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Risk of pneumonia associated with atypical antipsychotic use in nursing home residents with Parkinson's disease

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ABSTRACT

According to the American Geriatrics Society (AGS) Beers criteria, most atypical antipsychotic (AAPs) are inappropriate in patients with Parkinson's disease (PD) due to the risk of worsening Parkinsonian symptoms. This study evaluated the risk of pneumonia associated with inappropriate AAP use in elderly nursing home residents with PD. The study population encompassed older adults aged 65 years or older with a diagnosis of PD and with comorbid depression who started the AAP medication. Appropriate AAPs were defined as aripiprazole, clozapine or quetiapine according to 2015 Beers criteria, and inappropriate AAPs included olanzapine, asenapine, brexpiprazole, iloperidone, lurasidone, paliperidone, risperidone, or ziprasidone. Cox regression analyses involved propensity score-matched users of inappropriate and appropriate AAPs to examine the association between AAP use and risk of pneumonia. The mean age of patients in propensity-matched cohort (n = 12,076) was 82.15 years (SD = 6.97). The pneumonia incidence rates were 37.19 and 45.92 per person-year in appropriate and inappropriate AAP groups, respectively. Multivariable Cox regression analyses revealed increased risk of pneumonia [Hazard Ratio (HR) 1.20 (1.08–1.34)] for nursing home residents who were taking inappropriate compared to those taking appropriate AAP. In sensitivity analyses, the pneumonia risk was 1.28 (1.12–1.47) for risperidone vs. quetiapine and 1.29 (1.06–1.57) for olanzapine vs. quetiapine. The risk of pneumonia was significantly higher for patients with PD who used inappropriate AAP in comparison to appropriate AAP group in all analyses. This investigation warrants further attention regarding safety of atypical antipsychotics in PD.

1. Introduction

Parkinson's disease (PD) is one of the leading causes of morbidity and disability in older adults (Xu et al., 2014). The prevalence of PD ranges from 1% to 5% in the elderly population depending on the age group (De Lau and Breteler, 2006; Kowal et al., 2013). 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 (Weerkamp et al., 2014). Lack of dopamine is the cause of motor symptoms such as tremor, rigidity, and bradykinesia in PD patients (Jankovic, 2008). Additionally, non-motor features such as dysphagia and behavioral symptoms adversely affect the course of PD (Jankovic, 2008).

Antipsychotics are generally used for the treatment of behavioral symptoms of PD (Schrag, 2004). Weintraub et al. found that antipsychotics were prescribed for 50% of veterans with PD psychosis. Risperidone and olanzapine were used by 17.3% and 11.5% of the patients respectively who received antipsychotic treatment (Weintraub et al., 2011). However, antipsychotic use may antagonize dopamine receptors leading to aggravation of Parkinsonian symptoms (Schrag, 2004). 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 (AGS, 2015). Inappropriate antipsychotics can adversely affect voluntary movements in general and swallowing movements in specific in patients with PD (AGS, 2015; Miarons Font and Rofes Salsench, 2017).

Pneumonia is the leading cause of death among patients with PD (Xu et al., 2014). Dopaminergic pathways are involved in the swallowing reflex and coordination of swallowing and breathing (Gross

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et al., 2008). Oropharyngeal dysphagia is the manifestation of dysfunctional swallowing and is associated with a high risk of aspiration pneumonia (Almirall et al., 2013). Inappropriate antipsychotics can further aggravate this process, leading to a higher risk of pneumonia. However, the impact of antipsychotics on the swallowing reflex has not been studied in PD patients. A post hoc study of the pimavanserin clinical trial found that the risk of pneumonia was significantly higher for participants taking concurrent antipsychotics in comparison to those not using concurrent antipsychotics (Ballard et al., 2015). First and second generations of antipsychotics are associated with increased risk of pneumonia among all age groups (Nosè et al., 2015). The risk of pneumonia associated with antipsychotic use increases in older age (Dzahini et al., 2018).

Little is known about the safety profile of inappropriate antipsychotic use, especially regarding pneumonia, in PD patients. To our knowledge this study is the first study to evaluate the risk of pneumonia associated with inappropriate AAP use in elderly nursing home residents with PD. The study hypothesized that there is a higher risk of all-cause pneumonia in the elderly patients with PD using inappropriate AAPs in comparison with PD patients using appropriate AAPs due to worsening Parkinsonian symptoms. The study can provide evidence regarding the safety of antipsychotics in PD and thereby help to optimize the use of antipsychotic medications to improve the quality of geriatric care.

