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Antipsychotic drug dispensing in older adults with parkinsonism

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Abstract

Background: Antipsychotic drugs are commonly used to treat psychosis in patients with Parkinson's disease, however individuals with parkinsonism, particularly Parkinson's disease, present an additional layer of risk associated with antipsychotic use. The choice of antipsychotic is critical due to the potential for serious adverse effects.

Objective: To examine the frequency and pattern of antipsychotic prescribing to patients with Parkinson's disease and parkinsonism over time.

Methods: Individuals with parkinsonism aged 66 or older residing in community and long-term care settings in Ontario, Canada were studied in a retrospective cohort study from 2005 to 2013. Individuals were followed for prevalent and/or incident antipsychotic drug dispensing.

Results: In 2005, 15% of 22,837 individuals with prevalent parkinsonism were dispensed an antipsychotic drug. In 2013, 11% of 34,262 individuals with prevalent parkinsonism were dispensed antipsychotics. Primary care physicians represented the vast majority of prescribers. Of those receiving antipsychotics in 2013, 20% were dispensed a typical antipsychotic drug. Among individuals with incident parkinsonism, living in a nursing home, older age, male sex, a greater number of comorbidities and a prior diagnosis of dementia were significantly associated with an increased rate of receiving an antipsychotic during follow-up. Among those who received and antipsychotic, factors associated with typical antipsychotic exposure were absence of a prior diagnosis of dementia, higher Charlson comorbidity index, greater number of concurrent medications and more recent year of first parkinsonism diagnosis. Having seen a neurologist, psychiatrist or geriatrician was associated with a lower risk of being prescribed a typical antipsychotic.

Conclusions and Relevance: A substantial proportion of individuals with parkinsonism are exposed to antipsychotic drugs, and a substantial proportion of this use is accounted for by typical antipsychotics. Given the risks of prescribing these drugs to individuals with parkinsonism, education of prescribers, particularly primary care physicians, is needed.

Background

Parkinsonism is a term used to describe a clinical syndrome consisting of bradykinesia accompanied by one of either rigidity or tremor at rest. Parkinsonism can be caused by a number of processes, including neurodegenerative disorders, drugs and cerebrovascular disease. The most common cause of parkinsonism is Parkinson's disease, which is a neurodegenerative disorder whose cardinal motor characteristic is parkinsonism. The majority of patients with Parkinson's disease eventually develop dementia. A closely related, if not identical neurodegenerative disease, is dementia with Lewy bodies, in which dementia precedes parkinsonism.

Antipsychotic medications are an important drug class for the treatment of patients with Parkinson's disease and dementia with Lewy bodies in cases where hallucinations and psychosis can be disabling.[1] However, these drugs have been associated with mortality and morbidity in this population when compared with individuals not treated with antipsychotics,[2, 3] therefore an understanding of the indications for use, and a careful consideration of risks and benefits has been advised for the concurrent prescription of antipsychotics in people with parkinsonism.

The excess morbidity and mortality associated with antipsychotic use in people with parkinsonism may be related to their propensity to worsen parkinsonism and cause sedation, among other effects.[4] Antipsychotics have traditionally been divided into two groups: a) typical antipsychotics with high affinity for dopamine D2 receptors and a higher potential for causing associated adverse effects including parkinsonism; and b) atypical antipsychotics with a lower affinity at these receptors and a lower potential for causing or worsening parkinsonism. Among the antipsychotics available for use in Canada, quetiapine and clozapine are considered the least detrimental.[1, 5] Due to the risk of neutropenia with clozapine, quetiapine has been considered the first line agent although very recently newer atypical antipsychotics are becoming available which may also have an acceptable risk profile.[6]

While the appropriateness of use of antipsychotics in clinical settings such as behavioural and psychological symptoms of dementia has received more scrutiny in recent years, there has been little attention to how patterns of antipsychotic use have changed over time in patients with parkinsonism. We have previously examined patterns of antipsychotic dispensing to patients with parkinsonism in the Canadian province of Ontario over the years 1998-2003.[7] We found that of those starting dopaminergic agents, 35% used antipsychotic drugs within 7 years. Furthermore, in 2002, 9% of the antipsychotics used in a cohort of individuals with pre-existing parkinsonism were typical antipsychotics. Similarly, van de Vijver found a high

proportion of patients with Parkinson's disease receiving typical antipsychotics.[8] These results highlighted the need for a better understanding of risks and benefits by clinicians who prescribe these drugs.

In the current study, our objective was to examine changes in patterns of antipsychotic use among persons with parkinsonism from 2005 to 2013 including the type of antipsychotics being dispensed, individual clinical and demographic factors associated with exposure and the characteristics of the prescribing physician.

Methods

Sources of Data

Approximately 14 million residents of Ontario, Canada are Canadian citizens, permanent residents or landed immigrants who are insured under a universal health insurance plan that includes physician and hospital services. Individuals aged 65 years or older are additionally eligible for prescription drug coverage. Information on clinical diagnoses was obtained from: 1) The Canadian Institute for Health Information Discharge Abstract Database which records diagnoses contributing to hospitalizations and procedures performed during hospital stays, 2) The National Ambulatory Care Reporting System consisting of data on emergency department visits (2000 – present), 3) The Ontario Health Insurance Plan physician billing database consisting of information on inpatient and outpatient physician services, including a physician-assigned diagnosis code for each visit. The Registered Persons Database contains date of birth, sex and dates of death. The Ontario Drug Benefit (ODB) database (1992–present) records data on all outpatient prescription claims paid for by the provincial drug benefit plan. These datasets were linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES).

