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Comparative risk of Parkinsonism associated with olanzapine, risperidone and quetiapine in older adults-a propensity score matched cohort study

<<Query: Please confirm that given names (blue) and surnames/family names (vermilion) have been identified and spelled correctly. Ans: Yes, all the names are displayed correctly.>>Te-yuan<<Query: Please check if link to ORCID is correct. Ans: Yes, correct.>> Chyou[1], Revathi Nishtala[2], Prasad S. Nishtala*[3]

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Abstract

~~Objective~~Purpose

The ~~objective~~purpose of this study was to examine the incidence of Parkinsonism in new users of second-generation antipsychotics (SGAs) in older adults (≥65 years). In the secondary analyses, we examined the risk of Parkinsonism by type and dose of SGA and conducted age-sex interactions.

Method

This population-based study included older adults who had a new-onset diagnosis of Parkinsonism and who started taking olanzapine, risperidone or quetiapine between 1 January 2005, and 30 December 2016. The Cox proportional hazard (COXPH) model with inverse treatment probability weighted (ITPW) covariates was used to evaluate the risk of new-onset Parkinsonism associated with SGAs, using quetiapine as the reference. We used the Generalized Propensity Score method to evaluate the dose-response risk of Parkinsonism associated with SGAs.

Results

After ITPW adjustment for covariates, the COXPH model showed that compared to quetiapine, the use of olanzapine and risperidone were associated with an increased risk of Parkinsonism. The ITPW-hazard ratios are 1.76 (95% confidence interval 1.57-1.97) and 1.31 (95%CI 1.16-1.49), respectively. The dose-response risk of Parkinsonism was highest for olanzapine with a hazard ratio of 1.69 (95%CI 1.40-2.05) and the least for quetiapine with a hazard ratio of 1.22 (95%CI 1.14-1.31). The risk of Parkinsonism in the 65 to 74-year age group was higher for both sexes with risperidone compared to olanzapine, but the risk increased with olanzapine for both sexes in the 85+ age group.

Conclusion

The study found that the risk of new-onset Parkinsonism in older adults is 31% and 76% higher with risperidone and olanzapine respectively compared to quetiapine<<Query: Please resupply the abstract for this paper, structured under the following headings: Purpose, Methods, Results, Conclusion/s. Ans: The abstract is edited as per suggestion.>>.

Keywords: adverse effects; atypical antipsychotics; elderly; extrapyramidal side effects; pharmacoepidemiology

<<Query: Ethics Statement is required as per journal style. Please provide or confirm that there are no ethical approval is needed. Ans: The ethics approval is outlined in Section 2, 2.1.>>KEY POINTS

1. Is the risk of new-onset Parkinsonism affected by type and dose of second-generation antipsychotic?

2. In this cohort study of new users of SGAs in older adults (≥65 years) in New Zealand between 2005 and 2018, the use of olanzapine and risperidone were associated with an increased risk of new-onset Parkinsonism. The risk of new-onset Parkinsonism in older adults is 31% and 76% higher with risperidone and olanzapine respectively compared to quetiapine. The risk increased significantly with olanzapine for both sexes in the 85+ age group.

3. The use of quetiapine is associated with a relatively lower risk of new-onset Parkinsonism than olanzapine or risperidone in older adults. Prescribers should exercise caution when using olanzapine in the oldest old.

1 INTRODUCTION

Second-generation antipsychotics (SGAs) are widely prescribed in older adults for the management of behavioural and psychological symptoms of dementia (BPSD).[1] SGAs are associated with cardiovascular, metabolic and neurological adverse effects in older adults.[2-4] One of the most debilitating neurological adverse effects of SGAs in older adults is drug-induced Parkinsonism.[5,6]

Evidence from clinical trials and observational studies show an increase risk of Parkinsonism associated with SGAs.[7] Selection criteria for clinical trials are very stringent and often exclude older people with several comorbidities and are underpowered to detect small, but very important, differences in the rates of uncommon adverse effects.[8,9] This is particularly relevant to Parkinsonism associated with SGA use in older adults. In a real-world setting, older adults have more severe BPSD, higher comorbidity, and are frailer and hence have a higher baseline risk of harms from drug exposures than patients recruited in a clinical trial.[10] Hence, extrapolation of evidence derived from clinical trials to real-world patients is barely accurate.

