia or COPD. The use of inappropriate antipsychotics was higher in typical antipsychotics and antidepressant users and this might refer to the use of atypical antipsychotics for preexisting mental disorders. [23] On the other hand, patients who were taking levodopa or other antiparkinson drugs with dopaminergic properties were more likely to receive appropriate antipsychotics. The use of dopaminergic antiparkinson drugs is possibly an indicator for dopaminergic psychosis which prompts appropriate antipsychotics utilization. [24]

Generalizability of Findings

The study population consisted of nursing home residents with a diagnosis of PD and depression, since the original data source was a cohort of nursing home residents with depression. Patients with major depressive disorder might use antipsychotics for a number of

reasons including augmentation of antidepressant therapy and treatment of comorbid insomnia or anxiety symptoms.[25,26] This potentially leads to higher rates of antipsychotic use in patients with depression when compared to those without depression. On the other hand, the study patients might receive specific types of atypical antipsychotics based on evidence and recommendations for the treatment of depression. This might limit the generalizability of study findings for older patients with PD. However, the multivariable model included various covariates such as depressed mood indicators and anxiety to control for the reasons of antipsychotic use in depression.

Strengths and Limitations

This study has some strengths such as using a large nationally representative data, robust methodology and utilization of a large sample size. The MDS provides comprehensive assessment of nursing home residents on their functional status and clinical conditions which shares many common features with Parkinson's disease assessments. [27,28] The study linked MDS to Medicare claims to obtain additional information regarding individual and clinical characteristics. This provided enough flexibility to define a washout period to exclude prevalent users of atypical antipsychotics and to avoid prevalent user bias. [29] The MDS and Medicare claims are nationally representative data with good generalizability for elderly population. Utilizing a large sample size provided adequate power to examine the various factors associated with inappropriate antipsychotics use.

The limitations of the study include those inherent to the nature of the secondary data analysis and data availability. Miscoding and under-coding might occur in the process of administrative data collection. [30] The study findings were limited by the data source, definitions, and data analytical approaches. This study utilized data from a cohort of nursing home residents

with a diagnosis of depression. This might affect utilization pattern of atypical agents in the study cohort but it would not be a differential bias across the study groups. The methodological limitations also related to the availability of specific variables. One such factor was rating the severity of Parkinson disease, which is commonly performed using disability scales such as the Unified Parkinson Disease Rating Scale (UPDRS). Since Medicare data did not contain information on PD severity, we used relevant variables and proxies to control for the severity of PD in multivariable models. Finally, this study cannot establish a causal relationship between predictors and the outcome of inappropriate antipsychotic use due to nature of the study.

CONCLUSIONS

The incidence rate of inappropriate atypical antipsychotic use was relatively high, as more than one-third of PD patients received inappropriate agents among those who were treated with atypical antipsychotics in this study. Various socio-demographics and clinical factors were associated with inappropriate antipsychotic use among elderly patients with PD. Users of dopaminergic antiparkinson agents were more likely to be treated with appropriate antipsychotics and those with comorbidities such as dementia or COPD were more likely to receive inappropriate antipsychotics. Further research is warranted to evaluate rates and patterns of antipsychotic use after implementation of new guidelines for PD psychosis.

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MANUSCRIPT 2

RISK OF PNEUMONIA ASSOCIATED WITH ATYPICAL ANTIPSYCHOTIC USE IN ELDERLY PATIENTS WITH PARKINSON'S DISEASE

ABSTRACT

Objectives: According to the 2015 American Geriatrics Society (AGS) Beers criteria atypical antipsychotics (AAPs) are inappropriate in patients with Parkinson's disease (PD) except for aripiprazole, clozapine and quetiapine due to the risk of worsening Parkinsonian symptoms. This study evaluated the risk of pneumonia associated with inappropriate AAPs use in PD patients.

Methods: This retrospective cohort study used 2007 to 2010 minimum data set (MDS) linked Medicare data files. The study population encompassed older adults aged 65 years or older with a diagnosis of PD and without schizophrenia or bipolar disorder diagnoses who started one AAP. All patients had a diagnosis of depression, since the study sample was derived from a depression cohort. The study had two treatment arms: 1) appropriate AAPs i.e. aripiprazole, clozapine or quetiapine , and 2) inappropriate AAPs including olanzapine, asenapine, brexpiprazole, iloperidone, lurasidone, paliperidone, risperidone, or ziprasidone. A propensity score matching approach and Cox regression models were used to examine the relationship between AAP use and risk of pneumonia in patients with PD over 6-month follow-up. Sensitivity analyses were performed using frequently used antipsychotic agents.

Results: There were 16,161 patients aged 65 years or older with PD diagnosis and without schizophrenia/ bipolar disorder who started only one atypical antipsychotic in the study period. The mean age of the patients was over 82 years. There were 12,076 patients in the matched propensity score cohort. Overall incidence of pneumonia was 17.56% over 6-month follow-up; 16.35% in appropriate AAP group and 18.78% in inappropriate AAP group. Cox model for

matched cohort revealed increased risk of pneumonia [Hazard Ratio (HR) 1.20 (1.08 - 1.34)] for patients who used inappropriate vs. appropriate AAP. In sensitivity analyses, the pneumonia HR was 1.28 (1.12 - 1.47) for risperidone vs. quetiapine and the pneumonia HR was 1.29 (1.06 - 1.57) for olanzapine vs. quetiapine.

Conclusions: The risk of pneumonia was significantly higher for inappropriate AAP users in comparison to appropriate antipsychotic group in all analyses. This investigation provided a strong evidence base regarding safety of atypical antipsychotics in older patients with PD. Further research is needed to evaluate the risk of pneumonia in PD patients using newer antipsychotics.

INTRODUCTION

Parkinson's disease (PD) is a leading cause of morbidity and disability in elderly population. The prevalence of PD ranges from 1% to 5% in elderly population depending on the age group. [1,2] The PD prevalence has been estimated to be 5-10% in long term care facilities due to significant disability caused by Parkinsonian symptoms that leads to nursing home placement. [3] Lack of dopamine is the cause of motor symptoms such as tremor, rigidity, and bradykinesia in PD patients. [4] Additionally, non-motor features such as dysphagia and behavioral symptoms adversely affect the course of PD. [4]

Dopaminergic medications are the cornerstone of pharmacotherapy in PD. These medications may act as dopamine replacement (i.e. levodopa) or dopamine agonists. [5] Dopaminergic agents can alleviate Parkinsonian symptoms; however, use of these antiparkinson agents is associated with adverse events such as dopaminergic psychosis. [6] The probability of psychosis is between 25% and 60% for PD patients, in their lifetime course, depending on the diagnostic criteria used.[6] The most common symptom of PD psychosis is visual hallucination while delusions and systemized hallucinations are associated with sever psychosis. [6] In addition, psychotic features in PD patients might relate to underlying comorbidities such as dementia. [7]

Antipsychotics are generally used for the treatment of behavioral symptoms of PD; however, these drugs may antagonize dopamine receptors leading to aggravation of Parkinsonian symptoms. [8] The level of dopamine antagonist activity is lowest for clozapine and quetiapine in comparison to other atypical antipsychotics (AAPs) used in the past decade. [9] Amongst AAPs, aripiprazole is exceptionally a partial agonist for dopamine receptors rather than an antagonist. [9] The level of dopamine antagonist activity is an important factor in determining the safety of antipsychotics in terms of modifying Parkinsonian symptoms. [10] According to the 2015

American Geriatrics Society (AGS) Beers criteria atypical antipsychotics are inappropriate in PD patients except for aripiprazole, clozapine and quetiapine; due to the risk of worsening Parkinsonian symptoms. [11] Inappropriate antipsychotics such as risperidone can adversely affect voluntary movements in general and swallowing movements in specific in patients with PD. [11] Those inappropriate antipsychotics were associated with higher levels of dopamine antagonist activity in previous in-vitro studies. [9]

Pneumonia is the leading cause of death among patients with PD. [12] Dopaminergic pathways are involved in swallowing reflex and coordination of swallowing and breathing. [13] Oropharyngeal dysphagia is the manifestation of dysfunctional swallowing and is associated with high risk of aspiration pneumonia. [14] Inappropriate antipsychotics can further aggravate this process, leading to a higher risk of pneumonia. However, the impact of antipsychotics on swallowing reflex has not been studied well. Ballard et al., 2015 conducted a post hoc study of the pimavanserin clinical trial and found that the risk of pneumonia was significantly higher for participants taking concurrent antipsychotics in comparison to those not using concurrent antipsychotics. [15] Pintor et al., 2012 reported the occurrence of pneumonia in a small clinical trial on ziprasidone vs. clozapine in patients with Parkinson's disease psychosis. [16] There is an evidence gap in literature regarding the impact of different antipsychotics on the risk of pneumonia in PD patients.

Antipsychotics are commonly used in clinical practice for the treatment of PD psychosis.[17] According to an epidemiological study of Veterans Affairs data, risperidone and olanzapine were respectively prescribed for 17.3% and 11.5% of patients with PD psychosis who received antipsychotics treatment. [17] Previous observational studies have not examined the safety profile of inappropriate antipsychotic use in PD patients. To our knowledge this study is the first

attempt to evaluate the risk of pneumonia associated with inappropriate antipsychotic use in PD patients. The study hypothesized that there is a higher risk of pneumonia in elderly patients with PD using inappropriate AAPs vs. those using appropriate AAPs. Inappropriate antipsychotics in PD patients worsen Parkinsonian symptoms and can adversely affect voluntary movements in general and swallowing movements in specific in patients with PD. [11] The study can provide evidence regarding safety of antipsychotics in PD and thereby help to optimize the use of these medications which is important in the quality of geriatric care.

METHODS

Data Source

The study utilized 2007-2009 Minimum Data Set (MDS) cross-linked to Chronic Condition Warehouse (CCW) data files. The present retrospective cohort study involved patients with PD to examine relationship between AAPs use and risk of pneumonia. Medicare Part A, B and D claims files, MDS, and Master Beneficiary Summary File were used in this study. Medicare Part D provides information on prescription drugs for the Medicare beneficiaries. Medicare Part A provides hospital coverage. Information related to the use of Medicare Part B services is captured in the Medicare Provider Analysis and Review (MEDPAR) file. Medicare Part B provides supplementary medical insurance. Information related to the use of Medicare Part B services is captured in the Carrier file. The Minimum Data Set (MDS) is federally mandated standardized, primary screening and assessment tool to capture health status of each resident in Medicare and Medicaid certified nursing homes. [18]

Master Beneficiary Summary File (MBSF), including the Chronic Conditions (CC) segment was used in this study. The MBSF contains information regarding demographic characteristics and enrollment status in Medicare Parts A and B for Medicare beneficiaries. The

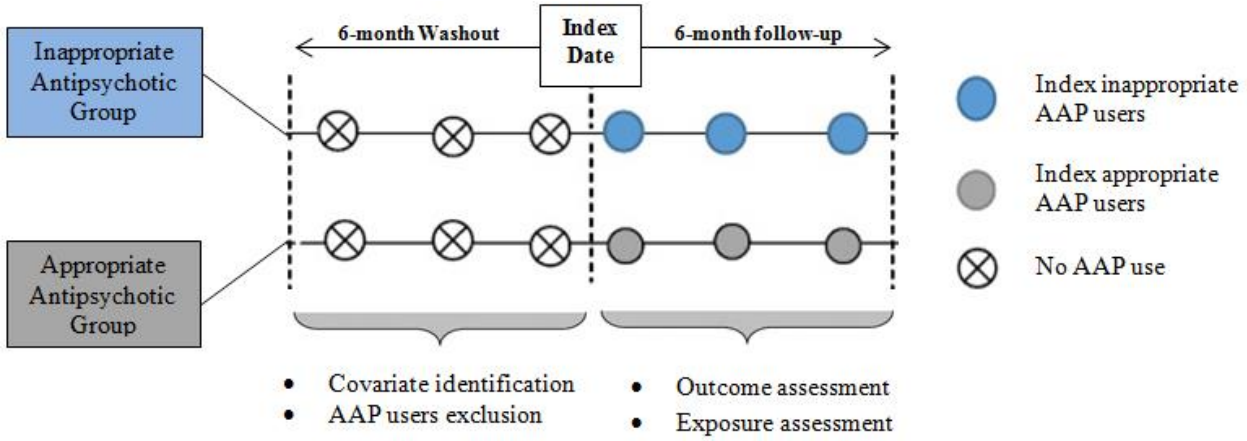
CC segment of the MBSF provides information about a set of 27 common or chronic conditions using inpatient and outpatient claims–based algorithms.[18] The study reused the Medicare and MDS database from a cohort of nursing home residents with a diagnosis of depression. This study was approved by the University of Houston Committee for the Protection of Human Subjects under the exempt category.