Inclusion criteria

We identified both prevalent and incident individuals with parkinsonism aged 66 years of age or older in each year between 2005 and 2013 according to an algorithm shown to have a sensitivity of 72% and a specificity of 99% in these databases.[9] One ICD diagnostic code for Parkinson's disease and 1 anti-parkinson drug prescription dispensed within 6 months of each other were required. At least one of the elements must have been satisfied within the year (July 1 – June 30, e.g. July 1 2004 through June 30 2005 for 2005) in order for the individual to be included in the prevalent parkinsonism cohort for that year. Although the diagnostic codes are for Parkinson's disease, we use the term parkinsonism because of the inability to reliably distinguish Parkinson's disease from other causes of parkinsonism in these databases. In a chart review validation study of the performance of the criteria, 83% of the individuals had Parkinson's disease and 17% had other causes of parkinsonism.[9] Incident cases were those that did not qualify for a diagnosis of parkinsonism based on these criteria in the preceding year. We excluded individuals who had an antipsychotic dispensed prior to the incident Parkinson's disease diagnostic code and individuals who had a diagnostic code for psychosis in the 5 years prior to the incident parkinsonism diagnostic code in order to minimize the inclusion of drug-induced parkinsonism. The index date for incident cases was the date of the first qualifying diagnostic code. In our prevalent cohort we did not specify the temporal relationship between antipsychotic exposure and the diagnosis of parkinsonism within that year or prior to that year. Understanding the temporal relationship

between first antipsychotic prescription and diagnosis of parkinsonism is only possible for a subset of our sample, whose first diagnosis of parkinsonism was after the age of 65 when drug dispensing information becomes available. We did not reduce our prevalent parkinsonism cohort to this subset in order to study the broader spectrum of individuals with any (and longer) disease duration, in whom antipsychotic use is more likely. To understand the implications of this we evaluated the proportion of those individuals over age 65 in whom the first antipsychotic prescription preceded the diagnosis of parkinsonism.

Descriptive variables and covariates

Quintiles of median neighbourhood income were inferred from postal codes. An individual was classified as residing in a nursing home if they did so for any period within the prevalence year. The Charlson Comorbidity Index[10] was used as a measure of illness complexity and calculated by looking back 5 years for the relevant diagnostic codes**.** Dementia was identified based on at least one code for dementia from a hospitalization, 3 physician claim records within a 2 year period or one prescription drug reimbursement record for a cholinesterase inhibitor.[11]

Outcome of interest

We examined both incident and prevalent antipsychotic use in order to understand both the first choice of antipsychotic drug in this sample and the full spectrum of use. At least one antipsychotic drug dispensed between July 1 and June 30 was considered prevalent use for that year. Incident use was examined in the incident parkinsonism cohort and was taken to be the first antipsychotic prescribed following the first diagnostic code for Parkinson's disease and in the absence of any antipsychotic use in the 5 years prior to the first diagnostic code for Parkinson's disease. The specific antipsychotic drug and the antipsychotic drug class (typical vs atypical antipsychotic) were recorded. Clozapine is available in Ontario but it is not reimbursed through the Ontario drug benefit program; therefore its use is not reliably captured in the ODB data. Clozapine use was therefore not included in the analysis.

Statistical analysis

In the prevalent parkinsonism cohort, the frequency of antipsychotic use and the proportion dispensed typical and atypical antipsychotics was described for 2005 and 2013. Proportions were compared between these two years using Chi-square tests. To examine factors associated with the rate of incident antipsychotic exposure, the cohort was restricted to incident cases of parkinsonism. Within this incident cohort, a survival analysis of

time to AP use was performed using a cause-specific hazard model[12] for the outcome of first antipsychotic dispensing. Follow-up was through first antipsychotic dispensing, death or the end date of March 31, 2015, whichever came first. Death was treated as a competing risk. Independent variables were age, sex, residence in a nursing home, Charlson comorbidity index, neighborhood income quintile and a history of dementia within the last 5 years. A secondary analysis was undertaken, fitting the model separately within each of two strata:residence in or outside of a nursing home within 6 months of the first diagnosis of parkinsonism. Cumulative incidence functions (CIFs) were used to estimate the cumulative incidence of AP use over time, treating death prior to AP use as a competing risk. The CIF analyses were stratified by LTC status.

To examine factors associated with antipsychotic type (typical or atypical) we performed a logistic regression analysis restricting the incident parkinsonism cohort to those individuals who received an antipsychotic during follow-up. The first antipsychotic prescription dispensed after the index date defined the antipsychotic type. Individuals receiving a typical and an atypical antipsychotic on the first dispensing date were excluded. Candidate variables were the same as those included in the survival analysis described above and additionally the number of concomitant medications, the specialty of the physician prescribing the antipsychotic, type of physician seen prior to antipsychotic prescribing (neurologist, psychiatrist and/or geriatrician vs none of these) and years (categorized as 2005-2009 or 2010-2014). A secondary analysis was performed stratified by nursing home residence at the index date.

Institutional review: ICES is a prescribed entity under section 45 of Ontario's Personal Health Information Protection Act. Section 45 authorizes ICES to collect personal health information, without consent, for the purpose of analysis or compiling statistical information with respect to the management of, evaluation or monitoring of, the allocation of resources to or planning for all or part of the health system. Projects conducted under section 45, by definition, do not require review by a Research Ethics Board. This project was conducted under section 45, and approved by ICES' Privacy and Compliance Office.

Results:

Table 1 shows the characteristics and antipsychotic exposure in the prevalent parkinsonism cohorts in 2005 and 2013 stratified by sex and residence in a nursing home. In 2005, 22,837 individuals over the age of 66 met the criteria for prevalent parkinsonism, rising to 34,262 by 2013. The proportion of individuals living in a nursing home was 20% in 2005 and 14% in 2013. In the subset of these individuals with first parkinsonism diagnosis after age 65, an antipsychotic was dispensed before the first diagnosis of parkinsonism in 9% in 2005 and 7% in 2013.

Antipsychotic prescribing, 2005 (Table 1)

Within the prevalent parkinsonism cohort, 15% were dispensed an antipsychotic drug within 6 months of January 1st 2005. Of those receiving antipsychotics, 22% were dispensed a typical antipsychotic drug. The proportion receiving any antipsychotic drug was higher in nursing home residents (38% in nursing home residents vs. 9% in community-dwelling individuals, Chi-square test $p<0.0001$, df=1) but the proportion of individuals receiving a typical antipsychotic was similar in both settings and between the sexes. Among the atypical antipsychotics, 49% of prescriptions dispensed were for quetiapine.