2. Methods

2.1. Data source

The study utilized 2007–2009 Minimum Data Set (MDS) cross-linked to Chronic Condition Warehouse (CCW) Medicare files. Medicare Part A, B and D claims files, MDS, and Master Beneficiary Summary File were used in this study. Medicare Part A provides hospital coverage. Medicare Part B provides supplementary medical insurance for non-hospital healthcare services. Medicare Part D provides coverage on prescription drugs for the Medicare beneficiaries. 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 (ResDAC, 2013).

The 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(ResDAC, 2013). The study cohort was derived from the MDS linked Medicare claims data involving elderly patients with depression who had at least one MDS assessment. This study was approved by the University of Houston Committee for the Protection of Human Subjects under the exempt category.

2.2. Study population and eligibility criteria

The study population encompassed nursing home residents 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 (AHRQ, 2013). All study participants had a diagnosis of comorbid depression, since the study sample was derived from a depression cohort. 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.

Nursing home residents were included in the cohort, if they received the first antipsychotic medication between July 1st, 2007 and June 30th, 2010 and had met continuous eligibility criteria for the 6 months pre-index period. 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.

2.3. Atypical antipsychotic exposure

The study had two exposure arms, namely appropriate and inappropriate atypical antipsychotics which were operationally defined based on 2015 AGS Beers criteria (AGS, 2015). The use of aripiprazole, clozapine, or quetiapine in PD patients was considered 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 (AHFS, 2016; Micromedex, 2016). The use of AAPs was 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 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, patients were censored due to loss to follow up for any reason such as death before the end of the study.

2.4. Outcome assessment

The primary dependent measure was the diagnosis of all-cause pneumonia in the study period identified using the clinical classification of conditions developed by the Agency for Healthcare Research and Quality (AHRQ). The operational definition of all-cause pneumonia was based on specific ICD-9-CM conditions such as viral and bacterial pneumonia, bronchopneumonia, specific pneumonia, and pneumonia not specified (AHRQ, 2013). 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 (AHRQ, 2013).

2.5. Covariates

Sociodemographic characteristics for descriptive and multivariable analyses were obtained from the MBSF. 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 (Morris et al., 1994). The Activities of Daily Living (ADL) were scored using ADL-Long Form (0–28) with higher scores indicating a worse functional status (Morris et al., 1999). 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) (González-Fernández et al., 2009; Merrill et al., 2013). The clinical characteristics comprised several comorbidities and co-medications such as antiparkinsonian agents and all these covariates were included in propensity score models.

2.6. Statistical analyses

Descriptive analysis was performed to describe sociodemographic characteristics, comorbidities, and co-medications during the 6-month baseline period for appropriate and inappropriate AAP users. 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 to 1 matching technique (Baser, 2006; Brookhart et al., 2006). The robust Cox regression model was used to evaluate the risk of pneumonia associated with use of inappropriate vs. appropriate atypical antipsychotics in the matched cohort over the study time period (Lu and Shen, 2014).

A number of sensitivity analyses were conducted to examine the robustness of the study findings. Intent-to-treat (ITT) analysis was performed to examine whether censoring information could affect the association between treatment and outcome. In the ITT analysis, patients were followed until they developed pneumonia, died or were lost to follow-up for any reason, or until the end of the study regardless of adherence status for the index AAP. The other sensitivity analysis involved head-to-head comparison of individual antipsychotics. Most frequently used appropriate and inappropriate AAPs were compared with each other using separate propensity score matching models. All statistical analyses were conducted using SAS 9.2 (SAS Institute, Cary, North Carolina) with a statistical significance level of $p < 0.05$.

3. Results

There were 109,280 nursing home residents using both MDS assessment and ICD-9 codes for PD (Fig. 1). The study cohort consisted of 16,161 nursing home residents met all criteria who initiated AAP between July 01, 2007 and June 30, 2010. The percentage of inappropriate antipsychotic use was 37.62% (N = 6,126) among those who initiated AAP before matching. The mean PS was 0.36 ± 0.089 in appropriate AAP and 0.40 ± 0.084 in inappropriate AAP groups. The one-on-one matching was performed and 6,038 nursing home residents remained in each exposure arm. Bivariate analyses involving McNemar's and paired t tests revealed no significant difference in sociodemographic and clinical characteristics of appropriate and inappropriate AAP users in the matched cohort (Table 1).