Study Population and Eligibility Criteria

The study population encompassed older adults aged 65 years or older with a diagnosis of PD who started one atypical antipsychotic medication in the study period. The diagnosis of PD was ascertained using both MDS assessment and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 332.0 in the Medicare Part A and B claims files. [19] As shown in Figure 1, the index date was the first day that AAP drug was dispensed to the patient. There was a 6-month washout before index date in which patients must have a MDS assessment and did not use AAPs. Each patient was followed for 6-month after index date to assess the study outcome.

Patients were included in the cohort, if they received the first antipsychotic medication between July 1st, 2007 and June 30th, 2010 and met continuous eligibility criteria for Medicare parts A, B and D coverage. Patients were excluded, if they had a baseline diagnosis of either bipolar disease or schizophrenia, since long-term antipsychotic therapy is generally required for severe mental disorders. Those who started more than one AAP at the same time were excluded. Typical antipsychotics users were not excluded from the analysis; rather the baseline use of typical agents was taken into account as a confounding factor.

Figure 1. Study design and time frame



Atypical Antipsychotics Exposure

The study had two treatment arms, namely appropriate and inappropriate atypical antipsychotics which were defined based on 2015 AGS Beers criteria.[11] The use of aripiprazole, clozapine, or quetiapine in PD patients was appropriate in this study. Conversely, inappropriate AAPs consisted of olanzapine, asenapine, brexpiprazole, iloperidone, lurasidone, paliperidone, risperidone, or ziprasidone. The information about atypical antipsychotic drugs in the US market was obtained from Micromedex. RED BOOK™ and AHFS Drug Information. [20,21] The use of AAPs were identified using Generic Name - Short Version (GNN) from the Prescription Drug Event Data. The Prescription Service Date (DOS) was used to determine the first prescription of antipsychotics in the study period.

The exposure to antipsychotic drugs changes when discontinuation, switching, or augmentation occur in the course of pharmacotherapy. [22] This affects the relationship between exposure and outcomes, thus the analysis involved censoring criteria for discontinuation and augmentation. In this study, discontinuation was defined based on 30 days gap between the estimated end date of an AAP prescription and the next refill. When switch from one AAP to

another antipsychotic occurred, the patient was censored based on discontinuation of the first AAP. The augmentation of two or more AAPs was another reason for censoring. Furthermore, the follow-up was terminated, when a patient died before end of the study.

Outcome Assessment

The primary dependent measure was the diagnosis of pneumonia in the study period identified using the clinical classification of conditions developed by the Agency for Healthcare Research and Quality. The operational definition of pneumonia was based on specific ICD-9-CM conditions such as viral and bacterial pneumonia, bronchopneumonia, specific pneumonia, and pneumonia not specified. [19] The clinical classification of conditions for pneumonia involved the following ICD-9-CM codes: 003.22, 020.3, 020.4, 020.5, 021.2, 022.1, 031.0, 039.1, 052.1, 055.1, 073.0, 083.0, 112.4, 114.0, 114.4, 114.5, 115.05, 115.15, 115.95, 130.4, 136.3, 480.0, 480.1, 480.2, 480.3, 480.8, 480.9, 481.xx, 482.0, 482.1, 482.2, 482.3, 482.30, 482.31, 482.32, 482.39, 482.4, 482.40, 482.41, 482.49, 482.8, 482.81, 482.82, 482.83, 482.84, 482.89, 482.9, 483.xx, 483.0, 483.1, 483.8, 484.1, 484.3, 484.5, 484.6, 484.7, 484.8, 485.xx, 486.xx, 513.0, and 517.1. Additionally, the definition of pneumonia included aspiration pneumonitis with the ICD-9 code 507.0 based on the clinical classification of conditions. [19]

Previous studies demonstrated that patients with PD were at higher risk of aspiration pneumonia. [23] However, lack of reliable markers for aspiration complicates the epidemiologic studies in this field. [24] Aspiration pneumonitis is a chemical injury to the lungs caused by the aspiration of sterile gastric contents, whereas aspiration pneumonia is an infectious process due to the inhalation of secretions contaminated with pathogenic bacteria. Although these syndromes are distinct clinical entities, there is overlap between them and as a result clinicians commonly fail to distinguish aspiration pneumonitis from aspiration pneumonia. [24] The clinical

classification of conditions for both pneumonia and aspiration pneumonitis have already been used in previous research.[25] Therefore, the analysis involved ICD-9 codes for both community acquired pneumonia and aspiration pneumonitis.

Covariates

Sociodemographic characteristics for descriptive and multivariable analyses were obtained from MBSF. This provided information regarding patients' age, sex, education, marital status, and geographical region. Although MDS assessments did not involve staging and severity of PD, the study database contained several measures related to PD severity including cognitive and functional impairment items. [26,27] These validated measures have been used in previous observational studies involving patients with neurological impairment. The current study utilized MDS-Derived Direct Cognition Scale (MDS-COG) to control for the severity of cognitive impairment in PD. The MDS-COG ranges from 0 to 9, with higher scores indicating greater severity of cognitive impairment. [26] The Activities of Daily Living were scored using ADL-Long Form (0-28) with higher scores indicating a worse functional status. [27] Other clinical variables relevant to PD severity included walk difficulty in room or corridor, clarity of speech, drug induced dyskinesia (ICD-9 code 333.85), and dysphagia (ICD-9 code 787.2x). [28,29] The clinical characteristics comprised several comorbidities based on the clinical classification of conditions. The analysis controlled for baseline pneumonia and co-medications including baseline typical antipsychotics, Selective Serotonin Reuptake Inhibitor (SSRI), Serotonin–Norepinephrine Reuptake Inhibitor (SNRI) and various pharmacotherapy for PD.

Statistical Analyses

All statistical analyses were conducted using SAS 9.2 (SAS Institute, Cary, North Carolina) with a statistical significance level of 0.05. Descriptive analysis was performed to

describe sociodemographic characteristics, comorbidities, and co-medications during the 6-month baseline period for appropriate and inappropriate AAP users. Chi-square tests and t-tests were applied for categorical variables and continuous measures respectively to examine the differences across treatment groups after propensity score (PS) matching.

Selection bias is a key concern in observational studies due to non-randomized assignment of patients to different treatment groups. PS matching is commonly used in observational studies to reduce selection bias such that the matched treatment groups differ only on treatment assignment. A propensity score is the probability of treatment assignment conditional on a set of baseline covariates. The covariates used for the calculation of propensity scores were selected based on previous literature, expert opinions, and as per their availability in the data source. These included sociodemographic factors such as age, gender and race; and clinical characteristics like functional status, co-morbidities and co-medications as previously described.

Propensity scores were calculated for each individual by regressing baseline covariates on the treatment. Patients with PD using inappropriate atypical antipsychotics (treatment group) were matched with patients taking appropriate atypical antipsychotics (control group) using the GREEDY 5 → matching technique. The GREEDY matching technique has been found to reduce the matched pair bias caused by incomplete and inexact matching. [30,31]In this technique members from the treatment group are matched to members of the control group on the first five digits of the propensity score. Patients who remain unmatched are then matched on four digits the propensity score. This process is repeated until cases are matched to controls on the one digit of the PS. For cases with multiple matched controls, a control is selected at random for PS matching. [30,31]

The Cox proportional hazards model was used to evaluate the risk of pneumonia associated with use of inappropriate vs. appropriate atypical antipsychotics in elderly patients with PD. The ID option of PROC PHREG in SAS v.9.2 was used to run the robust Cox regression. The traditional Cox regression assumes independence of observations. However, robust sandwich estimator in the robust Cox regression model allows for the clustering within matched pairs. The robust Cox regression model provides hazard ratio (HR) with minimal bias than the other PS-matched Cox regression models. [32]

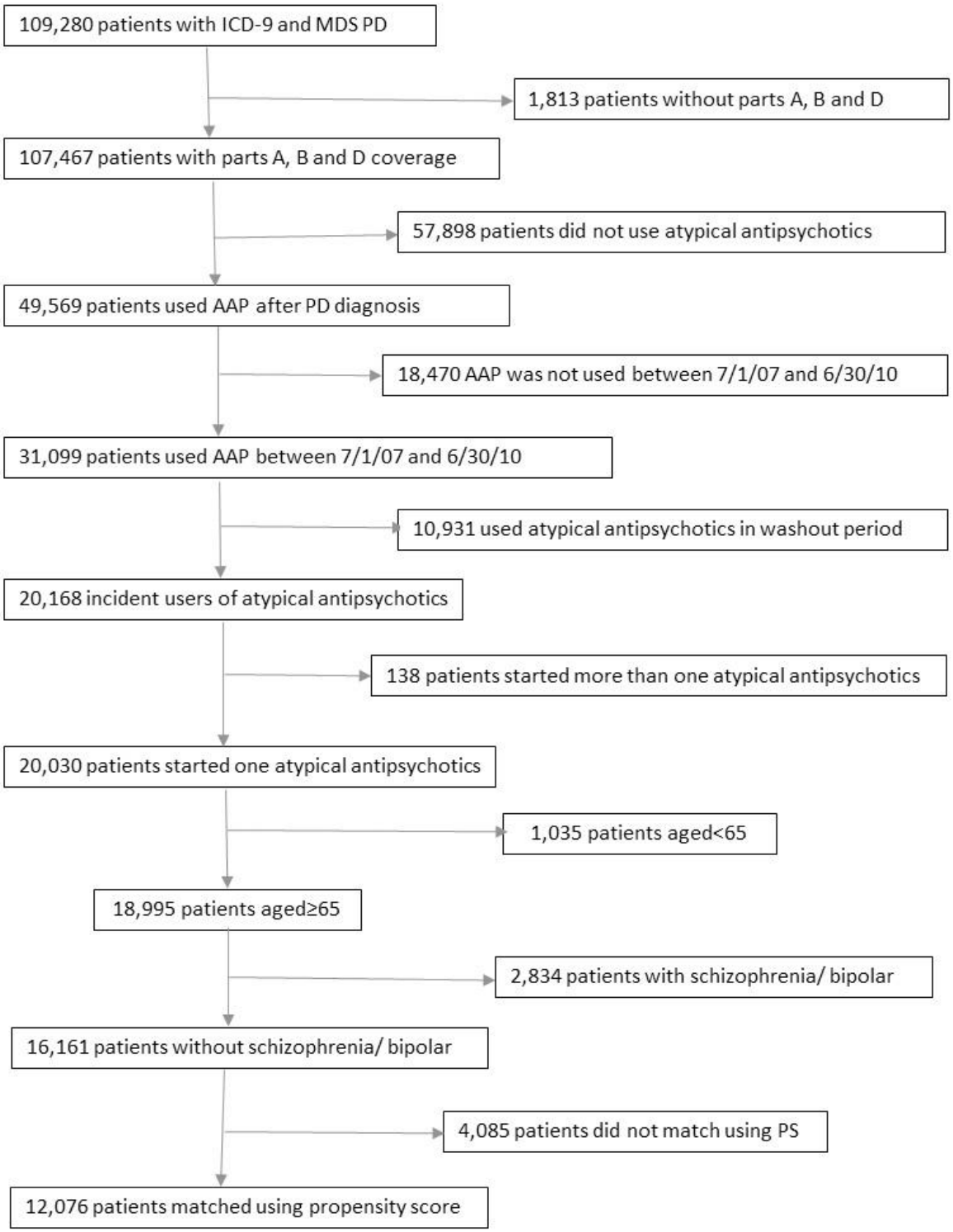
The Cox regression model requires testing for the proportional hazards assumption. This assumption was checked via different statistical approaches including Kaplan-Meier plots, log-minus-log survival plots, Schoenfeld residual test, and Supremum test. [32] The log-rank test was performed to assess the association between the type of AAP treatment and pneumonia-free survival. Therefore, a robust Cox hazard model was used to examine the risk of pneumonia across the 2 treatment groups. Patients were censored in the main analysis upon treatment discontinuation or augmentation with another AAP or end of follow-up.