Studies have shown that SGAs may have different extrapyramidal symptoms (EPS) adverse effect profile.[11] Hence epidemiological studies are needed to examine multiple antipsychotic exposures (type and dose) together with social and clinical risk factors for a longer period of follow up time from large and representative sample of real-world population of older adults.[12] However, observational studies are likely to provide biased estimates of risks due to confounding, because background characteristics of individuals may favour the use of certain treatments, which results in imbalance in observed characteristics between treatment groups.[13] A large cohort study (N = 25 769) conducted among older adults with dementia in Ontario found a 30% increased risk of Parkinsonism associated with first-generation antipsychotic use relative to SGA use[14] with a hazard ratio of 1.69 (95%CI 1.04-1.58) reported. Despite careful selection of covariates, the study was potentially vulnerable to confounding due to imbalance in the observed baseline characteristics in the exposed and non-exposed groups. Similarly, a population-based retrospective cohort study involving older adults in the Canadian province of Manitoba found a lower risk of Parkinsonism associated with incident use of risperidone

relative to first-generation antipsychotic use, at 30 days following exposure to risperidone the hazard ratio was 0.38 (95% CI 0.22-0.67).[15] This study did not investigate the effect of dose on incidence of Parkinsonism in older adults. In order to understand and quantify the risk of new-onset Parkinsonism posed by SGAs we need reliable population-level evidence with appropriate methods to control for confounding.[16] Currently, to our knowledge, research estimating the causal effect of new-onset Parkinsonism associated with SGAs under the context of confounding due to variations in background characteristics and comorbidity of individuals between treatment groups is limited.

In this study, we examined the association of Parkinsonism associated with SGAs using population-level data with adequate confounding control. We hypothesize that the association of SGAs on Parkinsonism is a class effect and all SGAs will have similar effect sizes concerning new-onset Parkinsonism.

2 METHOD

2.1 Ethics

The Ethical Implications of Research Activity Form (EIRA1-2960) to conduct this study was approved on 8 April 2019 by the University of Bath.

2.2 Data sources

We used a nationwide inpatient hospital data (2005-2016), National Minimum Data Set (NMDS), maintained by the Ministry of Health, New Zealand to conduct this study. We extracted all hospitalizations from the NMDS from 1 January 2006 to 31 December 2016 in which the primary reason for admission was Parkinsonism. The NMDS contains clinical (length of hospital stays, diagnosis, procedures) and demographic (age, sex, ethnicity, date of birth, date of event) information for each hospital admission. We excluded patients with a diagnosis of Parkinson's disease (G20) or patients treated for Parkinson's disease or patients taking a combination of SGAs. We also exclude drugs that have a potential association for causing secondary Parkinsonism (Figure 1).