The mean age of the nursing home residents was 82.15 (SD = 6.97) years. Most of the atypical antipsychotic users were female in appropriate AAP group [N = 3,649 (60.43%)], and in inappropriate AAP group [N = 3,708 (61.41%)]. Appropriate and inappropriate AAP users had 40.38% (N = 2438) and 39.30% (N = 2373) likelihood of dysphagia respectively. The proportion of patients with dementia was over 28% in both groups. The rates of levodopa prescription were 63.51% (N = 3,835) in appropriate AAP group and 62.69% (N = 3,785) among those who received inappropriate AAP. Three most frequently used AAP were quetiapine [N = 5,229 (43.30%)], risperidone [N = 3,812 (31.57%)] and olanzapine [N = 1,871 (15.49%)] in matched cohort (Table 2).

The rates of AAP discontinuation were 15.22% (N = 919) and 21.17% (N = 1,278) in appropriate and inappropriate groups respectively ($p < 0.01$) and treatment augmentation occurred in appropriate [N = 606 (10.04%)] and inappropriate [N = 972 (16.10%)] groups ($p < 0.01$). The mean follow-up time was 135.90 ± 67.39 days for appropriate AAP users and was 121.60 ± 73.27 days for inappropriate AAP users ($p < 0.01$). The Kaplan–Meier estimator, presented in Fig. 2 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.

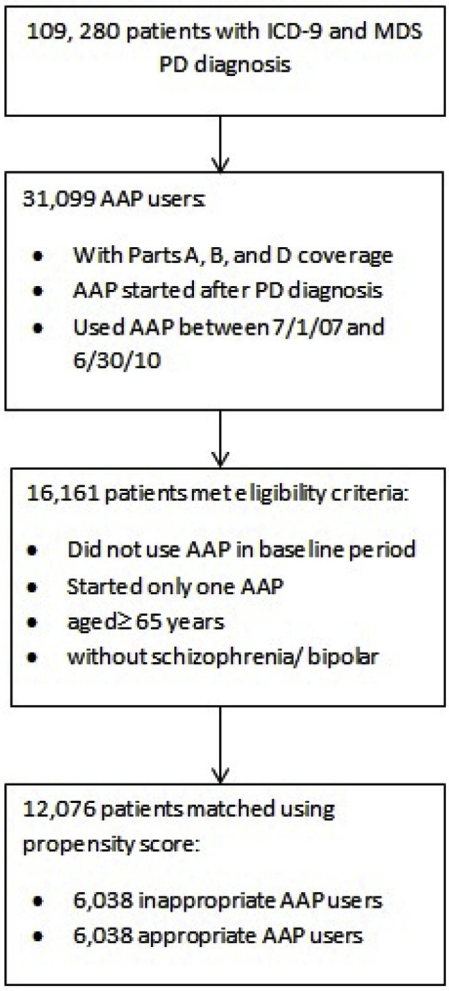

Fig. 1. Cohort identification flowchart.

The unadjusted rates of pneumonia were 16.35% (N = 987) in appropriate AAP group and 18.78% (N = 1134) in inappropriate AAP group over 6-month follow-up ($p = 0.0004$). The pneumonia incidence rates were 37.19 and 45.92 per person-year in appropriate and inappropriate AAP groups, respectively. 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 hazards model revealed an 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.

3.1. Sensitivity analyses

As shown in Table 3, 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 could not be performed for the risk of pneumonia associated with other individual antipsychotics due to inadequate sample size. The significance of findings

Table 1
Characteristics of appropriate and inappropriate atypical antipsychotics (AAP) in matched cohort.

Characteristic	Appropriate AAP (n = 6038)	Inappropriate AAP (n = 6038)	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, n (%)	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)	0.78
Coronary Artery Disease, n (%)	1,473 (24.40)	1,523 (25.22)	0.29
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)	0.14
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)

did not change in an additional analysis excluding baseline typical antipsychotic users from the cohort.

4. Discussion

More than one-third of the nursing home residents with PD used inappropriate agents among those who received AAPs. In this study, quetiapine was the most frequently used antipsychotic in PD patients, followed by risperidone and olanzapine. Use of quetiapine was consistently higher than other antipsychotics in previous studies involving elderly patients with PD, as quetiapine was considered to be safer than other antipsychotics in PD (Kim et al., 2003; Weintraub et al., 2011). Among the older generation of AAPs, clozapine is the only medication with acceptable efficacy for PD psychosis (Frieling et al., 2007); however, less than 1% used clozapine before and after matching. This is 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 (Goldman and Holden, 2014; Weintraub et al., 2011).