Primary care physicians represented the vast majority of prescribers of the dispensed antipsychotics, particularly in nursing homes. Outside of the nursing home setting, 31% of individuals prescribed antipsychotics had seen a neurologist or a psychiatrist in the preceding 6 months. In 27% of cases a neurologist or a psychiatrist was the physician who prescribed the antipsychotic therapy.

Antipsychotic prescribing, 2013 (Table 1)

By 2013, the proportion of individuals dispensed an antipsychotic within 6 months of January 1st had decreased to 11% compared with 15% in 2005 (Chi square $p<0.001$, df=1). Of those receiving antipsychotics, 20% were dispensed a typical antipsychotic drug. The proportion of quetiapine prescriptions among atypical antipsychotics had risen to 72% (Chi square $p<0.001$, df=1 $p<0.001$ compared with 49% in 2005). The distributions of type of assessing and prescribing physician changed little from 2005.

Incident Parkinsonism Cohort (Table 2)

The data in the incident parkinsonism cohort record the first antipsychotic drug dispensed and reflect a group of individuals where the Parkinson's disease diagnostic codes precede antipsychotic dispensing. We identified a total of 62,208 cases of incident parkinsonism across all years between 2005 and 2013. Among these, 4,697 resided in nursing homes. Median age was 77 years (interquartile range 71, 82) and 52% were female. Median follow-up among those with antipsychotic exposure was 42.8 months (interquartile range 22.0, 71.6). During follow-up 9,936 individuals were dispensed an antipsychotic drug. The cumulative incidence functions for antipsychotic dispensing and the competing risk of death are described in the Figure. The estimated cumulative incidence of antipsychotic dispensing was 14% at 5 years and 24% at 10 years for those who were not nursing home residents. The estimated cumulative incidence of antipsychotic dispensing was 30% at 5 years and 32% at 10 years for nursing home residents. In this incident cohort the patterns were similar to those seen in the prevalent cohort: among those entering the cohort in 2013 the first antipsychotic prescribed was quetiapine in 48% of individuals and was a typical antipsychotic in 20% of individuals.

Factors associated with antipsychotic exposure (Tables 3 and 4)

In the incident parkinsonism cohort, living in a nursing home, older age, male sex, a greater number of comorbidities and a prior diagnosis of dementia were statistically significantly associated with an increased rate of receiving an antipsychotic in the multivariable cause-specific hazard model. Being in the highest income quintile was associated with a decreased rate of receiving an antipsychotic. When the analysis was stratified by residence in a nursing home, results were similar to the unstratified analysis in the subgroup not residing in nursing homes. Within the nursing home cohort age was not significantly associated with the rate of antipsychotic prescribing. The magnitude of these associations was generally moderate with the exception of a prior history of dementia, where the association was of greater magnitude; the associated hazard ratios are shown in Table 3.

Among those exposed to an antipsychotic drug during follow-up, risk factors for typical antipsychotic exposure (compared with atypical antipsychotic use) were absence of a prior diagnosis of dementia, higher Charlson comorbidity index and greater number of concurrent medications in the multivariable logistic regression model (Table 4). Having seen a neurologist, psychiatrist or geriatrician was associated with a lower risk of being prescribed a typical antipsychotic. Finally, more recent year of first parkinsonism diagnosis (in the years 2010-2014 compared with 2005-2009) was associated with a higher risk of receiving a typical antipsychotic. The magnitude of these associations was generally modest with the exception again of the presence of dementia which was associated with a halving of the risk of typical antipsychotic prescribing, and seeing a

neurologist, psychiatrist or geriatrician which was associated with a 2/3 lower risk of typical antipsychotic prescribing. These relationships were similar inside and outside of nursing homes (Supplementary Table).

Discussion

We found that antipsychotics are commonly prescribed to older adults with parkinsonism in Ontario, with over 10% of individuals over the age of 65 receiving a prescription for these drugs as recently as 2013 and much higher rates within nursing homes. This higher exposure in nursing home residents likely reflects differences in the population treated in this setting, where behavioral and psychological symptoms of dementia are highly prevalent. The trend over time is for a moderate reduction in the proportion of individuals receiving these drugs, both inside and outside of nursing homes.

Individuals with parkinsonism, particularly Parkinson's disease, present an additional layer of risk associated with antipsychotic use. Not only do the above considerations concerning sedation and QT prolongation apply, but this population is considered to be at high risk of motor functioning worsening in addition to pre-existing parkinsonism when exposed to typical antipsychotics. Such worsening has implications not only for quality of life but also added risk of falls, leading to fractures and death. Use of these drugs is therefore strongly discouraged in the people with parkinsonism.[13] Despite this, we found that 1 in 5 individuals with parkinsonism dispensed an antipsychotic received a typical antipsychotic in both 2005 and 2013. This analysis includes individuals whose antipsychotic treatment predated parkinsonism, with the possibility of drug-induced parkinsonism. In the validation study of this definition for parkinsonism in this population, 6% of individuals were determined upon medical chart review to have drug-induced parkinsonism.[9] Our analysis suggest that this is the case for approximately 7-9% of individuals in our cohorts. Importantly, therefore, even in the incident parkinsonism cohort where the antipsychotic prescribing postdates the first diagnostic code for Parkinson's disease, the proportion of first antipsychotics dispensed that were typical antipsychotics was *greater* in the more recent years when adjusting for other risk factors.

Within the class of atypical antipsychotics not all drugs have the same propensity to cause or worsen parkinsonism. Clozapine and quetiapine are considered the drugs of first choice in this population, and risperidone and olanzapine have been shown to have the potential to worsen motor impairment.[5] Despite this, risperidone and olanzapine comprised a substantial proportion of recorded antipsychotic exposure in 2013. There is clearly room for improvement.