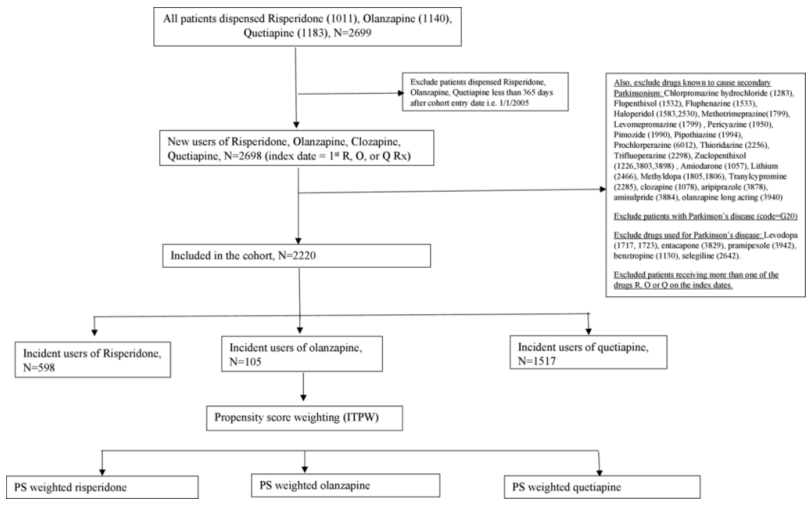

FIGURE 1 Cohort study design

2.3 Study population

Eligible patients were older adults aged 65 years of age at entry into the cohort on 1 January 2007. We defined the cohort entry as the date of first prescription for any atypical antipsychotic (olanzapine, risperidone or quetiapine). We defined incident use as a new prescription for olanzapine or risperidone or quetiapine with no previous prescription claims for those antipsychotics during the 12 months before cohort entry. We excluded older adults with a history of Parkinson's disease and those dispensed drugs known to cause secondary Parkinsonism. We also excluded individuals treated with drugs for the management of Parkinson's disease and taking a combination of SGAs of interest. The final cohort included N = 2220 incident users of SGAs of which 598 were risperidone users, 105 were olanzapine users and 1517 were incident users of quetiapine. We censored at new-onset diagnosis of Parkinsonism, end of study period (1 December 2016), discontinuation of risperidone, olanzapine, and quetiapine (90 days after end of treatment, crossover to another antipsychotic (either risperidone, olanzapine or quetiapine).

2.4 Exposures and covariates

We used dispensing claims data to determine SGA treatment exposure. We obtained de-identified dispensing claims data for individuals aged 65 years or older for the period 2006~~6~~5 to 2017 from the New Zealand (NZ) Ministry of Health (MoH). The Pharms database is a national dispensing claims database maintained by the MoH, which captures subsidized prescriptions dispensed by community pharmacies in NZ. The SGAs studied included new users of olanzapine, risperidone and quetiapine. These three SGAs are subsidised by Pharmaceutical Management Agency and are the most frequently used SGAs in older adults in NZ.[1,17] Covariates of interests included socio-demographic characteristics (age at cohort entry, gender and ethnicity), comorbidity and the use of effect-modifying drugs that increase the risk of Parkinsonism. The effect modifying drugs were FGAs, SGAs and other drugs. The low potency FGAs included levomepromazine, thioridazine and chlorpromazine hydrochloride. The high potency FGAs included trifluoperazine, zuclopenthixol, flupenthixol, methotrimeprazine, pericyazine, pipothiazine, prochlorperazine, fluphenazine and haloperidol.[18,19] The SGAs (ranked low to high risk of inducing Parkinsonism) included clozapine, olanzapine (long acting) aripiprazole, amisulpride[6] and others included amiodarone, lithium, methyldopa, and tranylcypromine.

Covariates of interests included socio-demographic characteristics, exposures to any above-mentioned effect-modifiers, and comorbidity. We used the medicines comorbidity index (MCI) to derive a comorbidity score. The MCI is an appropriate tool for measuring comorbidity, validated on the NMDS, and is an appropriate index for adjusting comorbidity in pharmacoepidemiological studies.[20] In brief the MCI includes 20 comorbid conditions identified through the New Zealand Burden of Diseases. Medicines relative to the specific comorbid conditions in the MCI are based on indications in the New Zealand Formulary and the Anatomical Therapeutic Chemical classification system.

To investigate a dose-response relationship with SGA exposure and new-onset Parkinsonism we conducted a subgroup analyses on the average daily dose of the SGAs, which was defined as the total SGA dosage an individual was dispensed between cohort entry and censoring, divided by exposure length. To calculate the total dosage of the SGA, we used the cumulative number of each SGA prescription dispensed between cohort entry and censoring multiplied by the daily dose by the duration in days. To calculate the exposure length, we counted the total number of days the individual was dispensed the SGA of interest between the cohort entry date and the end of the last prescription before censoring, and accounting for the possibility that prescriptions can overlap.

2.5 Outcomes

The primary outcome was the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) code for a new inpatient diagnosis of Parkinsonism. We used the ICD-10-AM codes to identify a diagnosis of secondary Parkinsonism (G21.0, G21.1, G21.2, G21.8, and G21.9).

2.6 Statistical analyses

Incident users of quetiapine from the control group as previous studies have demonstrated that the risk of Parkinsonism associated with quetiapine is the lowest among SGAs. We mitigated confounding by inverse treatment probability weighting (ITPW).[21,22] To derive the inverse treatment probability weights, we calculated the conditional treatment probability given the values of confounders, Pr(a SGA|confounders), as well as the unconditional treatment probability, Pr(a SGA), for each SGA of interests by running multinomial regressions. Then, stabilized inverse treatment probability weights were calculated as Pr(a SGA)/Pr(a SGA|confounders). We compared the population standard bias (PSB) before and after propensity-score weighting to assess how well the confounders were matched in the three SGA groups. Potential confounders include age (at cohort entry), sex, ethnicity, MCI (based on medical histories before cohort entry), and effect modifier exposures.