A number of sensitivity analyses were conducted to examine the robustness of the study findings. Intent-to-treat analysis was performed to examine whether censoring information could affect the association between treatment and outcome. The other sensitivity analyses involved head-to-head compression of individual antipsychotics. Most frequently used appropriate and inappropriate AAPs were retained in the cohort and the propensity score approach was applied to rematch individual AAP users on baseline characteristics. All assumptions for propensity score matching and survival analyses were checked again for the sensitivity analyses.

RESULTS

As shown in the cohort identification flowchart (Figure 2), the diagnosis of PD was confirmed for 109,280 patients using both MDS assessment and ICD-9 codes. Among them, the number of atypical antipsychotics users with continuous eligibility for Medicare parts A, B and D coverage was 31,099 in MDS-linked Medicare data between July1st, 2007 and Jun 30th, 2010. 10,931 patients were excluded because they used atypical antipsychotics in washout period and 138 patients were excluded because they started more than one antipsychotic drug at the same time in the study period. 16,161 patients aged 65 years or older and without schizophrenia/ bipolar disorder started only one atypical antipsychotic in the study period. The percentage of inappropriate antipsychotic use was 37.62% among AAP users before matching. 12,076 patients were matched using propensity score approach.

Figure 2. Cohort identification flowchart



Descriptive statistics are presented in Table 1 and Table 2. The mean age of the patients was over 82 years. Most of the atypical antipsychotic users were female in appropriate treatment group (60.43%) and in inappropriate AAP group (61.41%). The majority of the patients included in this study were white (>89%). Among indicators for the PD severity, appropriate and inappropriate AAP users had 40.38% and 39.30% likelihood of dysphagia respectively. The proportion of patients with dementia was over 28% and more than 71% of AAP users received either SSRIs or SNRIs in the baseline period. The rates of levodopa prescription were 63.51% in appropriate AAP group and 62.69% among those who received inappropriate AAP. More than 21% of the patients were treated with dopamine agonists and the prescription rates for other antiparkinson medications were lower. Three most frequently used AAP were quetiapine (54.60%), risperidone (23.71%) and olanzapine (11.64%) before matching.

Table 1. Characteristics of appropriate and inappropriate atypical antipsychotics users in matched cohort

Characteristic	Appropriate AAP (n= 6,038)	Inappropriate AAP (n=6,038)	P-Value
Age (mean ± SD)	82.18 ± 6.89	82.12 ± 7.05	0.62
Female, n (%)	3,649 (60.43)	3,708 (61.41)	0.27
White, n (%)	5,402 (89.47)	5,415 (89.68)	0.70
College education, n (%)	701 (11.61)	709 (11.74)	0.82
Married, n (%)	1,663 (27.54)	1,696 (28.09)	0.50
Region, n (%)			
Midwest	1,716 (28.42)	1,719 (28.47)	0.99
Northeast	1,105 (18.3)	1,114 (18.45)	
West	247 (4.09)	243 (4.02)	
South	2,970 (49.19)	2,962 (49.06)	
ADL Score (mean ± SD)	10.90 ± 7.33	10.89 ± 7.40	0.92
MDS Cognitive Score (mean ± SD)	4.21 ± 1.73	4.22 ± 1.69	0.76
Impaired Walking	3,028 (50.15)	2,997 (49.64)	0.57
Unclear Speech, n (%)	2,796 (46.31)	2,820 (46.70)	0.66
Dyskinesia, n (%)	104 (1.72)	104 (1.72)	1.00
Dysphagia, n (%)	2,438 (40.38)	2,373 (39.30)	0.23
Insomnia, n (%)	683 (11.31)	638 (10.57)	0.19
Abusive Behavior, n (%)	523 (8.66)	554 (9.18)	0.32
Depressed Mood Indicators, n (%)	1,573 (26.05)	1,529 (25.32)	0.36
Depressive Type Psychosis, n (%)	52 (0.86)	66 (1.09)	0.20
Anxiety, n (%)	2,832 (46.90)	2,829 (46.85)	0.96
Dementia, n (%)	1,747 (28.93)	1,785 (29.56)	0.45
Stroke, n (%)	1,634 (27.06)	1,635 (27.08)	0.98
Falls and Fractures, n (%)	5,318 (88.08)	5,328 (88.24)	
Coronary Artery Disease, n (%)	1,473 (24.40)	1,523 (25.22)	029
Congestive Heart Failure, n (%)	1,792 (29.68)	1,798 (29.78)	0.90
Dysrhythmia, n (%)	1,360 (22.52)	1,367 (22.64)	0.88
Hypertension, n (%)	4,891 (81.00)	4,907 (81.27)	0.71
Diabetes Mellitus, n (%)	2,116 (35.04)	2,124 (35.18)	0.88
Osteoarthritis, n (%)	2,960 (49.02)	2,878 (47.66)	0.1354
Cancer, n (%)	677 (11.21)	647 (10.72)	0.38
Pneumonia history, n (%)	2,170 (35.94)	2,183 (36.15)	0.81
Asthma, n (%)	312 (5.17)	342 (5.66)	0.23
COPD, n (%)	1,474 (24.41)	1,536 (25.44)	0.19
Charlson Comorbidity Index (mean ± SD)	5.75 ± 3.39	5.77 ± 3.43	0.69
Typical antipsychotics, n (%)	267 (4.42)	306 (5.07)	0.10
SSRI/ SNRI, n (%)	4,313 (71.43)	4,349 (72.03)	0.47
Levodopa, n (%)	3,835 (63.51)	3,785 (62.69)	0.35
Dopamine Agonists, n (%)	1,296 (21.46)	1,294 (21.43)	0.96

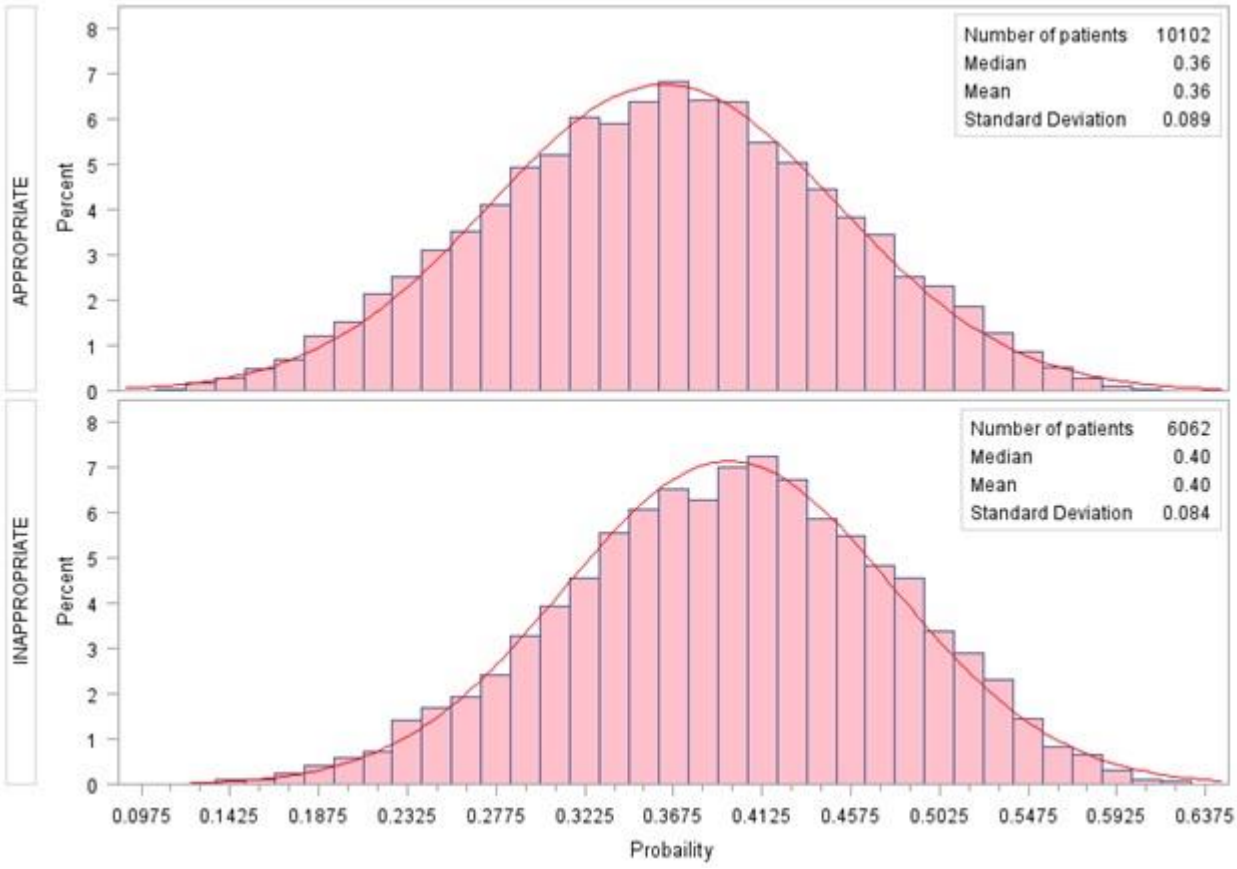
COMT Inhibitors, n (%)	601 (9.95)	595 (9.85)	0.86
MAO Inhibitors Type B, n (%)	197 (3.26)	204 (3.38)	0.72
Amantadine, n (%)	294 (4.87)	305 (5.05)	0.64
Anticholinergics, n (%)	284 (4.70)	300 (4.97)	0.50

Table 2. Proportion of atypical antipsychotic agents started in the cohort of patients with PD before and after matching

AAP	Before Matching, n (%)	After Matching, n (%)
Aripiprazole	1,205 (7.4)	774 (6.41)
Clozapine	62 (0.38)	35 (0.29)
Olanzapine	1,896 (11.64)	1,871 (15.49)
Paliperidone	20 (0.12)	19 (0.16)
Quetiapine	8,890 (54.60)	5,229 (43.30)
Risperidone	3,861 (23.71)	3,812 (31.57)
Ziprasidone	349 (2.14)	336 (2.78)
Total	16,283 (100.00)	12,076 (100.00)

Figure 3 demonstrates the distribution of the propensity score in the treatment groups. The two histograms were not identical; the mean PS in appropriate AAP was 0.36 ± 0.089 and 0.40 ± 0.084 was the mean PS in inappropriate AAP user group. The one-on-one matching was performed successfully and 6,038 patients remained in each treatment groups. Applying bivariate analyses, no significant difference were found in sociodemographic and clinical characteristics of the appropriate and inappropriate AAP users in the matched cohort.