A few epidemiological studies have used MDS database to assess characteristics of patients with PD and reported comparable results for demographic characteristics of nursing home residents with PD (Lapane et al., 1999; Mitchell et al., 1996). 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 to 4, the average 11/28 score, indicates some degrees of limitation in functional status but not extensive impairment (Morris et al., 1999). Similarly, the average direct MDS score 4/9 might suggest mild to moderate cognitive impairment in the study population (Hartmaier et al., 1994). Over 28% of the nursing home residents had a diagnosis of dementia and this is 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 (Kuehn, 2005). According to previous studies, dysphagia is one of the most important clinical conditions associated with aspiration pneumonia (Almirall et al., 2013). Approximately, 40% of the nursing home residents had a diagnosis of dysphagia which indicates a relatively high number of the nursing home residents with PD have difficulty swallowing (Kalf et al., 2012).

Propensity score matching was an efficient approach in this study to take into account the effect of observable 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 (Becker and Ichino, 2002). 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 persistent with medication use (Hollis and Campbell, 1999). The significant results for the risk of pneumonia in both analyses confirmed the robustness of the findings regardless of the censoring criteria. The risk of pneumonia was similar for risperidone and olanzapine when compared to quetiapine. This might be due to similar dopamine antagonist activity of risperidone and olanzapine (Kuroki et al., 2008). The class-specific effect of inappropriate AAPs reflects the risk of pneumonia due to individual inappropriate AAPs as it was demonstrated for risperidone and olanzapine, indicating that use of risperidone or olanzapine can increase the risk of pneumonia in PD patients.

Inappropriate antipsychotics potentially affect swallowing process in patients with PD due to high level of D_2 antagonist activity (Bieger, 1991). This increases the risk of aspiration pneumonia which is of particular concern for the elderly patients with PD (Dzahini et al., 2018). The study findings suggest that selection of appropriate antipsychotics in PD is critical to prevent serious adverse events related to antipsychotic use in PD, given that pneumonia is one of the most