We plotted Kaplan-Meir survival curves to study the time to first onset, and time to first change of SGA use including discontinuation, together with the Log-rank test P-value. Discontinuation is defined as not dispensed SGAs of interest for 90 days or longer. Hazard ratios and 95% confidence intervals were estimated with Cox proportional hazard (COXPH) regression with and without ITPW weighting. Schoenfeld residuals analyses were used to check for signs of non-proportional hazard, and a *P*-value less than .05 indicates the violation of the proportional-hazards assumption in COXPH regression.

In the secondary analyses, we used the generalized propensity score (GPS) method[23] to quantify the change in risk of Parkinsonism in response to one unit increase in the average daily dose of the SGA. GPS assumes that the multiple treatments are continuous variables.

2.7 Sensitivity analyses

We conducted additional sensitivity analyses. To reduce potential bias from differential follow-up times between SGA users, we limited the maximal follow-up to 100 days.

All analyses were performed with the use of R software, version 3.2.1.5.[24]

3 RESULTS

3.1 Study participants

There were 2220 incident SGA users with 922 622 person-days of follow up (Table 1**).** The total population were weighted by inverse treatment probability weights (ITPW) to mitigate confounding. PSB calculations indicate that all confounders were balanced within the three groups after ITPW weighting (PSB < 0.2, Figure 2). There were 487 of new-onset Parkinsonism among the 2220 incident SGA users. The median time to new-onset Parkinsonism was 257 days (IQR = [68, 642]).

TABLE **Table 1** Selected baseline characteristics of the cohort (N = 2220)

Variable	Olanzapine (n = 105)	Quetiapine (n = 1517)	Risperidone (n = 598)
Age group (%)			
65-74 years	46 (43.8)	250 (16.5)	103 (17.2)
75-84 years	49 (46.6)	889 (58.6)	295 (49.3)

Variable	Olanzapine (n = 105)	Quetiapine (n = 1517)	Risperidone (n = 598)
85 years +	10 (9.5)	378 (24.9)	200 (33.4)
Ethnicity (%)			
NZ-European	96 (91.4)	1401 (92.4)	533 (89.1)
Māori	2 (1.9)	16 (1.1)	19 (3.2)
Other	7 (6.7)	100 (6.6)	46 (7.7)
Sex (%)			
Female	47 (44.8)	579 (38.2)	261 (43.6)
Male	58 (55.2)	938 (61.8)	337 (56.4)
Taking Effect modifier (%)			
No	40 (38.1)	260 (17.1)	244 (40.8)
Yes	65 (61.9)	1257 (82.9)	354 (59.2)

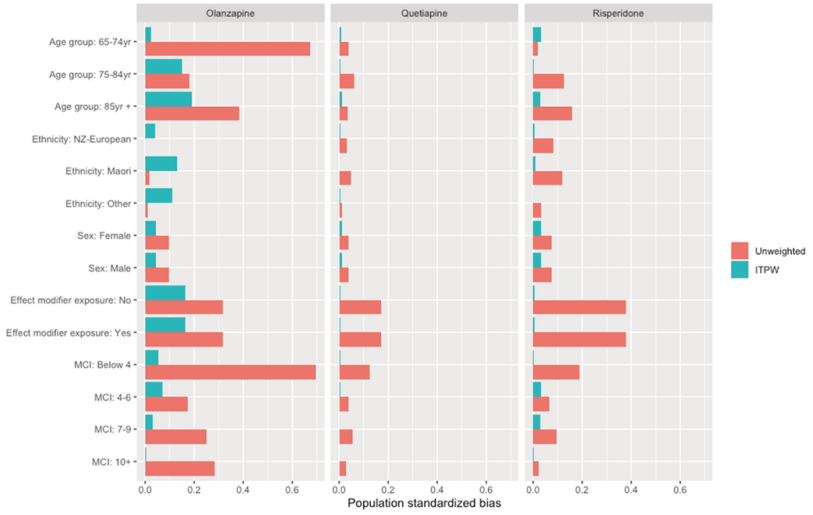

FIGURE 2 Selected baseline characteristics after propensity score matching

3.2 Outcomes

Survival analysis confirms that olanzapine and risperidone are associated with “higher” risk of Parkinsonism compared to quetiapine (Figure 3). Despite olanzapine being associated with a “higher” risk of Parkinsonism compared to quetiapine, users of olanzapine are less likely to discontinue treatment or switch to another SGA (Figure 4). However, users who initiate risperidone or olanzapine are more likely to switch to quetiapine (Figure 4). Schoenfeld residuals analysis permits the calculation of hazard ratios of new-onset Parkinsonism due to SGA exposures by COXPH regression. Compared to quetiapine users, hazard ratio calculations indicate that the risks of Parkinsonism onset in individuals exposed to risperidone and olanzapine are 31% and 76% higher respectively (Figure 5).