Figure 3. The histogram of propensity scores for appropriate and inappropriate atypical antipsychotics



Cox Proportional Hazards Regression

The Proportional hazards assumption was met, using visual tests such as Kaplan-Meier plots and numeric tests like Schoenfeld residual test. During study period, 2,197/12,076 (18.19%) of patients discontinued AAP treatment and the rate of AAP augmentation was 1,578/12,076 (13.07%). A total number of 3,291 patients was censored before the end of follow-up due to treatment discontinuation or augmentation, each one occurred first. The average follow-up time was 142 days in this study. The Kaplan–Meier estimator, presented in Figure 4 showed that the hazard of pneumonia was consistently higher for inappropriate AAP users vs. appropriate AAP group. The log-rank test statistic was significant indicating that there was a significant difference in the pneumonia-free survival of the treatment groups.

Figure 4. Kaplan-Meier survival curves for incidence of pneumonia across appropriate and inappropriate treatment groups

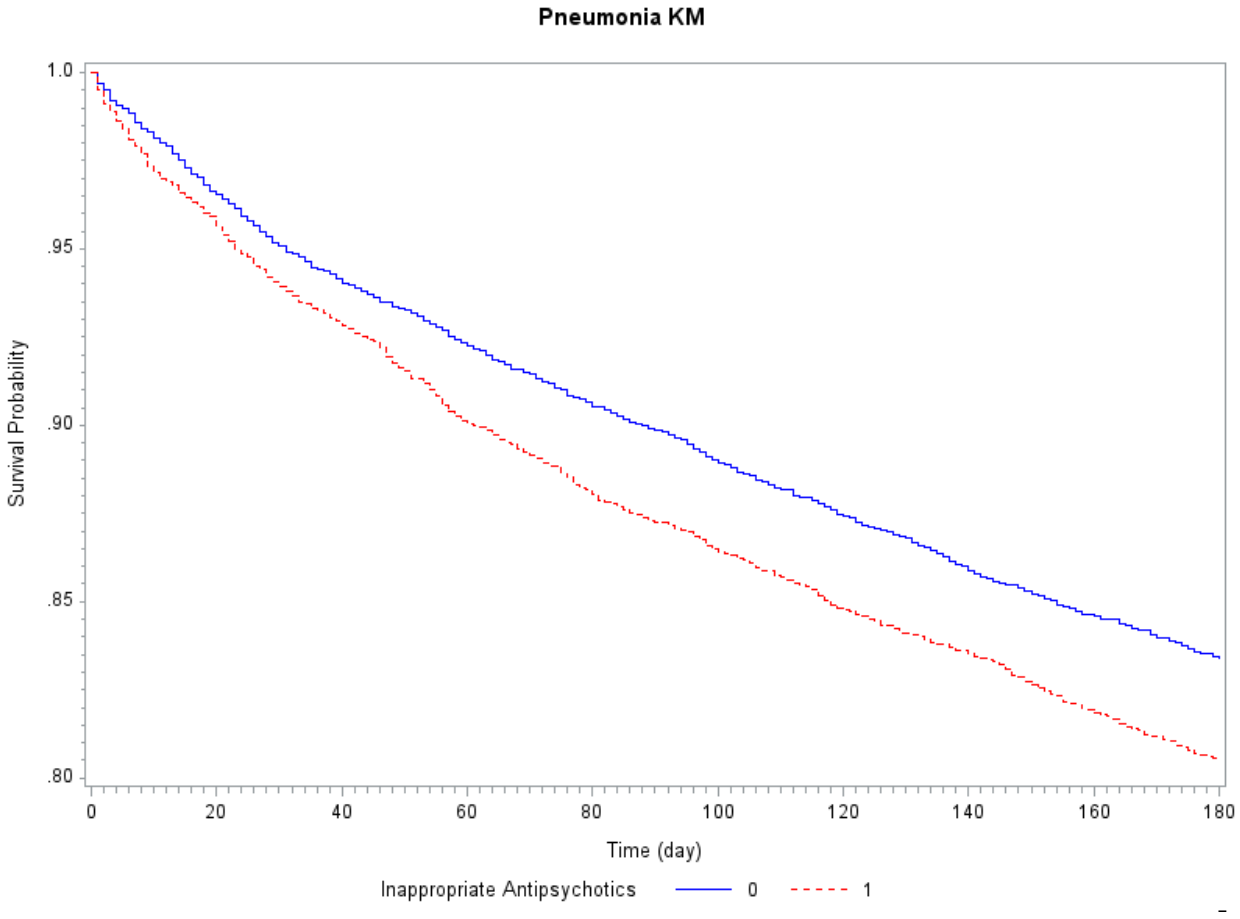


Table 3. Relationship between AAP exposure and the outcome of pneumonia

	Pneumonia (No)	Pneumonia (Yes)	Total
Appropriate AAP	5,051 (83.65)	987 (16.35)	6,038 (50.00)
Inappropriate AAP	4,904 (81.22)	1,134 (18.78)	6,038 (50.00)
Total	9,955 (82.44)	2,121 (17.56)	1,2076 (100.00)

Table 3 summarizes the outcome of pneumonia across the two treatment groups. The incidence of pneumonia was 17.56% over 6-month follow-up;16.35% in appropriate AAP group and 18.78% in inappropriate AAP group. The main analysis included 12,076 patients and applied censoring in the survival model to examine the relationship between the outcome of pneumonia, assigned treatment and time. The Cox proportional model revealed increased risk of pneumonia with Hazard Ratio (HR) 1.20 (95% CI: 1.08 - 1.34) for patients who used inappropriate vs. appropriate AAP in the matched cohort.

Sensitivity Analyses

As shown in Table 4, all sensitivity analyses confirmed a significantly higher risk of pneumonia for inappropriate vs. appropriate AAP users. The assumptions for propensity score matching and survival analyses were met prior to conducting sensitivity analyses. The estimated pneumonia HR was 1.16 (95% CI: 1.06 - 1.27) in the intent-to-treat analysis. The pneumonia HR was also higher for risperidone vs. quetiapine [1.28 (95% CI: 1.12 - 1.47)] and for olanzapine vs. quetiapine [1.29 (95% CI: 1.06 - 1.57)]. Direct comparison was not performed for the risk of pneumonia associated with other individual antipsychotics due to inadequate sample size.

Table 4. Main and Sensitivity Analyses

	Sample Size	Hazard Ratio (95% CI)	P-Value
Main Analysis	12,076	1.20 (1.08 - 1.34)	<0.01*
Sensitivity Analyses			
Intent to Treat	12,076	1.16 (1.06 - 1.27)	<0.01*
Risperidone vs. Quetiapine	7,628	1.28 (1.12 - 1.47)	<0.01*
Olanzapine vs. Quetiapine	3,758	1.29 (1.06 - 1.57)	<0.01*

* Indicate p value <0.05

DISCUSSION

More than one-third of PD patients used inappropriate agents among those who received AAPs; however the study data were collected before the introduction of 2015 Beers criteria regarding inappropriate antipsychotics in PD. The study found that quetiapine was the most frequently used antipsychotic in PD patients, followed by risperidone and olanzapine. The use of quetiapine was consistently higher than other antipsychotics in previous studies of elderly patients with PD, as quetiapine was considered to be safer than other antipsychotics for those patients. [33] Risperidone and olanzapine are effective for delirium and other neurobehavioral conditions that might justify these findings. [34] Among older generation of AAPs, clozapine is the only medication with acceptable efficacy for PD psychosis; [35] however, less than 1% used clozapine before and after matching. This was consistent with previous epidemiological findings on the use of antipsychotics in PD; indicating that clozapine use might be restricted in patients with PD due to the risk of adverse events and blood monitoring requirement. [6,17]

The mean age of patients was over 82 years and most of them were female and white. A few epidemiological studies used MDS database to assess characteristics of patients with PD and reported comparable results for demographic characteristics of nursing home residents with PD. [36,37] However, the present study involved patients using antipsychotic medications and this might be associated with different characteristics such as higher age. The average ADL-Long-Form scale was approximately 11/28 in the study population. Since this ADL scale is the sum of 7 items ranging from 0-4, the average 11/28 score, indicates some degrees of limitation in functional status but not extensive impairment. [38] Similarly, the average direct MDS score 4/9 might suggest mild to moderate cognitive impairment in the study population. [39] Over 28% of patients had a diagnosis of dementia and this was of particular concern for AAP users, given that

a black-box warning was issued in 2005 regarding the safety of atypical antipsychotics in patients with dementia. [40] According to previous studies dysphagia is one of the most important clinical conditions associated with aspiration pneumonia. [14] Approximately, 40% of patients had a diagnosis of dysphagia identified by ICD-9 codes which indicates a relatively high number of nursing home residents with PD have difficulty swallowing. [41]

The statistical analysis involved survival analysis of propensity score matched data which had been used extensively in previous observational research. [42] Multivariable survival analysis without matching could be an alternative approach for the study but this might need a larger sample size to conduct the analysis with enough power. [43] Propensity score matching was an efficient approach in this study to take into account the effect of confounders on the relationship between AAP use and pneumonia. The average treatment effect on the treated (ATT) was reported for those who received inappropriate vs. appropriate AAP based on one-on-one matching. [44] The risk of pneumonia for inappropriate antipsychotic users remained significantly higher in comparison to appropriate AAP group across all sensitivity analyses. Some information might be lost in the main analysis when patients were censored based on treatment discontinuation or augmentation. Intent-to-treat analysis examined the safety of treatment without censoring those who were not compliant with medication use. [45] The significant results for the risk of pneumonia in the both analyses confirmed the robustness of the findings regardless of the censoring criteria. The risk of pneumonia was close for risperidone and olanzapine when compared to quetiapine. This might be the result of similar dopamine antagonist activity for risperidone and olanzapine. [9] However, the mechanisms behind the risk of pneumonia in PD cannot be inferred from the study findings.

The study findings suggest that selection of appropriate antipsychotics in PD is crucial to prevent serious adverse events related to antipsychotic use in PD, given that pneumonia is the first cause of mortality in PD patients. Inappropriate antipsychotics adversely affect swallowing process due to high level of D_2 antagonist activity. This increases the risk of aspiration pneumonia which is of particular concern for PD patients. This investigation provided a strong evidence base regarding safety of atypical antipsychotics in elderly patients with PD. Further research is needed to evaluate the risk of pneumonia in PD patients using newer antipsychotic medications.

Generalizability of Findings

This study used data from a cohort of nursing home residents with a diagnosis of depression. This might affect utilization pattern of atypical agents in the study cohort but it would not be a differential bias across the study groups, since there was no difference between the treatment groups in terms of depression diagnosis. However, this comorbid condition may limit the generalizability of results. PD patients with depression are generally sicker than those without depression and they might use antipsychotics for augmentation of antidepressant therapy. [46,47] Considering these limitations, the study findings can explain the risk of pneumonia in PD patients using atypical antipsychotics, given that the mechanism of aspiration pneumonia in PD is independent from depression.

Strength and Limitation

This study used a large nationally representative data, involving federally mandated assessments of nursing home residents all over the United States and Medicare claims database. Clinical trials generally include healthy adults and it limits the understanding of the safety aspect of the antipsychotic use among vulnerable patients with PD. This study generated real-world

evidence regarding the risk of pneumonia, the leading cause of mortality among elderly patients with PD who were treated with antipsychotics. The current study used a large sample and applied a robust methodology to examine the relationship between antipsychotics exposure and the outcome of pneumonia. Several covariates related to the severity of PD, comorbidities and co-medications were included in the models.