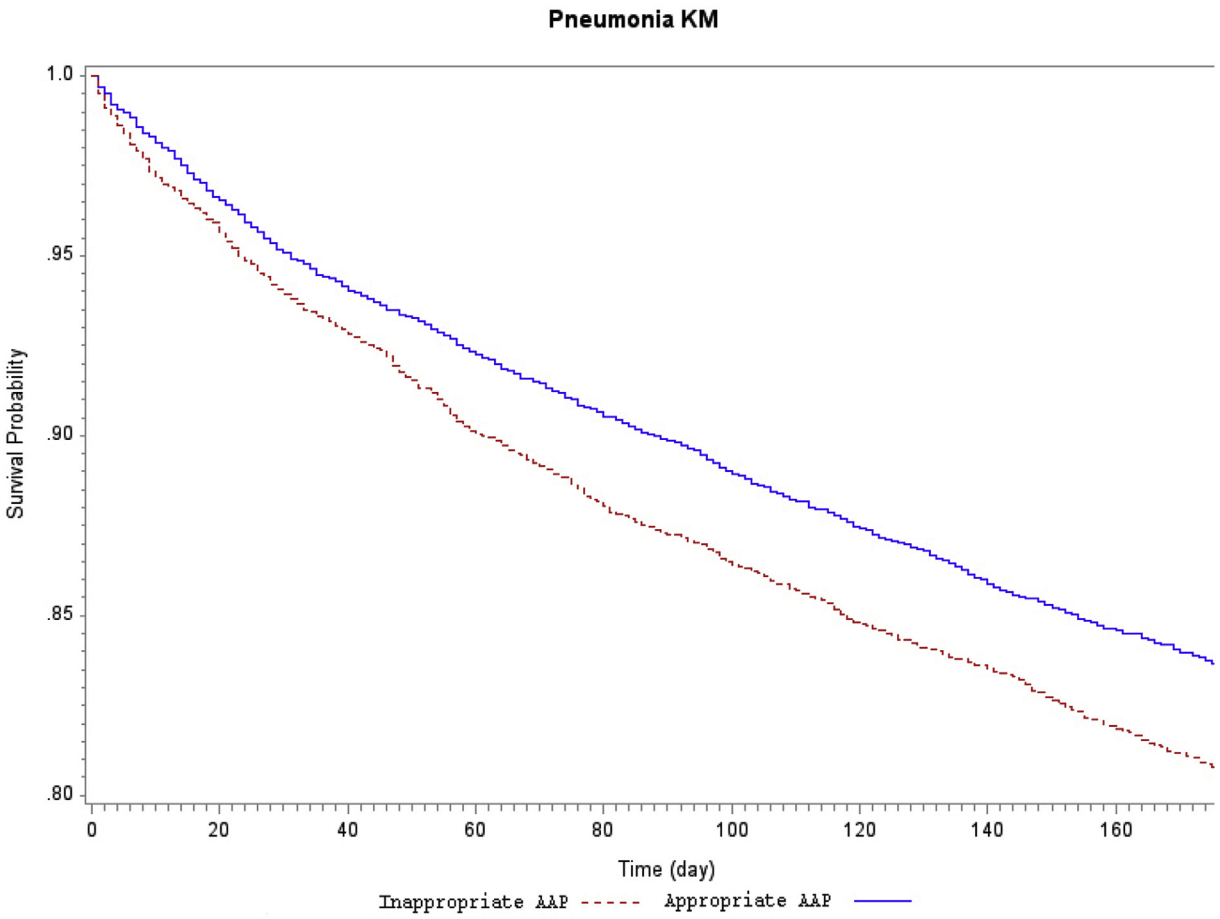

Fig. 2. Kaplan-Meier Survival Curves for incidence of pneumonia across Appropriate and Inappropriate Atypical Antipsychotics (AAP).

common causes of mortality in PD patients. Further research is needed to evaluate the risk of pneumonia in PD patients using newer antipsychotic medications.

4.1. Generalizability of findings

The study cohort was derived from the MDS-linked Medicare claims data involving elderly with depression who had at least one MDS assessment. This might affect utilization pattern of atypical agents in the study cohort. However, 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. Also, nursing home residents with PD were diagnosed with comorbid conditions such as dementia, dysphagia, and others; these comorbidities were adjusted to address generalizability of results. However, PD patients with depression can be severe than those without depression in general because of the use of antipsychotics for augmentation of antidepressant therapy (Nemeroff, 2005; Pontone et al., 2016). In spite of these limitations, the study findings have implications regarding pneumonia risk assessment in PD patients using atypical antipsychotics, given that the mechanism of aspiration pneumonia in PD is independent of depression.

4.2. Strengths and limitations

This study used large nationally representative data, involving federally mandated assessments of the nursing home residents all over the United States and Medicare claims data. Clinical trials generally exclude sicker patients which limits available information regarding 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. However, there are study limitations due to the inherent nature of the secondary data analysis. Miscoding and under-coding might occur in the process of administrative data collection (ResDAC, 2017). Data availability was another restriction for the analysis. One such factor was the severity measures of

Table 3
Risk of pneumonia: Inappropriate vs. Appropriate atypical antipsychotics (AAP).

	Sample Size (Number of Events)		Hazard Ratio (95% CI)	P-Value
	Appropriate AAP	Inappropriate AAP		
Main Analysis	6,038 (836)	6,038 (934)	1.20 (1.08–1.34)	< 0.01[a]
Intent to Treat	6,038 (987)	6,038 (1134)	1.16 (1.06–1.27)	< 0.01[a]
Risperidone vs. Quetiapine	3,814 (494)	3,814 (587)	1.28 (1.12–1.47)	< 0.01[a]
Olanzapine vs. Quetiapine	1,879 (250)	1,879 (295)	1.29 (1.06–1.57)	< 0.01[a]

[a] Indicate p value < 0.05.

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. There is a possibility of residual confounding due to unmeasured confounders.

5. Conclusions

This study evaluated the risk of pneumonia associated with inappropriate antipsychotic use in nursing home residents with PD based on the 2015 American Geriatrics Society (AGS) Beers criteria. The risk of pneumonia was significantly higher for inappropriate AAP users in comparison to the appropriate AAP users. In addition, multiple sensitivity confirmed a significantly higher risk of pneumonia for inappropriate vs. appropriate AAP users. The increased risk with inappropriate AAPs as a class was reflected in individual agents – users of risperidone and olanzapine had increased risks of pneumonia than quetiapine users. This investigation provided evidence-base regarding the safety of AAPs in elderly patients with PD.