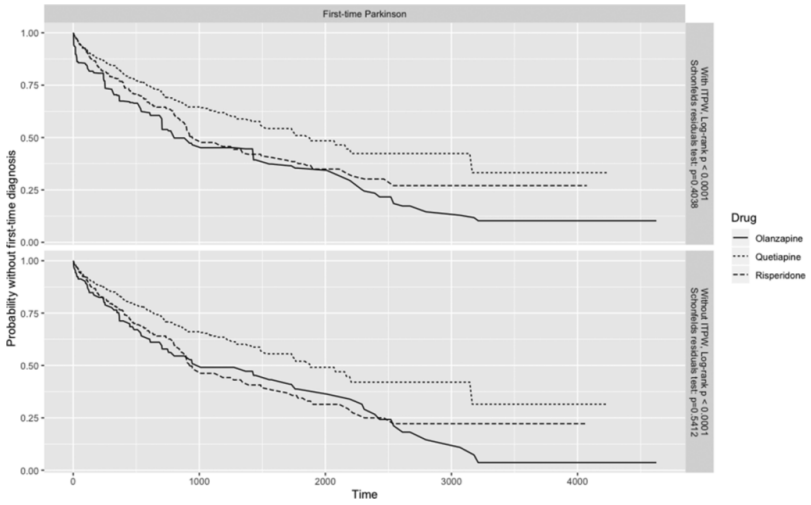

FIGURE 3 Kaplan–Meier curves for the risk of new-onset Parkinsonism with second-generation antipsychotics