The limitations of the study consist of those inherent to the nature of the secondary data analysis. Miscoding and under-coding might occur in the process of administrative data collection.[48] The study results were limited by the operational definitions, data source, and analytical approaches. The study database was reused from a previous cohort of nursing home residents with depression and this might affect the generalizability of the study findings to other settings. Data availability was another restriction for the analysis. One such factor was the severity measures of Parkinson disease, which can be assessed using validated measures such as the Unified Parkinson Disease Rating Scale (UPDRS). The Medicare data did not contain information on PD severity; however, relevant variables and proxies were obtainable from MDS and Medicare data to take into account the severity of PD in the analysis. Finally, this study cannot establish a causal relationship between exposure to inappropriate antipsychotics and the outcome of pneumonia due to limitations of the study.

CONCLUSIONS

This study evaluated the risk of pneumonia associated with inappropriate antipsychotic use in PD patients based on 2015 American Geriatrics Society (AGS) Beers criteria. The risk of pneumonia was significantly higher for inappropriate atypical antipsychotic users in comparison to appropriate antipsychotic group in all analyses. This investigation provided a strong evidence

base regarding safety of atypical antipsychotics in elderly patients with PD. Further research is needed to evaluate the risk of pneumonia in PD patients using newer antipsychotic medications.

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MANUSCRIPT 3

RISK OF MORTALITY ASSOCIATED WITH ATYPICAL ANTIPSYCHOTIC USE IN ELDERLY PATIENTS WITH PARKINSON'S DISEASE

ABSTRACT

Objectives: The use of antipsychotic medications is generally inappropriate in patients with Parkinson's disease (PD), due to the risk of worsening Parkinsonian symptoms. According to the 2015 American Geriatrics Society (AGS) Beers criteria, aripiprazole, clozapine and quetiapine are excluded from the list of inappropriate antipsychotics in PD. This study examined the risk of all-cause-mortality in patients with PD using inappropriate antipsychotic (AAP) agents vs. other AAPs.

Methods: The study used 2007-2010 Minimum Data Set (MDS) linked Medicare data and applied a retrospective cohort design involving propensity score matching to achieve the study objective. The study population encompassed older adults aged 65 years or older with a diagnosis of PD and without schizophrenia or bipolar disorder who started one AAP after 6-month washout period. The treatment groups were classified into: 1) appropriate AAPs (i.e. aripiprazole, clozapine or quetiapine) 2) inappropriate AAPs including olanzapine, asenapine, brexpiprazole, iloperidone, lurasidone, paliperidone, risperidone, or ziprasidone. The primary dependent measure was the all-cause-mortality within 6-month after start of atypical antipsychotics. The analysis involved a propensity-matched approach and Cox proportional hazards models to evaluate the risk of all-cause-mortality in patients with PD using inappropriate AAP agents. Sensitivity analyses were performed using frequently used antipsychotic agents.

The impact of inappropriate AAP use on mortality was evaluated using pneumonia as a mediator.

Results: There were 16,161 patients with PD diagnosis aged 65 years or older, without schizophrenia/ bipolar disorder who started one atypical antipsychotic in the study period and 12,076 patients were matched using propensity score approach. The mortality rate was 16.28% in the matched cohort over 6-month follow-up; 5.65% in appropriate AAP group and 16.91% in inappropriate AAP group. The Cox proportional hazards models revealed increased risk of all-cause mortality [Hazard Ratio (HR) 1.13 (95% CI: 1.01 - 1.28)] for patients who used inappropriate vs. appropriate AAP. There was a significant association between inappropriate AAP use and risk of death in sensitivity analysis, when risperidone compared to quetiapine [HR: 1.20 (95% CI: 1.03 - 1.40)]. However, there was a significant relationship between pneumonia and death in all analyses. The impact of inappropriate AAP use on mortality was not significant when pneumonia was modeled as a mediator.

Conclusions: The study found a significant association between inappropriate antipsychotic use and all-cause-mortality. However, pneumonia is a mediator between inappropriate AAP use and the risk of mortality in PD patients. This study provided strong evidence regarding the risk of mortality due to inappropriate antipsychotic use mainly mediated by pneumonia in older patients with PD.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder, associated with significant disability and mortality.[1] The prevalence of Parkinson's disease has been estimated to be 0.3% in general population, 1% - 5% in the elderly and 5% - 10% in nursing home residents.[2,3]

Parkinson's disease symptoms usually begin in the fifth or sixth decade of life, and the disease incidence increases steadily thereafter.[4] Both motor and non-motor symptoms contribute to disability and impaired quality of life of patients with PD. Additionally, numerous complications such as dopaminergic induced psychosis are associated with PD. [5] The medical costs incurred for patients with PD were $14.4 billion in 2010; and by applying 3% discount rate for each year, the medical costs of PD was estimated at $17.7 in 2017. [3,6]

Dopaminergic medications are the cornerstone of pharmacotherapy in PD. These medications may act as dopamine replacement (i.e. levodopa) or dopamine agonists. [7] Dopaminergic agents can alleviate Parkinsonian symptoms; however, use of these antiparkinson agents is associated with adverse events such as dopaminergic psychosis. [8] The probability of psychosis is between 25% and 60% for PD patients, in their lifetime course, depending on the diagnostic criteria used.[8] The most common symptom of PD psychosis is visual hallucination while delusions and systemized hallucinations are associated with sever psychosis. [8] In addition, psychotic features in PD patients might relate to underlying comorbidities such as dementia. [9]

Atypical antipsychotics are frequently used for the management of psychotic symptoms in patients with PD.[10] The rate of antipsychotic use in PD patients was from 15% to 30% in long term facilities, according to previous studies.[2] The prevalence of antipsychotic use was 50% in a large cohort of veterans with PD psychosis.[10] The efficacy of atypical antipsychotics in the treatment of PD psychosis has not been evaluated in large clinical trials; however, clozapine has

found to be an effective treatment for PD psychosis. [2,11] In spite of effectiveness, clozapine is not commonly used in clinical practice, due to the risk of adverse events and the blood monitoring requirement. [10] There are mixed findings regarding the effect of other atypical antipsychotics on the psychotic features of PD.[2,11]

Antipsychotic use is related to adverse events such as pneumonia, in addition to worsening movement PD symptoms.[11,12] Pneumonia is the leading cause of death among patients with PD.[1] The possible mechanisms of aspiration pneumonia in PD include impairment of swallow reflex and discoordination of breathing and swallowing. Antipsychotics potentially aggravate swallowing impairment by blocking Dopamine receptors type 2, leading to higher risk of aspiration pneumonia in patients with PD.[13] Inappropriate antipsychotics that worsen Parkinsonian symptoms might aggravate impairment of swallowing. According to the 2015 American Geriatrics Society (AGS) Beers criteria, except for aripiprazole, quetiapine, and clozapine, antipsychotic medications are considered generally inappropriate in PD. [14] Inappropriate antipsychotics have been implicated for increased risk of aspiration pneumonia in general and mortality in specific.

Despite advances in medical care, the mortality rate in patients with PD remains higher than expected for age.[15] The mortality rate of PD was reported to be 50% in 3 years in a large cohort study of PD patients residing in nursing homes.[2,16] Weintraub et al. 2016 conducted a cohort study and found the mortality rate among Medicare beneficiaries with PD was 64% in 6 years follow-up.[17] There exist disparities in PD related mortality by gender and race, since the survival of patients with PD was lower amongst male and African-American individuals. Infections such as pneumonia and cardiovascular disease were the most common causes of death among Medicare beneficiaries with PD. [17] According to a systematic review by Xu et al., 2014,

the risk of all-cause mortality increases by 2.22 fold for patients with PD, in comparison to the general population; and age is the most important determinant of mortality in PD.[1]

To our knowledge, there is a gap in literature regarding the risk of mortality associated with antipsychotic use in PD. Specifically; no comparison is available regarding the risk of mortality across different types of antipsychotics. This study aimed to examine the risk of all-cause-mortality in patients with PD using inappropriate vs. appropriate antipsychotic agents. The study findings can provide strong evidence base regarding the safety of antipsychotics in PD and thereby would help providers to select the safer treatment options for PD.

METHODS

Data Source

The current study used 2007-2010 Minimum Data Set (MDS) linked Medicare data to determine the study objective. Medicare Part D was launched in 2006 and it provides prescription drug coverage to the Medicare beneficiaries. Medicare Part A provides hospital coverage and Part B provides supplementary medical insurance to the Medicare beneficiaries. The MDS is a national standardized assessment tool used to assess functional capabilities and identify any health problems among residents living in Medicare or Medicaid certified nursing homes. [18]

The Medicare Provider Analysis and Review file (Part A), carrier file (Part B), the prescription drug claims file (Part D), the MDS, and the Master Beneficiary Summary File (MBSF) along with its chronic condition (CC) segment were used in this study. The CC segment contains information from on 27 common CCs ascertained using inpatient and outpatient claims data. All these files are available from the Conditions Data Warehouse (CCW) as Research

Identifiable Files (RIFs). [18] The study reused the Medicare and MDS database from a cohort of nursing home residents with a diagnosis of depression. The present study was approved under the exempt category by the University of Houston Committee for the Protection of Human Subjects.

Study Design

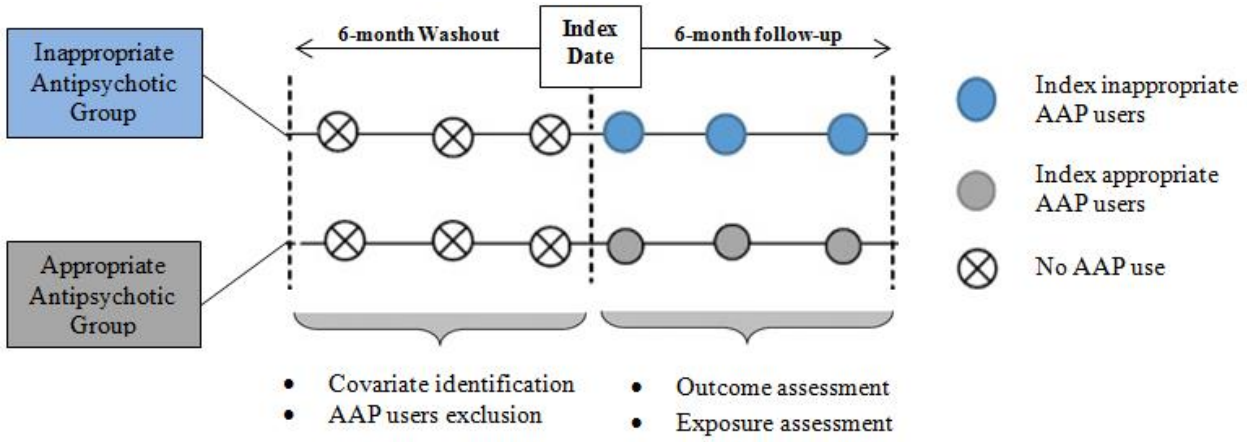
A retrospective cohort design involving propensity score matching was used to examine the association between atypical antipsychotic use and risk of mortality in elderly PD patient with psychosis. Patient with PD were identified using MDS and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 332.0 in the Medicare Part A or B claims files. Patients with PD were selected in the cohort if they were over 65 years of age and were continuously enrolled into Medicare parts A, B, and D during the 12 months baseline and 24 months follow-up periods. Patients who received diagnosis of either bipolar disease or schizophrenia during the baseline were excluded from the study as these patients were chronic users of antipsychotic medications.