These data point to a need for education of physicians treating patients with parkinsonism to optimize treatment. Our results indicate that primary care physicians are the main prescribers of these drugs, both

inside and outside of the nursing home setting. Not only are they the prescribers, but the older adults they are caring for have usually not seen a specialist to guide treatment in the last 6 months. If educational efforts are to have an impact, therefore, they need to be directed towards primary care physicians. This conclusion is supported by the finding that the risk of typical antipsychotic exposure was 3 times greater among those who had not seen a neurologist, psychiatrist or geriatrician in the preceding 6 months. . Another opportunity for improved outcomes in patients with parkinsonism may be greater involvement of specialists; in the United States neurological care for patients with Parkinson's disease is associated with longer survival, longer time to nursing home placement and lower incidence of hip fracture.[14]

Not unexpectedly, we found that older residents, with more comorbidities and living in nursing homes were more likely to be dispensed antipsychotic drugs. The reason underlying the association of antipsychotic dispensing with male sex is unclear. The same was found in our prior study in the same population[7]. We are not aware of any other reports of sex differences in antipsychotic prescribing in Parkinson's disease or parkinsonism. In contrast with our results, in a cohort of women over age 65 in New Zealand[15] and the UK[16] had a higher risk of being prescribed an antipsychotic. In the elderly living in the province of Manitoba, Canada, male sex was associated with sub-optimal use of antipsychotics, defined as high dose and in combination with benzodiazepines.[17] Specifically among individuals with Alzheimer's disease, a large study of psychotropic drug prescribing in the US and New Zealand did not find sex differences in antipsychotic prescribing. Male sex as a potential risk factor for antipsychotic exposure in individuals with parkinsonism deserves study in other populations. This may be particularly important since male sex has been associated with a higher likelihood of severe adverse events after initiation of antipsychotics,[18] In addition the risk of Parkinson's disease is higher in men, so the additional association of antipsychotic prescribing with male sex only increases the burden of any resulting morbidity.

These patterns of use of antipsychotic drugs are occurring in the context of published studies reporting the association between mortality and morbidity and antipsychotic use in individuals with dementia.[4, 19] Safety reports emerging in the early 2000s from re-examination of clinical trial results highlighted a higher risk of mortality associated with both typical and atypical antipsychotic drug use. These reports led to warnings issued by national agencies in both Europe and North America. Antipsychotic drug use has been associated with higher risk of all-cause mortality,[19, 20] falls, fractures, cerebrovascular and cardiovascular events among patients with dementia[4, 21] Proposed explanations for the higher mortality rates include QT prolongation leading to cardiac events[22] and sedation leading to falls. The highest risks have been found with typical (conventional) compared with atypical antipsychotics.[19, 20].

Compared with our results, greater reductions in antipsychotic use among individuals with dementia (with or without parkinsonism) have been found in other studies. For example, in the UK, the prevalence of antipsychotic use at the first diagnosis of dementia decreased from 20% to 7% between 1995 and 2011, with concomitant increases in the use of antidepressants and anxiolytics.[23] Similar findings were noted in Denmark, where prevalence of antipsychotic drug use decreased from 31.3% in 2000 to 20.4% in 2012.[24] However, much more modest changes in antipsychotic prescribing were noted over the period 2004 to 2013 in long term care residents with dementia in Ontario, Canada.[25]

Both in and out of nursing homes older age, more comorbid illness and more concomitant medications were independently associated with a higher chance of receiving a typical antipsychotic. These findings raise the concern that attention to best practice principles of antipsychotic prescribing may be particularly poor in the most ill patients who, like the oldest old, are likely at highest risk for adverse effects of these drugs.[26] Considering alternatives to antipsychotics such as behavioural interventions where possible can minimize the negative impact of these drugs in these groups of individuals.

A strength of our study is the fact that it has a large sample which provides the opportunity for an unselected picture of antipsychotic prescribing. It must be kept in mind that we lack data on clozapine because of an alternate method of reimbursement of clozapine prescriptions in Ontario. Due to the concern about neutropenia, however, there is a requirement for surveillance of white blood cell counts during treatment with clozapine, prescribing of this drug is limited. Published information from the United States indicate that in 2011 clozapine represented less than 2%of antipsychotic prescribing to patients with Parkinson's disease.[27] We must also acknowledge that parkinsonism is identified by an algorithm based on diagnostic codes that has imperfect sensitivity (approximately 70%). Thus we will be missing not only individuals who remain undiagnosed but also individuals who were diagnosed but whose physician visits were not given a diagnostic code for parkinsonism. It is likely that the latter group have other comorbid conditions that take priority at the outpatient visit, to which is attributed only a single diagnostic code. Our multivariable analysis suggests that these individuals are more likely to receive antipsychotics and thus our results may underestimate true rates of antipsychotic use in this population. Another limitation is the lack of information on the indication for antipsychotic prescribing and the alternative strategies that have been used to manage symptoms. Antipsychotics, and specifically the use of typical antipsychotics is common in the context of acute delirium.[28] However alternative strategies are needed to avoid additional comorbidity in this population. For example, The

National Institute for Health and Care Excellence (UK) guidelines for health and care excellence guidance "Delerium: diagnosis, prevention and management" recommend starting with non-pharmacological solutions and if necessary, the use of typical or atypical antipsychotics. Specifically, they recommend to "Use antipsychotic drugs with caution or not at all for people with conditions such as Parkinson's disease or dementia with Lewy bodies" [29] Canadian guidelines specifically state that haloperidol is not recommended if there is pre-existing Parkinson disease or Lewy body dementia.[30] Worsening parkinsonism has several possible serious consequences including increasing length of stay, risk of falls and dysphagia with aspiration. A prospective study examining the decision-making process for antipsychotic prescribing practices would be an important next step toward achieving improvements in care for this population.

In this large study our data indicate that antipsychotic prescribing patterns have changed little within the past 10 years and that typical and atypical antipsychotics associated with worsening parkinsonism continue to be frequently used. Neurologists and psychiatrists are involved in the management of the patients' antipsychotic medications in a minority of cases. Further education of primary care physicians regarding how best to choose mediations in patients with parkinsonism and particularly on the need to minimize the use of antipsychotic therapy could improve the health of the older adults with Parkinson's disease and parkinsonism.

References

1. Armstrong MJ, Weintraub D. The Case for Antipsychotics in Dementia with Lewy Bodies. Movement Disorders Clinical Practice 2017;4(1):32-35.
2. Weintraub D, Chiang C, Kim HM, et al. Association of Antipsychotic Use With Mortality Risk in Patients With Parkinson Disease. JAMA neurology 2016;73(5):535-541.
3. Weintraub D, Chiang C, Kim HM, et al. Antipsychotic Use and Physical Morbidity in Parkinson Disease. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry 2017;25(7):697-705.