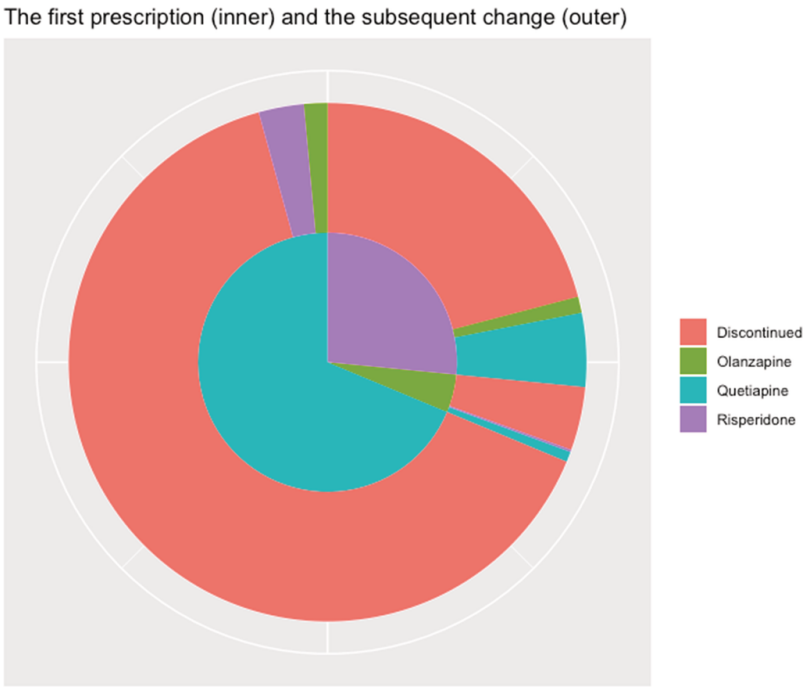

FIGURE 4 Switching of antipsychotics during the study period

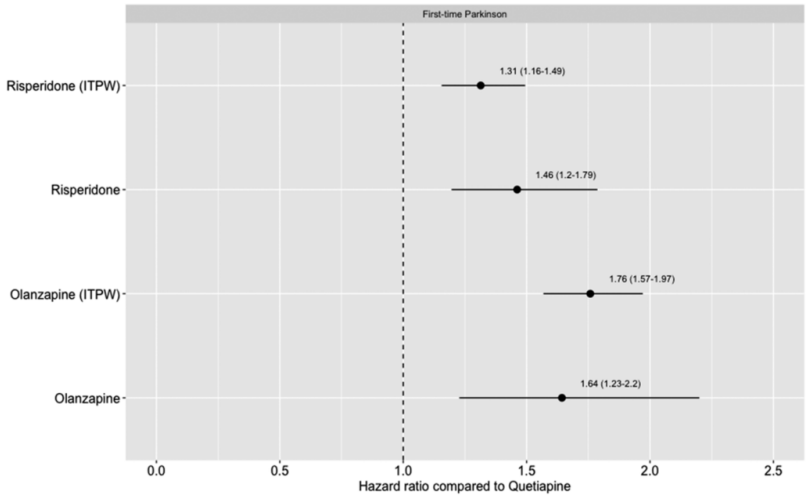

FIGURE 5 Hazard ratios for new-onset Parkinsonism with second-generation antipsychotics

3.3 Secondary analyses

Dose-response risk of Parkinsonism revealed a higher risk of new-onset Parkinsonism with olanzapine followed by risperidone and quetiapine (Figure 6). Age-sex interactions revealed risk of Parkinsonism in 65 to 74-year-old was higher with risperidone compared to olanzapine for both sexes, but the risk increased significantly high for both sexes with olanzapine in the 85+ age group (Figure 7).

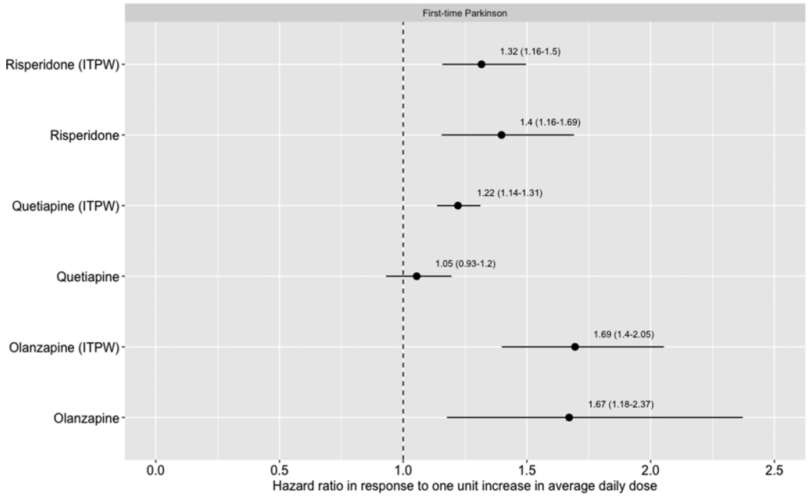

FIGURE 6 Dose–response risk of new-onset Parkinsonism for second-generation antipsychotics

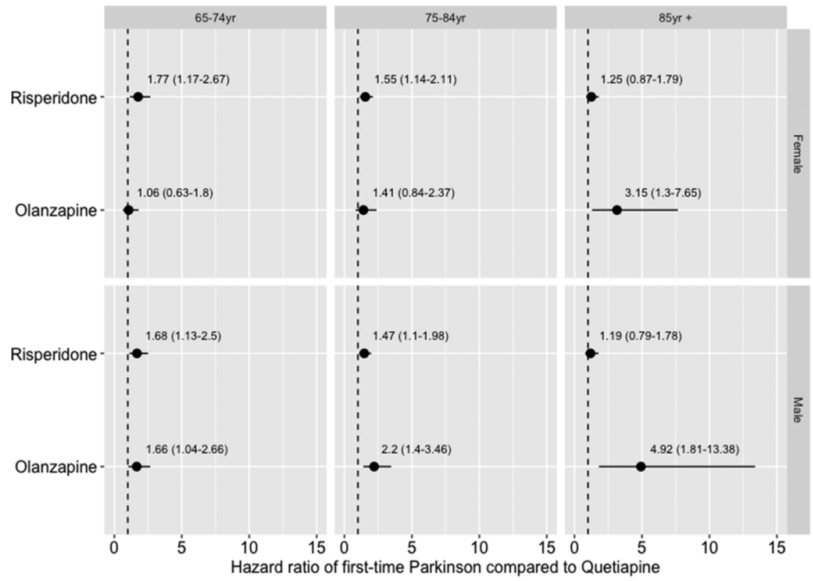

FIGURE 7 Risk of new-onset Parkinsonism for second-generation antipsychotics stratified by sex and age groups