Atypical Antipsychotics Exposure

The exposures to inappropriate and appropriate antipsychotics were defined according to 2015 AGS Beers criteria. [14] The use of aripiprazole, clozapine and quetiapine was appropriate antipsychotic exposure. Inappropriate antipsychotics encompassed olanzapine, asenapine, brexpiprazole, iloperidone, lurasidone, paliperidone, risperidone, or ziprasidone. The list of atypical antipsychotic drugs in the US market was obtained from Micromedex RED BOOK™ and AHFS Drug Information. [19,20] Generic Name - Short Version (GNN) from the Prescription Drug Event Data was used to identify the use of AAPs. The first prescription of antipsychotics

was identified based on Prescription Service Date (DOS). As shown in Figure 1, the index date was the first day that AAP drug was dispensed to the patient.

Figure 1. Study design and time frame



This study accounted for treatment discontinuation, switching, and augmentation which could change the exposure status. [21] The censoring criteria for discontinuation and augmentation were incorporated in the analysis. Treatment discontinuation was defined based on a 30 days gap between the estimated end date of an AAP prescription and the next refill. Medication switch was not an independent censoring criterion in this study because treatment switch occurs after discontinuation of the first AAP. Treatment augmentation was another reason for censoring when a second AAP was added to the therapy.

Outcome Assessment

The study outcome was the all-cause-mortality within 180 days after start of atypical antipsychotics. The information regarding the occurrence of death was obtained from Master Beneficiary Summary Files. The cohort patients were followed until death or reaching the end of follow-up period.

Sociodemographic characteristics - including age, sex, race, education, marital status, and geographical region - were obtained from Master Beneficiary Summary Files. The MDS assessment and CCW were used to determine the clinical characteristics of the study population. This provided us with several measures related to PD severity including cognitive and functional impairment items. [22,23] These validated measures have been applied in previous research involving patients with neurological disorders. The present study used the MDS-Derived Direct Cognition Scale (MDS-COG) to control for the severity of cognitive impairment in PD. The MDS-COG has a 0 to 9 score range, with higher scores reflecting greater severity of cognitive impairment. [22] The Activities of Daily Living were measured using ADL-Long Form (0-28) with higher scores reflecting a worse functional status. [23] The analysis used other variables for PD severity including walk difficulty in room or corridor, clarity of speech, drug induced dyskinesia (ICD-9 code 333.85), and dysphagia (ICD-9 code 787.2x). [24,25]

Since pneumonia is the main cause of death in PD patients, the propensity score matching included pneumonia as a baseline covariate and development of pneumonia in the follow-up period was modeled as a mediator between AAP use and mortality. The diagnosis of pneumonia was identified using the clinical classification of conditions developed by the Agency for Healthcare Research and Quality. [26] The propensity score matching also included several comorbidities along with Charlson Comorbidity Index (CCI). The CCI contains 19 classes of comorbidity to predict the risk of mortality for patients who may have those co-morbid conditions. [27] The propensity score model also included baseline typical antipsychotics, Selective Serotonin Reuptake Inhibitor (SSRI), Serotonin–Norepinephrine Reuptake Inhibitor (SNRI) and various pharmacotherapy for PD.

Statistical Analyses

Univariate and bivariate analyses were performed to describe patients' characteristics and to examine the differences between treatment groups in the matched cohort. Clinical trials are considered as gold standard for estimating the treatment effects but they generally include healthy adults that limit the understanding of the safety aspect of the medications such as antipsychotic use among vulnerable elderly patients with PD. Observational studies provide evidence regarding medication safety and treatment effects in real-world population. This evidence is often limited by selection bias due to pretreatment difference between the two groups, owing to non-random assignment of the patient to the treatment and control group. [28,29] Propensity score (PS) matching is frequently used to adjust for the pretreatment difference between the treatment groups. The propensity score technique was proposed by Rosenbaum and Rubin. A propensity score is the conditional probability of assignment to a treatment group based on a set of baseline covariates. Various covariates were included for the calculation of propensity scores such as sociodemographic variables, functional status, comorbid conditions and co-medications. [28,29]

Logistic regression model was used for the calculation of propensity scores. For matching PS using inappropriate atypical antipsychotics (treatment group) with patients taking appropriate atypical antipsychotics (control group), the GREEDY 5→1 matching technique was used. In this technique patients from the treatment group are matched to members of the control group on the first five digits of the propensity score. The remaining unmatched cases to the controls on the four digits the propensity score. This process is repeated until all the cases have been matched to the controls. If more than one control patient are found for a case then, a control patient is randomly selected for matching it with the case. [28,29]

Similarities between the two treatment groups before and after matching were examined using chi-square tests for categorical variables and t-tests for continuous variables. Survival analysis was conducted on the PS matched cohort using Cox regression model to compare the risk of mortality between the two treatment groups. An ID option of PROC PHREG in SAS v.9.2 was used to perform the robust Cox regression. Conventional Cox regression models assume independence of observations. However, robust Cox regression model uses the robust sandwich estimator to adjust for the clustering within matched pairs. This allows for unbiased estimation of treatment effects when compared to the other PS-matched Cox regression models. The Cox regression model assumes that the hazards of occurring of the event are constant over time (proportional hazards assumption). [30]

The proportional hazards assumption was tested via Kaplan-Meier plots, log-minus-log survival plots, Schoenfeld residual test, and Supremum test. Thus, a robust Cox hazard model was used to examine the association between antipsychotic use and risk of mortality in elderly patients with PD. Patients were censored in the main analysis upon treatment discontinuation or augmentation with another AAP or end of follow-up. In the next step, extended Cox regression with time-varying covariates was used to model pneumonia as a mediator between inappropriate AAP use and mortality in follow-up period. Time to mortality was examined in a multivariable Cox regression model taking into account both inappropriate AAP use and pneumonia as predictors for death. A number of sensitivity analyses were conducted to examine the robustness of the study findings. Intent-to-treat analysis was performed to examine whether censoring information could affect the association between treatment and outcome. The other sensitivity analyses involved head-to-head compression of individual antipsychotics. Most frequently used appropriate and inappropriate AAPs were retained in the cohort and the propensity score

approach was applied to rematch individual AAP users on baseline characteristics. The assumptions for propensity score matching and survival analyses were checked for the sensitivity analyses. All statistical analyses were conducted using SAS 9.2 (SAS Institute, Cary, North Carolina) with a statistical significance level of 0.05.

RESULTS

The diagnosis of PD was ascertained for 109,280 patients, using both MDS assessment and ICD-9 code (332.0). As shown in the cohort identification flowchart (Figure 2), the number of PD patients using atypical antipsychotics with continuous eligibility for Medicare parts A, B and D coverage was 31,099 in MDS-linked Medicare data between 1-Jul-2007 and 30-Jun-2010. 10,931 patients were excluded because they used atypical antipsychotics in washout period and 138 patients were excluded because they started more than one antipsychotic drug at the same time in the study period. 16,161 patients aged 65 years or older and without schizophrenia/ bipolar disorder started only one atypical antipsychotic in the study period. . The proportion of inappropriate antipsychotic use was 37.62% among AAP users before matching. 12,076 patients were matched using propensity score approach.

Figure 2. Cohort Identification Flowchart

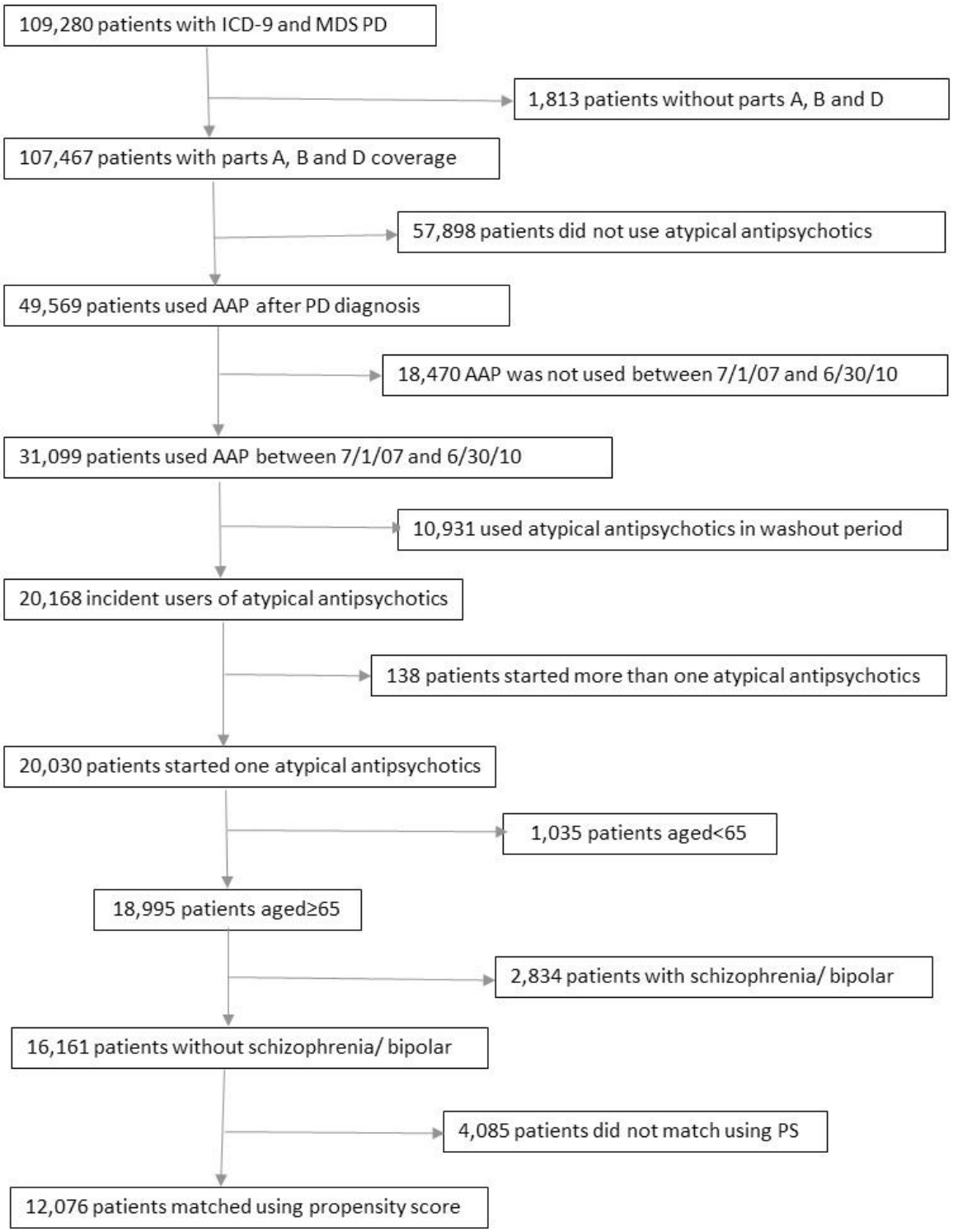


Table 1 presents the baseline characteristics of patients in the match cohort. The mean age of the cohort was over 82 years. Most of the atypical antipsychotic users were female in appropriate treatment group (60.43%) and in inappropriate AAP group (61.41%). The majority of the patients included in this study were white (>89%). Dysphagia rate was 40.38% and 39.30% in appropriate and inappropriate AAP users respectively. The percentage of dementia patients was over 28% in the cohort. More than 71% of AAP users were treated with SSRIs/ SNRIs in the baseline period. Levodopa prescription rates were 63.51% and 62.69% among appropriate and inappropriate AAP users respectively. More than 21% of the patients used dopamine agonists in baseline period and other antiparkinson medications were used with lower the prescription rates. As shown in Table 2, three most frequently used AAP were quetiapine (54.60%), risperidone (23.71%) and olanzapine (11.64%) before matching.