Conflicts of interest

None.

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N/A.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.07.005.

References

AGS, 2015. American geriatrics society 2015 updated Beers criteria for potentially inappropriate medication use in older adults. J. Am. Geriatr. Soc. 63 (11), 2227–2246.
AHFS, 2016. Clinical Drug Information. http://www.ahfsdruginformation.com/, Accessed date: 27 June 2017.
AHRQ, 2013. MEPS Medical Conditions. https://meps.ahrq.gov/data_stats/download_data/pufs/h162/h162doc.pdf, Accessed date: 26 May 2017.
Almirall, J., Rofes, L., Serra-Prat, M., Icart, R., Palomera, E., Arreola, V., Clavé, P., 2013. Oropharyngeal dysphagia is a risk factor for community-acquired pneumonia in the elderly. Eur. Respir. J. 41 (4), 923–928.
Ballard, C., Isaacson, S., Mills, R., Williams, H., Corbett, A., Coate, B., Pahwa, R., Rascol, O., Burn, D.J., 2015. Impact of current antipsychotic medications on comparative mortality and adverse events in people with Parkinson disease psychosis. J. Am. Med. Dir. Assoc. 16 (10) 898. e891-898. e897.
Baser, O., 2006. Too much ado about propensity score models? Comparing methods of propensity score matching. Value Health 9 (6), 377–385.
Becker, S.O., Ichino, A., 2002. Estimation of average treatment effects based on propensity scores. STATA J. Promot. Commun. Stat. Stata 2 (4), 358–377.
Bieger, D., 1991. Neuropharmacologic correlates of deglutition: lessons from fictive swallowing. Dysphagia 6 (3), 147–164.
Brookhart, M.A., Schneeweiss, S., Rothman, K.J., Glynn, R.J., Avorn, J., Stürmer, T., 2006. Variable selection for propensity score models. Am. J. Epidemiol. 163 (12), 1149–1156.
De Lau, L.M., Breteler, M.M., 2006. Epidemiology of Parkinson's disease. Lancet Neurol. 5 (6), 525–535.
Dzahini, O., Singh, N., Taylor, D., Haddad, P., 2018. Antipsychotic drug use and pneumonia: systematic review and meta-analysis. J. Psychopharmacol. 32 (11), 1167–1181.
Frieling, H., Hillemacher, T., Ziegenbein, M., Neundörfer, B., Bleich, S., 2007. Treating dopamimetic psychosis in Parkinson's disease: structured review and meta-analysis. Eur. Neuropsychopharmacol. 17 (3), 165–171.
Goldman, J.G., Holden, S., 2014. Treatment of psychosis and dementia in Parkinson's disease. Curr. Treat. Options Neurol. 16 (3), 281.
González-Fernández, M., Gardyn, M., Wyckoff, S., Ky, P.K., Palmer, J.B., 2009. Validation of ICD-9 Code 787.2 for identification of individuals with dysphagia from administrative databases. Dysphagia 24 (4), 398–402.
Gross, R.D., Atwood Jr., C.W., Ross, S.B., Eichhorn, K.A., Olszewski, J.W., Doyle, P.J., 2008. The coordination of breathing and swallowing in Parkinson's disease. Dysphagia 23 (2), 136–145.
Hartmaier, S.L., Sloane, P.D., Guess, H.A., Koch, G.G., 1994. The MDS Cognition Scale: a valid instrument for identifying and staging nursing home residents with dementia using the Minimum Data Set. J. Am. Geriatr. Soc. 42 (11), 1173–1179.
Hollis, S., Campbell, F., 1999. What is meant by intention to treat analysis? Survey of published randomised controlled trials. BMJ 319 (7211), 670–674.
Jankovic, J., 2008. Parkinson's disease: clinical features and diagnosis. J. Neurol. Neurosurg. Psychiatry 79 (4), 368–376.
Kalf, J., De Swart, B., Bloem, B., Munneke, M., 2012. Prevalence of oropharyngeal dysphagia in Parkinson's disease: a meta-analysis. Park. Relat. Disord. 18 (4), 311–315.