4. Lapeyre-Mestre M. A Review of Adverse Outcomes Associated with Psychoactive Drug Use in Nursing Home Residents with Dementia. Drugs Aging 2016;33(12):865-888.
5. Seppi K, Weintraub D, Coelho M, et al. The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the non-motor symptoms of Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society 2011;26 Suppl 3:S42-80.
6. Divac N, Stojanovic R, Savic Vujovic K, Medic B, Damjanovic A, Prostran M. The Efficacy and Safety of Antipsychotic Medications in the Treatment of Psychosis in Patients with Parkinson's Disease. Behavioural neurology 2016;2016:4938154.
7. Marras C, Kopp A, Qiu F, et al. Antipsychotic use in older adults with Parkinson's disease. Movement Disorders 2007;22(3):319-323.
8. van de Vijver DA, Roos RA, Jansen PA, Porsius AJ, de Boer A. Antipsychotics and Parkinson's disease: association with disease and drug choice during the first 5 years of antiparkinsonian drug treatment. European Journal of Clinical Pharmacology 2002;58(2):157-161.
9. Butt DA, Tu K, Young J, et al. A validation study of administrative data algorithms to identify patients with Parkinsonism with prevalence and incidence trends. Neuroepidemiology 2014;43(1):28-37.
10. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45(6):613-619.
11. Jaakkimainen RL, Bronskill SE, Tierney MC, et al. Identification of Physician-Diagnosed Alzheimer's Disease and Related Dementias in Population-Based Administrative Data: A Validation Study Using Family Physicians' Electronic Medical Records. Journal of Alzheimer's disease : JAD 2016;54(1):337-349.
12. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. Circulation 2016;133(6):601-609.
13. McKeith I, Fairbairn A, Perry R, Thompson P, Perry E. Neuroleptic sensitivity in patients with senile dementia of Lewy body type. Bmj 1992;305(6855):673-678.
14. Willis A, Schootman M, Evanoff B, Perlmutter J, Racette B. Neurologist care in Parkinson disease: A utilization, outcomes, and survival study. Neurology 2011;77(9):851-857.
15. Jackson G, Gerard C, Minko N, Parsotam N. Variation in benzodiazepine and antipsychotic use in people aged 65 years and over in New Zealand. N Z Med J2014. p. 67-78.
16. Shah SM, Carey IM, Harris T, DeWilde S, Cook DG. Antipsychotic prescribing to older people living in care homes and the community in England and Wales. Int J Geriatr Psychiatry 2011;26(4):423-434.
17. Alessi-Severini S, Dahl M, Schultz J, Metge C, Raymond C. Prescribing of psychotropic medications to the elderly population of a Canadian province: a retrospective study using administrative databases. PeerJ 2013; 1:e168.
18. Rochon PA, Gruneir A, Gill SS, et al. Older men with dementia are at greater risk than women of serious events after initiating antipsychotic therapy. J Am Geriatr Soc 2013;61(1):55-61.
19. Gill SS, Bronskill SE, Normand SL, et al. Antipsychotic drug use and mortality in older adults with dementia.[summary for patients in Ann Intern Med. 2007 Jun 5;146(11):I52; PMID: 17548405]. Annals of Internal Medicine 2007;146(11):775-786.
20. Rochon PA, Normand SL, Gomes T, et al. Antipsychotic therapy and short-term serious events in older adults with dementia. Archives of Internal Medicine 2008;168(10):1090-1096.
21. Wooltorton E. Olanzapine (Zyprexa): increased incidence of cerebrovascular events in dementia trials. Canadian Medical Association Journal 2004;170(9):1395.
22. Danielsson B, Collin J, Jonasdottir Bergman G, Borg N, Salmi P, Fastbom J. Antidepressants and antipsychotics classified with torsades de pointes arrhythmia risk and mortality in older adults - a Swedish nationwide study. British journal of clinical pharmacology 2016;81(4):773-783.
23. Martinez C, Jones RW, Rietbrock S. Trends in the prevalence of antipsychotic drug use among patients with Alzheimer's disease and other dementias including those treated with antidementia drugs in the community in the UK: a cohort study. BMJ Open 2013;3(1).
24. Norgaard A, Jensen-Dahm C, Gasse C, Hansen HV, Waldemar G. Time trends in antipsychotic drug use in patients with dementia: a nationwide study. Journal of Alzheimer's disease : JAD 2016;49(1):211-220.
25. Vasudev A, Shariff SZ, Liu K, et al. Trends in Psychotropic Dispensing Among Older Adults with Dementia Living in Long-Term Care Facilities: 2004–2013. The American Journal of Geriatric Psychiatry 2015;23(12):1259-1269.

26. Brahma DK, Wahlang JB, Marak MD, Ch. Sangma M. Adverse drug reactions in the elderly. Journal of Pharmacology & Pharmacotherapeutics 2013;4(2):91-94.
27. Weintraub D, Chen P, Ignacio RV, Mamikonyan E, Kales HC. Patterns and trends in antipsychotic prescribing for Parkinson disease psychosis. Arch Neurol 2011;68(7):899-904.
28. Nguyen PV-Q, Malachane A, Minh TTV. Antipsychotic prescription patterns in the management of delirium symptoms in hospitalized elderly patients. Proceedings of Singapore Healthcare 2017;26(4):230-234.
29. Delerium Guideline Development Group. Delerium: diagnosis, prevention and management. National Institute for Health and Care Excellence Guidance: National Institute for Health Care Excellence (UK); 2010. https://www.nice.org.uk/guidance/cg103/chapter/1-Guidance#treating-delirium
30. Gage L, Hogan DB. CCSMH Guideline Update: The Assessment and Treatment of Delirium. Toronto: Canadian Coalition for Seniors' Mental Health (CCSMH); 2014.