Table 1. Characteristics of appropriate and inappropriate atypical antipsychotics users in matched cohort

Characteristic	Appropriate AAP (n= 6,038)	Inappropriate AAP (n=6,038)	P-Value
Age (mean ± SD)	82.18 ± 6.89	82.12 ± 7.05	0.62
Female, n (%)	3,649 (60.43)	3,708 (61.41)	0.27
White, n (%)	5,402 (89.47)	5,415 (89.68)	0.70
College education, n (%)	701 (11.61)	709 (11.74)	0.82
Married, n (%)	1,663 (27.54)	1,696 (28.09)	0.50
Region, n (%)			
Midwest	1,716 (28.42)	1,719 (28.47)	0.99
Northeast	1,105 (18.3)	1,114 (18.45)	
West	247 (4.09)	243 (4.02)	
South	2,970 (49.19)	2,962 (49.06)	
ADL Score (mean ± SD)	10.90 ± 7.33	10.89 ± 7.40	0.92
MDS Cognitive Score (mean ± SD)	4.21 ± 1.73	4.22 ± 1.69	0.76
Impaired Walking	3,028 (50.15)	2,997 (49.64)	0.57
Unclear Speech, n (%)	2,796 (46.31)	2,820 (46.70)	0.66
Dyskinesia, n (%)	104 (1.72)	104 (1.72)	1.00
Dysphagia, n (%)	2,438 (40.38)	2,373 (39.30)	0.23
Insomnia, n (%)	683 (11.31)	638 (10.57)	0.19
Abusive Behavior, n (%)	523 (8.66)	554 (9.18)	0.32
Depressed Mood Indicators, n (%)	1,573 (26.05)	1,529 (25.32)	0.36
Depressive Type Psychosis, n (%)	52 (0.86)	66 (1.09)	0.20
Anxiety, n (%)	2,832 (46.90)	2,829 (46.85)	0.96
Dementia, n (%)	1,747 (28.93)	1,785 (29.56)	0.45
Stroke, n (%)	1,634 (27.06)	1,635 (27.08)	0.98
Falls and Fractures, n (%)	5,318 (88.08)	5,328 (88.24)	
Coronary Artery Disease, n (%)	1,473 (24.40)	1,523 (25.22)	029
Congestive Heart Failure, n (%)	1,792 (29.68)	1,798 (29.78)	0.90
Dysrhythmia, n (%)	1,360 (22.52)	1,367 (22.64)	0.88
Hypertension, n (%)	4,891 (81.00)	4,907 (81.27)	0.71
Diabetes Mellitus, n (%)	2,116 (35.04)	2,124 (35.18)	0.88
Osteoarthritis, n (%)	2,960 (49.02)	2,878 (47.66)	0.1354
Cancer, n (%)	677 (11.21)	647 (10.72)	0.38
Pneumonia history, n (%)	2,170 (35.94)	2,183 (36.15)	0.81
Asthma, n (%)	312 (5.17)	342 (5.66)	0.23
COPD, n (%)	1,474 (24.41)	1,536 (25.44)	0.19
Charlson Comorbidity Index (mean ± SD)	5.75 ± 3.39	5.77 ± 3.43	0.69
Typical antipsychotics, n (%)	267 (4.42)	306 (5.07)	0.10
SSRI/ SNRI, n (%)	4,313 (71.43)	4,349 (72.03)	0.47
Levodopa, n (%)	3,835 (63.51)	3,785 (62.69)	0.35
Dopamine Agonists, n (%)	1,296 (21.46)	1,294 (21.43)	0.96

COMT Inhibitors, n (%)	601 (9.95)	595 (9.85)	0.86
MAO Inhibitors Type B, n (%)	197 (3.26)	204 (3.38)	0.72
Amantadine, n (%)	294 (4.87)	305 (5.05)	0.64
Anticholinergics, n (%)	284 (4.70)	300 (4.97)	0.50

Table 2. Proportion of atypical antipsychotic agents started in the cohort of patients with PD before and after matching

AAP	Before Matching, n (%)	After Matching, n (%)
Aripiprazole	1,205 (7.4)	774 (6.41)
Clozapine	62 (0.38)	35 (0.29)
Olanzapine	1,896 (11.64)	1,871 (15.49)
Paliperidone	20 (0.12)	19 (0.16)
Quetiapine	8,890 (54.60)	5,229 (43.30)
Risperidone	3,861 (23.71)	3,812 (31.57)
Ziprasidone	349 (2.14)	336 (2.78)
Total	16,283 (100.00)	12,076 (100.00)

The distribution of the propensity scores across treatment groups is presented in Figure 3. The mean of the propensity scores in appropriate AAP users was 0.36 ± 0.089 and inappropriate AAP users' propensity score was 0.40 ± 0.084; therefore, there was sufficient overlap in the characteristics of the treatment groups. The one-on-one matching was conducted successfully and 6,038 patients remained in each treatment groups. No significant difference was found in sociodemographic and clinical characteristics of the appropriate and inappropriate AAP users after matching. The Proportional hazards assumption was met, using visual and numeric approaches. During study period, a total number of 3,291 patients were censored before the end of follow-up due to treatment discontinuation or augmentation, each one occurred first. The average follow-up time was 142 days in this study. Figure 4 presented the Kaplan–Meier curves for the hazard of mortality that was slightly higher for inappropriate AAP users vs. appropriate AAP group.

Figure 3. The histogram of propensity scores for appropriate and inappropriate atypical antipsychotics

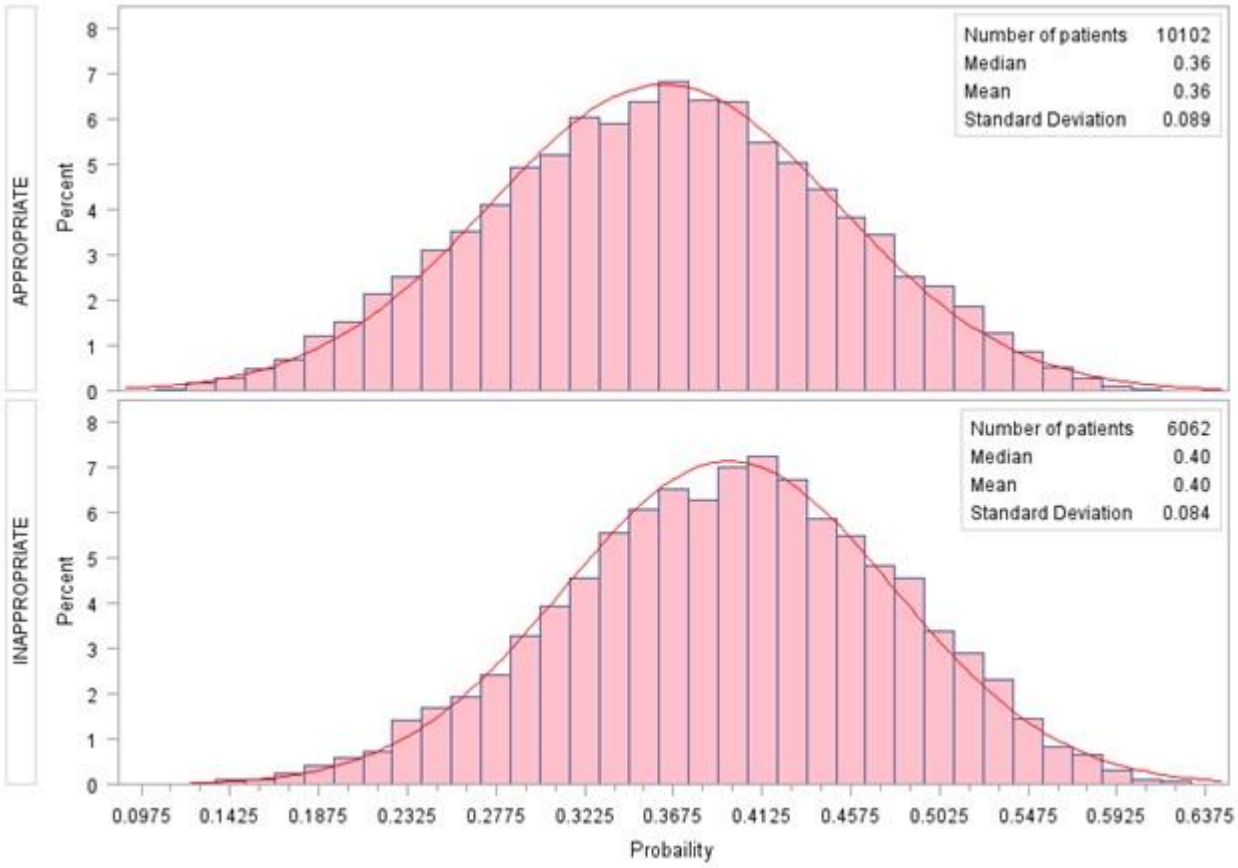
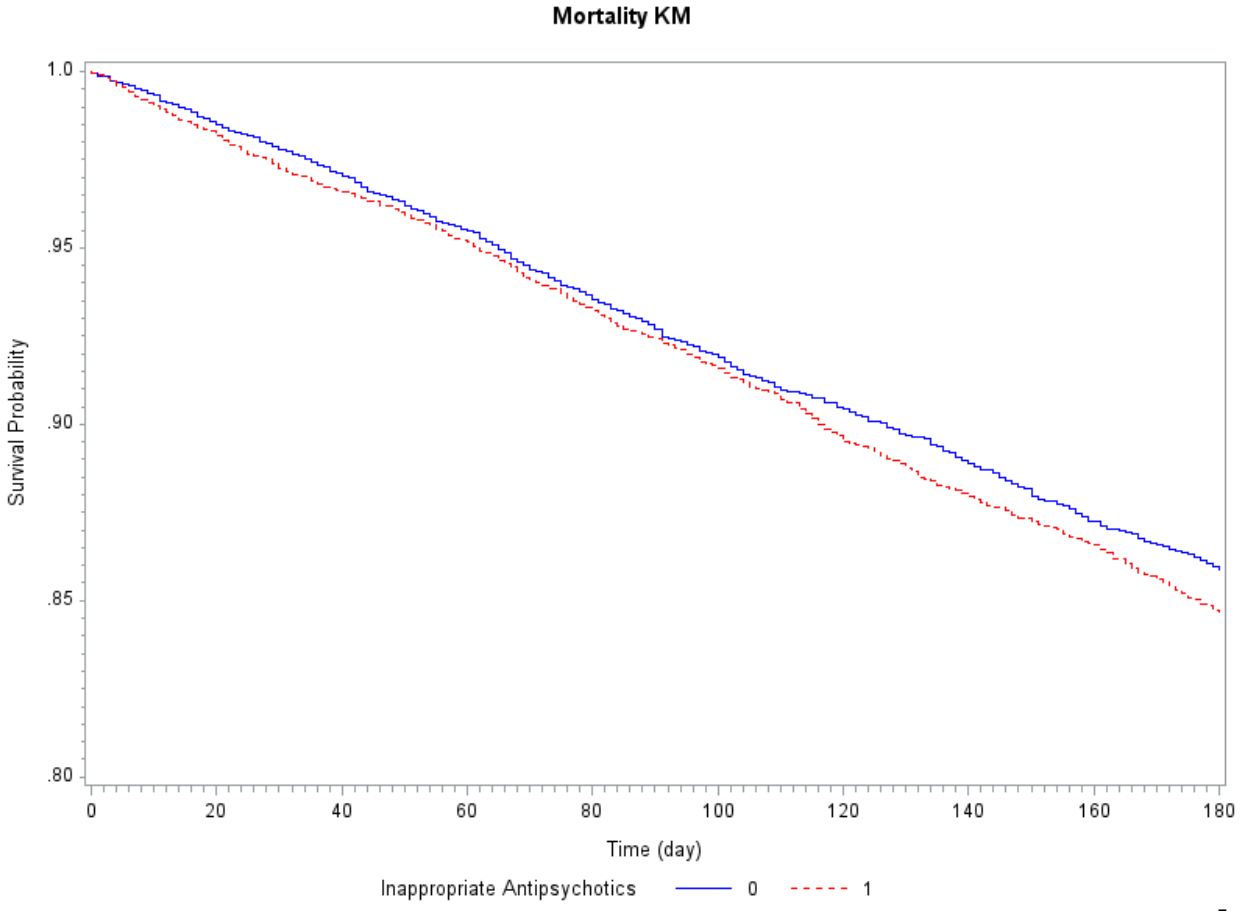


Figure 4. Kaplan-Meier survival curves for all-cause-mortality across appropriate and inappropriate treatment groups



The mortality rates across the two treatment groups are presented in Table 3. The mortality rate was 16.28% in the study cohort over 6-month follow-up, 15.65% in appropriate AAP group and 16.91% in inappropriate AAP group. The relationship between the type of AAP used and the occurrence of death was examined for 12,076 patients in the main analysis which applied censoring criteria in the survival model (Table 4). The Cox proportional hazards models revealed increased risk of all-cause mortality [Hazard Ratio (HR) 1.13 (95% CI: 1.01 - 1.28)] for patients who used inappropriate vs. appropriate AAP. There was a significant association between inappropriate AAP use and risk of death in sensitivity analysis, when risperidone compared to quetiapine [HR: 1.20 (95% CI: 1.03 - 1.40)]. The risk of mortality was not significantly different between olanzapine and quetiapine users; and in the intent-to-treat analysis.