Kim, K.Y., Bader, G.M., Kotlyar, V., Gropper, D., 2003. Treatment of delirium in older adults with quetiapine. J. Geriatr. Psychiatry Neurol. 16 (1), 29–31.
Kowal, S.L., Dall, T.M., Chakrabarti, R., Storm, M.V., Jain, A., 2013. The current and projected economic burden of Parkinson's disease in the United States. Movement disorders. Off. J. Mov. Disord. Soc. 28 (3), 311–318.
Kuehn, B.M., 2005. FDA warns antipsychotic drugs may be risky for elderly. JAMA 293 (20) 2462-2462.
Kuroki, T., Nagao, N., Nakahara, T., 2008. Neuropharmacology of second-generation antipsychotic drugs: a validity of the serotonin–dopamine hypothesis. Prog. Brain Res. 172, 199–212.
Lapane, K.L., Fernandez, H.H., Friedman, J.H., 1999. Prevalence, clinical characteristics, and pharmacologic treatment of Parkinson's disease in residents in long-term care facilities. Pharmacotherapy 19 (11), 1321–1327.
Lu, J., Shen, D., 2014. Survival Analysis Approaches and New Developments Using SAS. Pharmaceutical Industry SAS Users Group Proceedings.
Merrill, R.M., Lyon, J.L., Matiaco, P.M., 2013. Tardive and spontaneous dyskinesia incidence in the general population. BMC Psychiatry 13 (1), 152.
Miarons Font, M., Rofes Salsench, L., 2017. Antipsychotic medication and oropharyngeal dysphagia: systematic review. Eur. J. Gastroenterol. Hepatol. 29 (12), 1332–1339.
Micromedex, 2016. RED BOOK. http://www.micromedexsolutions.com/micromedex2/4.34.0/WebHelp/RED_BOOK/Introduction_to_REDB_BOOK_Online.htm, Accessed date: 27 June 2017.
Mitchell, S.L., Kiely, D.K., Kiel, D.P., Lipsitz, L.A., 1996. The epidemiology, clinical characteristics, and natural history of older nursing home residents with a diagnosis of Parkinson's disease. J. Am. Geriatr. Soc. 44 (4), 394–399.
Morris, J.N., Fries, B.E., Mehr, D.R., Hawes, C., Phillips, C., Mor, V., Lipsitz, L.A., 1994. MDS cognitive performance scale. J. Gerontol. 49 (4), M174–M182.
Morris, J.N., Fries, B.E., Morris, S.A., 1999a. Scaling ADLs within the MDS. J. Gerontol. Ser. A Biol. Sci. Med. Sci. 54 (11), M546–M553.
Nemeroff, C.B., 2005. Use of atypical antipsychotics in refractory depression and anxiety. J. Clin. Psychiatry 66, 13–21.
Nosè, M., Recla, E., Trifirò, G., Barbui, C., 2015. Antipsychotic drug exposure and risk of pneumonia: a systematic review and meta-analysis of observational studies. Pharmacoepidemiol. Drug Saf. 24 (8), 812–820.
Pontone, G.M., Bakker, C.C., Chen, S., Mari, Z., Marsh, L., Rabins, P.V., Williams, J.R., Bassett, S.S., 2016. The longitudinal impact of depression on disability in Parkinson disease. Int. J. Geriatr. Psychiatry 31 (5), 458–465.
ResDAC, 2013. CMS MDS and OASIS Assessment Data.
ResDAC, 2017. Sources and Use of Medicare Enrollment Information. http://resdac.umn.edu/sites/resdac.umn.edu/files/Sources%20and%20Use%20of%20Medicare%20Enrollment%20Information%20(Slides).pdf, Accessed date: 23 June 2017.
Schrag, A., 2004. Psychiatric aspects of Parkinson's disease. J. Neurol. 251 (7), 795–804.
Weerkamp, N.J., Tissingh, G., Poels, P.J., Zuidema, S.U., Munneke, M., Koopmans, R.T., Bloem, B.R., 2014. Parkinson disease in long term care facilities: a review of the literature. J. Am. Med. Dir. Assoc. 15 (2), 90–94.
Weintraub, D., Chen, P., Ignacio, R.V., Mamikonyan, E., Kales, H.C., 2011. Patterns and trends in antipsychotic prescribing for Parkinson disease psychosis. Arch. Neurol. 68 (7), 899.
Xu, J., Gong, D.D., Man, C.F., Fan, Y., 2014. Parkinson's disease and risk of mortality: meta-analysis and systematic review. Acta Neurol. Scand. 129 (2), 71–79.