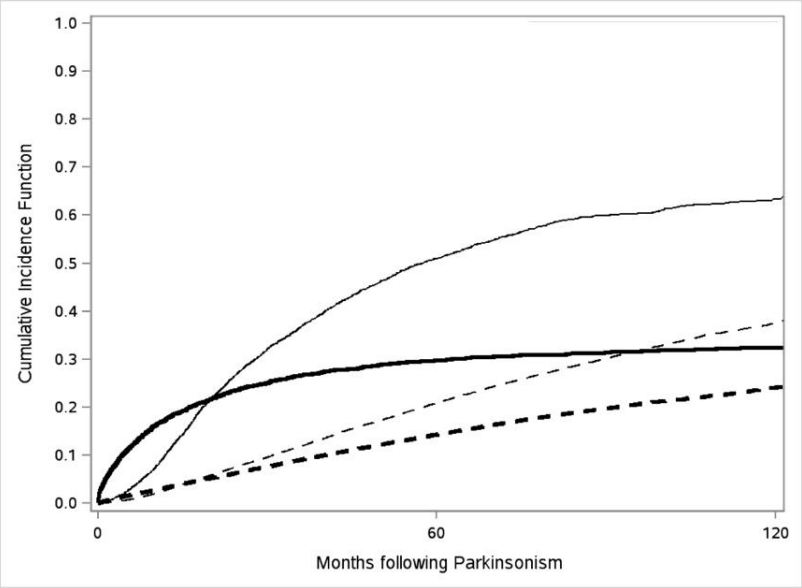

Figure Title: Estimated cumulative incidence function for antipsychotic dispensing and death.

Figure legend: Incidence is stratified by residence in a nursing home (=long term care, LTC) at the start of observation. Solid lines are for individuals in nursing homes at the index date, dashed lines are for individuals living in the community. Bold lines are for the outcome of antipsychotic dispensing, non-bold lines are for the outcome of death.

Table 1: Demographics and antipsychotic prescribing in the prevalent parkinsonism cohort, stratified by residential setting, sex and year

		2005				2013			
		Female		Male		Female		Male	
		NH N=2,727	Community N=8,880	NH N=1,915	Community N=9,315	NH N=2,746	Community N=14,898	NH N=2,072	Community N=14,546
Age on Jan 1st	Mean ± SD	82.73 ± 6.53	77.10 ± 6.67	80.93 ± 6.44	76.30 ± 6.31	83.92 ± 6.73	77.23 ± 7.21	81.30 ± 6.80	76.55 ± 6.75
Income Quintile	*missing*	15 (0.6%)	45 (0.5%)	16 (0.8%)	62 (0.7%)	20 (0.7%)	63 (0.4%)	17 (0.8%)	57 (0.4%)
	1 (low)	665 (24.4%)	1,915 (21.6%)	413 (21.6%)	1,666 (17.9%)	658 (24.0%)	3,021 (20.3%)	484 (23.4%)	2,414 (16.6%)
	2	541 (19.8%)	1,853 (20.9%)	385 (20.1%)	1,936 (20.8%)	507 (18.5%)	3,069 (20.6%)	380 (18.3%)	2,864 (19.7%)
	3	494 (18.1%)	1,749 (19.7%)	361 (18.9%)	1,801 (19.3%)	521 (19.0%)	2,904 (19.5%)	395 (19.1%)	2,831 (19.5%)
	4	575 (21.1%)	1,657 (18.7%)	392 (20.5%)	1,805 (19.4%)	534 (19.4%)	2,995 (20.1%)	409 (19.7%)	3,036 (20.9%)
	5 (high)	437 (16.0%)	1,661 (18.7%)	348 (18.2%)	2,045 (22.0%)	506 (18.4%)	2,846 (19.1%)	387 (18.7%)	3,344 (23.0%)
Charlson Comorbidity Index	0	638 (23.4%)	1,978 (22.3%)	404 (21.1%)	1,993 (21.4%)	590 (21.5%)	3,176 (21.3%)	397 (19.2%)	2,795 (19.2%)
	1	649 (23.8%)	1,001 (11.3%)	438 (22.9%)	1,118 (12.0%)	589 (21.4%)	1,558 (10.5%)	448 (21.6%)	1,457 (10.0%)
	2+	622 (22.8%)	1,203 (13.5%)	563 (29.4%)	1,619 (17.4%)	704 (25.6%)	2,222 (14.9%)	662 (31.9%)	2,666 (18.3%)
	No hospitalization	818 (30.0%)	4,698 (52.9%)	510 (26.6%)	4,585 (49.2%)	863 (31.4%)	7,942 (53.3%)	565 (27.3%)	7,628 (52.4%)
Parkinsonism Duratio	<1	650 (23.8%)	3,229 (36.4%)	436 (22.8%)	3,191 (34.3%)	513 (18.7%)	4,362 (29.3%)	384 (18.5%)	4,317 (29.7%)

n (years)									
	1 to <3	455 (16.7%)	1,826 (20.6%)	355 (18.5%)	1,997 (21.4%)	480 (17.5%)	3,222 (21.6%)	378 (18.2%)	3,208 (22.1%)
	3 to <5	395 (14.5%)	1,261 (14.2%)	258 (13.5%)	1,352 (14.5%)	370 (13.5%)	2,394 (16.1%)	328 (15.8%)	2,286 (15.7%)
	5+	1,227 (45.0%)	2,564 (28.9%)	866 (45.2%)	2,775 (29.8%)	1,383 (50.4%)	4,920 (33.0%)	982 (47.4%)	4,735 (32.6%)
Antiparkinson Prescribing Physician Specialty	No antiparkinson drug use	294 (10.8%)	1,339 (15.1%)	238 (12.4%)	1,397 (15.0%)	211 (7.7%)	1,512 (10.1%)	205 (9.9%)	1,882 (12.9%)
	Neurologist (N)	681 (25.0%)	2,981 (33.6%)	566 (29.6%)	3,746 (40.2%)	878 (32.0%)	4,695 (31.5%)	785 (37.9%)	6,172 (42.4%)
	Psychiatrist (P)	43 (1.6%)	127 (1.4%)	10 (0.5%)	106 (1.1%)	28 (1.0%)	227 (1.5%)	14 (0.7%)	179 (1.2%)
	Geriatrician (G)	73 (2.7%)	164 (1.8%)	61 (3.2%)	204 (2.2%)	88 (3.2%)	295 (2.0%)	77 (3.7%)	319 (2.2%)
	N, P and/or G	54 (2.0%)	230 (2.6%)	53 (2.8%)	277 (3.0%)	74 (2.7%)	172 (1.2%)	65 (3.1%)	211 (1.5%)
	Primary care physician only	1,461 (53.6%)	3,167 (35.7%)	884 (46.2%)	2,526 (27.1%)	1,441 (52.5%)	7,264 (48.8%)	910 (43.9%)	4,934 (33.9%)
	Other	121 (4.4%)	872 (9.8%)	103 (5.4%)	1,059 (11.4%)	26 (0.9%)	733 (4.9%)	16 (0.8%)	849 (5.8%)
Antipsychotic Exposure		979 (35.9%)	833 (9.4%)	778 (40.6%)	789 (8.5%)	847 (30.8%)	1,106 (7.4%)	754 (36.4%)	1,065 (7.3%)
Antipsychotic Drug Type	Typical antipsychotic	183 (18.7%)	283 (34.0%)	133 (17.1%)	150 (19.0%)	102 (12.0%)	209 (18.9%)	115 (15.3%)	122 (11.5%)
	Atypical	889	598	729 (93.7%)	673	808 (95.4%)	948 (85.7%)	714 (94.7%)	976 (91.6%)