Table 3. Relationship between AAP exposure and the outcome of mortality

	Death (No)	Death (Yes)	Total
Appropriate AAP	5,093 (84.35)	945 (15.65)	6,038 (50.00)
Inappropriate AAP	5,017 (83.09)	1,021 (16.91)	6,038 (50.00)
Total	10,110 (83.72)	1,966 (16.28)	1,2076 (100.00)

Chi-square test p-value = 0.06

Table 4. Risk Of Mortality Associated With Inappropriate AAP Use

	Sample Size	Hazard Ratio (95% CI)	P-Value
Main Analysis	12,076	1.13 (1.01 - 1.28)	0.04*
Sensitivity Analyses			
Intent to Treat	12,076	1.09 (1.00 - 1.20)	0.06
Risperidone vs. Quetiapine	7,628	1.20 (1.03 - 1.40)	0.02*
Olanzapine vs. Quetiapine	3,758	1.01 (0.82 - 1.26)	0.91

* Indicate p value <0.05

In addition, pneumonia was included in multivariable cox regression models as a mediator between AAP use and mortality. As shown in Table 5, there was a significant relationship between pneumonia and death in all analyses and the impact of inappropriate AAP use was not significant on mortality when pneumonia was modeled as a mediator between AAP use and death. The HR of death was 4.56 (95% CI: 3.48 - 5.98) for those who developed pneumonia in the follow-up period in comparison to those without pneumonia.

Table 5. Risk Of Mortality Associated With Inappropriate AAP Use With Pneumonia As A Mediator

	Inappropriate AAP, HR (95% CI) for Mortality	P-Value	Pneumonia, HR (95% CI) for Mortality	P-Value
Main Analysis	1.10 (0.96 - 1.25)	0.16	4.56 (3.48 - 5.98)	<0.01*
Sensitivity Analyses				
Intent to Treat	1.06 (0.95 - 1.17)	0.30	4.95 (4.03 - 6.08)	<0.01*
Risperidone vs. Quetiapine	1.15 (0.98 - 1.36)	0.09	4.09 (2.92 - 5.73)	<0.01*
Olanzapine vs. Quetiapine	0.94 (0.74 - 1.20)	0.62	8.54 (4.56 - 15.98)	<0.01*

* Indicate p value <0.05

DISCUSSION

This study found that quetiapine was the most frequently used antipsychotic in patients with PD followed by risperidone and olanzapine. The use of quetiapine was consistently higher than other antipsychotics in previous studies of older patients with PD, since quetiapine was considered to be safer than other antipsychotics for those patients. [31] Risperidone and olanzapine can be effective for treating delirium and other neurobehavioral conditions associated with PD that might justify the high prescription rates of these antipsychotics . [32] Based on 2015 Beers criteria, 37.62% of PD patients used inappropriate AAP before matching; however, the study data were collected before implementation of recent guidelines for AAP therapy in PD. Clozapine was the only AAP with evidence level B for patients with PD psychosis; however, less than 1% of patients used clozapine in the study cohort. Previous epidemiological studies on the use of antipsychotics in PD found similar results; indicating that clozapine use might be restricted in patients with PD due to blood monitoring requirement and the risk of adverse events. [8,10]

The demographic characteristics of patients included in the cohort were comparable with previous observational studies on nursing home residents in the United States. [27,28] The mean age of the cohort was over 82 years and most PD patients were female and white. The use of atypical antipsychotics was one of the eligibility criteria in this study that might be associated with some characteristics such as higher age. The present study used ADL-Long-Form scale as a measure of functional status with the mean of 11/28 in the study population. The ADL-Long-Form scale is the sum of 7 items ranging from 0-4; thus, the mean of 11/28 indicates some degrees of restrictions in functional status but not extensive impairment. [33] The average MDS-COG score was 4/9, suggesting mild to moderate cognitive impairment in the study population. [34] The

percentage of dementia diagnosis was over 28% in the study population. This was of particular concern for dementia patients treated with AAP; given that the Food and Drug Administration (FDA) issued a black-box warning in 2005 regarding the risk of atypical antipsychotic use in patients with dementia. [35]

According to previous studies, pneumonia is the leading cause of death in patients with PD and there is a strong association between community-acquired pneumonia and dysphagia. [1,36] The present study took into account baseline clinical characteristics including pneumonia, dysphagia and other covariates that might be associated with AAP treatment and the outcome of mortality. Propensity score matching was an efficient approach in this study to account for the effect of various confounders on the relationship between AAP use and pneumonia. The average treatment effect on the treated (ATT) was reported for those who received inappropriate vs. appropriate AAP based on one-on-one matching. [37]

The study found a significant association between inappropriate antipsychotic use and all-cause-mortality in the initial analyses. In mediator analyses, pneumonia had a strong association with mortality in all analyses. When pneumonia was modeled as a mediator between AAP use and mortality, the impact of inappropriate AAPs on the risk of mortality was not significant. This indicates that inappropriate antipsychotic use increases the risk of pneumonia leading to a higher risk of death. The study could not establish a direct relationship between inappropriate antipsychotic use and the risk of mortality. Since pneumonia had a strong association with mortality, prevention strategies for pneumonia can reduce the risk of death in PD patients who need antipsychotic treatment. The prevention strategies for pneumonia involve rehabilitation techniques for swallowing as well as optimizing use of high risk medications. [38] Selection of appropriate antipsychotics is important for the safety of patients with PD. This study

provided evidence regarding safety of AAPs in PD based on 2015 Beers criteria. Therefore, the study results can be used in developing prevention strategies for PD patients with regards to the risks of pneumonia and mortality associated with AAP use. Further research is needed to find safer treatment options for patients with PD who are vulnerable to serious adverse events.

Generalizability of Findings

The study data were reused from a cohort of older adults with depression; thus, the patients included in the cohort had a diagnosis of depression. This might not bias the study findings, since there was no difference between the treatment groups in terms of comorbid depression. However, considering this limitation is important for generalization of the results. PD patients with depression might be sicker than those without depression and they might use antipsychotics as adjuvant therapy for depression. [39,40] Therefore, the study findings might overestimate the risk of mortality associated with antipsychotics use, if the results generalize to PD patients without depression.

Strengths and Limitations

The present study used MDS linked Medicare data which provided large representative sample of elderly patients with PD residing in nursing homes. Medicare and MDS data provided rich source of information for examining medication safety of atypical antipsychotics in elderly patients in real world treatment settings. This study used four years of data which helped in constructing longitudinal study and control for various risk factors and confounders associated with the use of atypical antipsychotics and risk of pneumonia and mortality in elderly PD patients. Various sensitivity analyses were conducted to confirm the robustness of study findings and results were consistent with the main analysis.

This study has some limitations. Medicare and MDS are secondary data sources and thus have limitations due to under and improper coding. This might also limit the accuracy of these secondary data sources in capturing diseases diagnosis. [41] The study database was reused from a previous cohort of nursing home residents with depression and this might affect the generalizability of the study findings to other settings. Pharmacy claims data provides information regarding medication refill but they cannot be used to ascertain whether patient actually took the medication or not. Risk factors and confounders used for the calculation of propensity score were limited to those available in the claims data. Information related to the severity of PD could not be captured using claims data. However, various proxy variables from MDS and Medicare data were used to account for the severity of PD. There might be a chance for unobserved confounding. However, various sensitivity analyses that were conducted confirmed the study findings. Also, this is a retrospective study using observational data, thus, causality could not be established. Lastly, results of this study may not be generalizable to older patients in other treatment settings.

CONCLUSIONS

This study examined association between inappropriate atypical antipsychotic use and all-cause-mortality, considering pneumonia as a mediator for the risk of death. Inappropriate atypical antipsychotics were defined base on 2015 American Geriatrics Society (AGS) Beers criteria. The prescription rates for inappropriate atypical antipsychotics were relatively high for nursing home residents with PD. The study found a significant association between inappropriate antipsychotic use and all-cause-mortality. However, pneumonia is a mediator between AAP use and mortality in PD patients. This study provided strong evidence regarding the risk of mortality due to inappropriate antipsychotic use mainly mediated by pneumonia in older patients with PD.

Further research is needed to examine the risk of mortality in PD patients using newer antipsychotic medications.

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CONCLUSIONS AND IMPLICATIONS

This study is the first attempt to identify incidence and predictors of inappropriate antipsychotic use among older patients with PD. According to the 2015 American Geriatrics Society (AGS) Beers criteria, antipsychotics are generally inappropriate medications in PD, except for aripiprazole, quetiapine, and clozapine. The incidence rate of atypical antipsychotic use was 17.50% in a 2-year follow-up; and more than one-third of PD patients received inappropriate agents among those who were treated with atypical antipsychotics. Among clinical characteristics, dementia and COPD were associated with higher risk of inappropriate antipsychotics utilization. The use of dopaminergic antiparkinson drugs is possibly an indicator for dopaminergic psychosis which prompts appropriate antipsychotic utilization. The study found that levodopa users were more likely to receive appropriate antipsychotics.

This study used a neuro-pharmacological rationale to examine the risks of medication-related morbidity and mortality in PD patients using inappropriate atypical antipsychotic agents. Inappropriate antipsychotics are associated with higher levels of D_2 antagonist activity and this can worsen Parkinsonian symptoms such as dysphagia which is correlated with aspiration pneumonia. The risks of pneumonia and all-cause-mortality were significantly higher for PD patients who received inappropriate vs. appropriate antipsychotics. Pneumonia was a mediator between atypical antipsychotic use and mortality in PD patients.

The study findings suggest that selection of appropriate antipsychotics in PD is crucial to prevent serious adverse events related to antipsychotic use in PD, given that pneumonia is the first cause of death in PD patients. This investigation provided a strong evidence base regarding safety of atypical antipsychotics in elderly patients with PD. The study findings can be used in developing prevention strategies for PD patients with regards to the risks of pneumonia and

mortality associated with AAP use. The results can help in optimizing the use of atypical antipsychotics in PD to improve quality of geriatric care.