4 DISCUSSION

A propensity score analyses conducted on a population of older adults showed that SGAs increased the risk of new-onset Parkinsonism. Our study showed that the olanzapine followed by risperidone had the highest risk compared to quetiapine in older adults. Our study findings are partly in contrast to that reported by Marras et al who found that the risk of Parkinsonism in older adults with dementia was similar among quetiapine, olanzapine or risperidone users.[7] We did not restrict our analyses to adults with dementia and that the difference in the study populations may be the primary reason for this discordant finding.

The safety profiles of SGAs vary because of their dissimilarities to dopamine-2 (D2) receptor, 5-hydroxytryptamine receptor 2A (5-HT2A) affinity and anticholinergic activity.[25] Olanzapine, but not risperidone or quetiapine has central anticholinergic activity, and both olanzapine and risperidone have higher 5-HT2A affinity relative to quetiapine. It is postulated that both antiserotonergic and anticholinergic actions may help to counter the impact of the D2 blockade of these SGAs on the basal ganglia.[26] Our findings are plausible with these biological mechanisms.

Our study demonstrated a dose-response risk of Parkinsonism associated with SGAs. This finding is consistent with a retrospective cohort study conducted in older adults in Ontario. However, their study did not stratify the cohort by type of SGAs and dose.[14] Our study is unique and extends prior studies by demonstrating a dose-response risk of Parkinsonism by type and dose of commonly used SGAs in older adults. The finding of the dose-related risk of Parkinsonism greater with olanzapine than risperidone warrants further investigation. A review conducted by Tarsy et al ranked risperidone > olanzapine > quetiapine > clozapine < in the descending order of causing acute EPS, but highlighted that risperidone has a lower risk of inducing EPS at low doses.[6] A double-blind trial conducted by Tran et al found that risperidone was associated with a higher risk of EPS than olanzapine, but the trial included risperidone doses (4-12 mg day) which has much higher than the average daily dose in our study.[27]

Interestingly, our study found differences in age and sex interactions by type of SGA. A higher risk of Parkinsonism is associated with olanzapine in both sexes across all ages compared to risperidone. While there is a paucity of literature to compare age and sex interactions with specific type of SGAs, a large population-

based study found that the incidence of drug-induced Parkinsonism increased with older age and was higher in women at all ages.28

Quetiapine may be a suitable alternative following an unsuccessful trial of non-pharmacological interventions for the management of BPSD because of its lesser propensity to cause Parkinsonism than other SGAs and has a relatively safer metabolic and cardiovascular profile than olanzapine or risperidone.

4.1 Strengths

This study has several strengths, including its large size, nationwide coverage of older adults in NZ, and use of a propensity score matching method to control for confounding. The new user design eliminated the bias likely to be introduced by including prevalent users of SGAs. We also demonstrated a dose-response relationship with SGA exposure and risk of new-onset Parkinsonism.

4.2 Limitations

We extracted the exposures and the outcomes from the administrative data sources used in these analyses. We did not ascertain if individuals prescribed SGAs have taken them as this could potentially lead to misclassification of antipsychotic exposure. We excluded clozapine in our study due to the small numbers of clozapine users. We only included variables available in the prescription and hospital discharge data for computing propensity scores and did not validate the ICD-10-AM codes for Parkinsonism to confirm a diagnosis. Literature has also identified that there is a potential for under-reporting and under recognizing Parkinsonism in hospital patients and the elderly.29,30 The NMDS data only allowed us to identify individuals with new-onset Parkinsonism in patients admitted to hospitals. Hence replication of this study in a more general population with a clinical assessment of Parkinsonism is needed. The retrospective nature of our study design is prone to bias and residual confounding despite controlling our analyses for age, sex, ethnicity and comorbidity using propensity scores.

5 CONCLUSION

The study found that the risk of new-onset Parkinsonism in older adults is 31% and 76% higher with risperidone and olanzapine respectively compared to quetiapine. A higher risk of Parkinsonism is associated with olanzapine in both sexes across all ages compared to risperidone.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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