	antipsychotic	(90.8%)	(71.8%)		(85.3%)				
	Aripiprazole	0	0	0	0	15 (1.8%)	44 (4.0%)	17 (2.3%)	39 (3.7%)
	Olanzapine	212 (21.7%)	139 (16.7%)	163 (21.0%)	131 (16.6%)	109 (12.9%)	130 (11.8%)	115 (15.3%)	102 (9.6%)
	Paliperidone*								
	Quetiapine	387 (39.5%)	273 (32.8%)	354 (45.5%)	404 (51.2%)	551 (65.1%)	662 (59.9%)	524 (69.5%)	745 (70.0%)
	Risperidone	418 (42.7%)	251 (30.1%)	339 (43.6%)	205 (26.0%)	242 (28.6%)	190 (17.2%)	171 (22.7%)	156 (14.6%)
	Ziprasidone*								
Antipsychotic Prescribing Physician Specialty	Neurologist (N)	45 (4.6%)	85 (10.2%)	60 (7.7%)	135 (17.1%)	60 (7.1%)	136 (12.3%)	91 (12.1%)	229 (21.5%)
	Psychiatrist (P)	57 (5.8%)	131 (15.7%)	36 (4.6%)	86 (10.9%)	55 (6.5%)	192 (17.4%)	48 (6.4%)	144 (13.5%)
	Geriatrician (G)	29 (3.0%)	46 (5.5%)	33 (4.2%)	69 (8.7%)	50 (5.9%)	72 (6.5%)	31 (4.1%)	84 (7.9%)
	N, P and/or G	6 (0.6%)	24 (2.9%)	8 (1.0%)	31 (3.9%)	17 (2.0%)	22 (2.0%)	22 (2.9%)	27 (2.5%)
	Primary care phyisician only	787 (80.4%)	464 (55.7%)	592 (76.1%)	367 (46.5%)	654 (77.2%)	633 (57.2%)	550 (72.9%)	516 (48.5%)
	Other	55 (5.6%)	83 (10.0%)	49 (6.3%)	101 (12.8%)	11 (1.3%)	51 (4.6%)	12 (1.6%)	65 (6.1%)

Type of Physician seen 6 months prior antipsychotic exposure	*No physician visit*	22 (2.2%)	28 (3.4%)	8 (1.0%)	17 (2.2%)	8 (0.9%)	33 (3.0%)	10 (1.3%)	20 (1.9%)
	Neurologist (N)	99 (10.1%)	133 (16.0%)	120 (15.4%)	227 (28.8%)	113 (13.3%)	221 (20.0%)	127 (16.8%)	349 (32.8%)
	Psychiatrist (P)	69 (7.0%)	80 (9.6%)	55 (7.1%)	62 (7.9%)	72 (8.5%)	108 (9.8%)	63 (8.4%)	73 (6.9%)
	Geriatrician (G)	31 (3.2%)	38 (4.6%)	46 (5.9%)	38 (4.8%)	23 (2.7%)	69 (6.2%)	61 (8.1%)	66 (6.2%)
	N, P and/or G	59 (6.0%)	58 (7.0%)	65 (8.4%)	76 (9.6%)	56 (6.6%)	107 (9.7%)	60 (8.0%)	117 (11.0%)
	Primary care physician only	692 (70.7%)	482 (57.9%)	473 (60.8%)	354 (44.9%)	572 (67.5%)	546 (49.4%)	424 (56.2%)	425 (39.9%)
	Other	7 (0.7%)	14 (1.7%)	11 (1.4%)	15 (1.9%)	<=5 (0.4%)	22 (2.0%)	9 (1.2%)	15 (1.4%)

NH=nursing home

Table 2: Characteristics of individuals with incident parkinsonism who are exposed to antipsychotic drug therapy, by year of exposure, sex and residential setting

		2005				2013			
		Female		Male		Female		Male	
		NH N=288	Community N=2,413	NH N=182	Community N=2,392	NH N=279	Community N=3,175	NH N=194	Community N=3,198
Age at Parkinsonism Incidence	Mean ± SD	82.64 ± 6.99	76.38 ± 6.65	81.16 ± 6.50	75.93 ± 6.35	84.19 ± 6.98	76.96 ± 7.20	81.53 ± 6.69	76.43 ± 6.77
First antipsychotic type	Both	<=5	11 (2.1%)	<=5	18 (2.8%)	<=5	9 (4.3%)	0	11 (3.8%)
	Typical Antipsychotic	21 (25%)	105 (20%)	9 (15%)	99 (15.6%)	18 (31.6%)	29 (13.9%)	16 (35.6%)	54 (18.8%)
	Atypical Antipsychotic	61 (74%)	418 (78.3%)	50 (82.0%)	517 (81.5%)	38 (66.7%)	170 (81.7%)	29 (64.4%)	223 (77.4%)
Type of Atypical Antipsychotic first prescribed	Aripiprazole*	0	<=5	0	<=5	<=5	15 (7.2%)	0	<=15
	Olanzapine	11 (13.3%)	56 (10.5%)	9 (14.8%)	66 (10.4%)	7 (12.3%)	18 (8.7%)	<=5	19 (6.6%)
	Paliperidone*	0	<=5	0	<=5	<=5	0	0	<=5
	Quetiapine	22 (26.5%)	217 (40.6%)	17 (27.9%)	291 (45.9%)	15 (26.3%)	101 (48.6%)	18 (40.0%)	150 (52.1%)
	Risperidone	28 (33.7%)	142 (26.6%)	24 (39.3%)	159 (25.1%)	15 (26.3%)	36 (17.3%)	<=10	42 (14.6%)
Antipsychotic Prescribing Physician Specialty	Neurology	0	26 (4.9%)	0	46 (7.3%)	<=5	9 (4.3%)	0	15 (5.2%)
	Psychiatry	0	13 (2.4%)	0	19 (3.0%)	0	13 (6.3%)	0	12 (4.2%)
	GM	0	13 (2.4%)	0	22 (3.5%)	0	9 (4.3%)	0	10 (3.5%)
	FP/EM	<=5	11 (2.1%)	<=5	<=5	<=5	<=5	<=5	<=5

PC physician	73 (88.0%)	391 (73.2%)	52 (85.2%)	436 (68.8%)	51 (89.5%)	147 (70.7%)	41 (91.1%)	201 (69.8%)
Internal Medicine	<=5	7 (1.3%)	0	8 (1.3%)	0	<=5	<=5	<=10
Others	<=5	13 (2.4%)	<=5	20 (3.2%)	0	6 (2.9%)	<=5	8 (2.8%)
missing	6 (7.2%)	60 (11.2%)	<=5	78 (12.3%)	<=5	17 (8.2%)	0	31 (10.8%)

*Some data suppressed to minimize re-identification risk due to small numbers in cells.

NH=nursing home, GM=geriatric medicine, FP=family practic, EM=emergency medicine, PC=primary care

Table 3: Hazard ratios for exposure to an antipsychotic drug among individuals with incident parkinsonism, by residential setting at index date

	Overall			Not in nursing home at index date			Nursing home at index date		
Covariates	**DF**	**Hazard ratio (95% CI)**	**p-value**	**DF**	**Hazard ratio (95% CI)**	**p-value**	**DF**	**Hazard ratio (95% CI)**	**p-value**
Number of observation used		**61928**			**57264**			**4664**	
Residence in a nursing home at index date	1	1.87 (1.75, 1.99)	<.0001						
Age at index date	1	1.04 (1.04, 1.04)	<.0001	1	1.04 (1.04, 1.05)	<.0001	1	1.00 (0.99, 1.01)	0.5361
Male	1	1.27 (1.22, 1.32)	<.0001	1	1.24 (1.19, 1.30)	<.0001	1	1.34 (1.20, 1.49)	<.0001

		1			1			1		0.5691
Income Quintile (ref = 1 low)	2		0.99 (0.93, 1.05)	0.7483		1.00 (0.93, 1.07)	0.9863		0.95 (0.80, 1.13)	0.3794
	3	1	1.03 (0.97, 1.09)	0.3764	1	1.02 (0.96, 1.10)	0.4912	1	1.07 (0.91, 1.26)	0.1929
	4	1	1.00 (0.94, 1.07)	0.9101	1	0.99 (0.92, 1.06)	0.6888	1	1.11 (0.95, 1.31)	0.9520
	5 (high)	1	0.94 (0.88, 1.00)	0.0397	1	0.93 (0.87, 0.99)	0.0333	1	1.01 (0.85, 1.19)	0.0173
Charlson (ref: No hospitalization)	0	1	1.05 (0.99, 1.10)	0.0989	1	1.06 (1.00, 1.12)	0.0348	1	0.82 (0.70, 0.97)	0.6241
	1	1	1.25 (1.18, 1.33)	<.0001	1	1.25 (1.17, 1.34)	<.0001	1	1.04 (0.89, 1.22)	0.3441
	2+		1.33 (1.26, 1.40)	<.0001		1.38 (1.30, 1.47)	<.0001		0.94 (0.82, 1.07)	

	1		1		1	40.0007
History of Dementia	2.53 (2.40, 2.66)	<.0001	3.07 (2.90, 3.25)	<.0001	1.20 (1.08, 1.34)	

DF=degrees of freedom

Table 4: Odds ratios for typical (versus atypical) antipsychotic drug dispensing among individuals with incident parkinsonism exposed to antipsychotics

Covariates		DF	Odds Ratio(95% CI)	p-value
Number of observation used			**9653**	
Residence in a nursing home		1	0.94 (0.80, 1.10)	0.407
Age at parkinsonism Incidence (ref=66-75)	76-85	1	1.02 (0.90, 1.15)	0.7751
	86+	1	1.15 (0.99, 1.35)	0.0752
Male sex		1	0.99 (0.90, 1.11)	0.9206
Income Quintile (ref = 1, lowest)	2	1	1.04 (0.88, 1.22)	0.6513
	3	1	1.03 (0.88, 1.22)	0.7004
	4	1	1.02 (0.87, 1.20)	0.7943
	5 (high)	1	1.04 (0.88, 1.23)	0.6051
Charlson (ref: No hospitalization)	0	1	1.14 (0.99, 1.31)	0.0607
	1	1	1.06 (0.90, 1.25)	0.4771
	2+	1	1.36 (1.18, 1.56)	<.0001
Number of Concurrent Medications		1	1.10 (1.08, 1.11)	<.0001
History of Dementia		1	0.54 (0.47, 0.62)	<.0001
Antipsychotic Prescribing Physician Specialty	PCP vs other	1	0.98 (0.86, 1.12)	0.8058
Physician seen 6 months prior to antipsychotic	N/P/G vs PCP/other	1	0.36 (0.32, 0.41)	<.0001
Years (ref= 2005-2009)	2010-2014	1	1.19 (1.07, 1.33)	0.0015

PCP=primary care physician, N/P/G=neurologist, psychiatrist or geriatrician, DF=degrees of freedom