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Risk of delirium associated with antimuscarinics in older adults: A case-time-control study

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Abstract

Background: Older adults are at an increased risk of delirium because of age, polypharmacy, multiple comorbidities and acute illness. Antimuscarinics are the backbone of the pharmacological management of overactive bladder. However, the safety profiles of antimuscarinics vary because of their dissimilarities to muscarinic receptor-subtype affinities and are associated with differential central anticholinergic adverse effects.

Objective: This study aimed to examine delirium risk in new users of oxybutynin and solifenacin in older adults (≥ 65 years). In the secondary analyses, we examined the risk of delirium by type and dose of antimuscarinic.

Method: We applied a case-time-control design to investigate delirium risk in older adults who started taking oxybutynin and solifenacin. We used a nationwide inpatient hospital data (2005–2016), National Minimum Data Set, maintained by the Ministry of Health, New Zealand (NZ), to identify older adults with a new-onset diagnosis of delirium. Eligible patients were older adults aged 65 at entry into the cohort on 1/1/2006. We used dispensing claims data to determine antimuscarinic treatment exposure. The antimuscarinic included in the study were new users of oxybutynin and solifenacin. These two antimuscarinics are subsidised by the Pharmaceutical Management Agency and are the most frequently used antimuscarinic in NZ. A conditional logistic regression model was used to compute matched odds ratios (MORs) and 95% confidence intervals (CIs). In the case-time-control design, we made separate analyses to evaluate the dose–response risk of delirium.

Results: We identified 4818 individuals (mean age 82.14) from 2005 to 2015 with incident delirium and were exposed to at least one of the antimuscarinic of interest. The case-time-control matched odds ratio (MOR) for delirium with oxybutynin was (2.06, 95% confidence interval [CI] 1.07–3.96). Solifenacin was not associated with delirium (0.89 95%CI 0.64–1.23). In the sensitivity analyses, the case-time-control MOR for delirium using a shorter risk period (0–3 days) did not change the results. The dose–response risk of delirium was significant for oxybutynin (0.05, 95%CI 0.02–0.08) but not for solifenacin (−0.01, 95%CI −0.03 to 0.00). In addition, in the subgroup analyses, a statistically significant association of delirium was found for oxybutynin but not for solifenacin in the non-dementia cohort (2.11,95% CI 1.08–4.13) and the dementia cohort (1.25, 95%CI 0.05–26.9).

Conclusion: The study found that oxybutynin but not solifenacin is associated with a risk of new-onset delirium in older adults. The higher blockade of M1 and M2 receptors by oxybutynin is likely to contribute to delirium than solifenacin, which is highly selective for the M3 receptor subtype. Therefore, the treatment choice with an M3 selective agent must be given due consideration, particularly in those with pre-existing cognitive impairment.

KEYWORDS
adverse effects, antimuscarinics, delirium, elderly, pharmacoepidemiology

Key Points

Antimuscarinics are the backbone of the pharmacological management of overactive bladder. It is increasingly recognised that antimuscarinics are associated with differential effects on cognitive functioning.

The safety profiles of antimuscarinics vary because of their dissimilarities to muscarinic receptor-subtype affinities. Individual drug characteristics, including an affinity for the muscarinic receptor subtype M1 and M2 in the brain, ability to cross the blood–brain barrier, drug metabolism and concurrent use of drugs with anticholinergic properties, can increase the risk of delirium in older adults.

In this case-time-control study of new users of oxybutynin and solifenacin in older adults (≥ 65 years), the use of oxybutynin is associated with an increased risk of new-onset delirium. The dose-–response risk of delirium was significant for oxybutynin but not for solifenacin.

Oxybutynin but not solifenacin is associated with a risk of new-onset delirium in older adults. Therefore, prescribers should exercise caution when using oxybutynin in the oldest old, particularly those with pre-existing cognitive impairment.

1 | INTRODUCTION

Antimuscarinics are the backbone of the overactive bladder's pharmacological management (OAB).[1–3] Oxybutynin, darifenacin, propiverine, tolterodine, fesoterodine, solifenacin and trospium are widely used to manage OAB in older adults.[1,2] Currently, oxybutynin and solifenacin oral formulations are the most frequently used antimuscarinics for the treatment of OAB in New Zealand. The selection of the most appropriate antimuscarinic for treating OAB in older adults depends on their adverse effects profile, as broadly, all of them have similar efficacy.[4–6] Antimuscarinics are associated with peripheral and central anticholinergic adverse effects.[7,8] One of the most debilitating central anticholinergic adverse effects of antimuscarinics in older adults is drug-induced delirium.[9]

Older adults are predisposed to an increased risk of delirium due to polypharmacy, anticholinergic burden, age-related deficits in drug clearance, compromised cholinergic neurotransmission, and impaired blood–brain barrier (BBB) function.[10,11] It is now increasingly recognised that antimuscarinics are associated with differential central anticholinergic adverse effects.[12,13] Antimuscarinics that block cholinergic receptors in the brain can contribute to impaired attention, delayed memory, delirium and drowsiness.[7] Individual drug characteristics include an affinity for the muscarinic receptor subtype M1 and M2 in the brain, the ability to cross the blood–brain barrier (BBB), drug metabolism, and concurrent use of anticholinergic drugs increase the risk of delirium in older adults.[14] Data from systematic reviews and network meta-analyses (mostly from healthy study participants) report a wide array of antimuscarinics' adverse effects in older adults.[6,15] Still, there is insufficient data from trials on the rate and magnitude of individual CNS adverse effects, including delirium. Instead, they report CNS adverse events as a composite measure, mostly from the healthy population, to draw any meaningful inferences to a frail older population. In a real-world setting, older adults have higher comorbidity and are frailer and hence have a higher baseline risk of harm from drug exposures than patients recruited in a clinical trial. Hence, the extrapolation of evidence from healthy participants in clinical trials to real-world frail older patients is barely accurate.

To understand and quantify the risk of new-onset delirium posed by antimuscarinics, we need reliable population-level evidence with appropriate control for confounding. A case–control design has been used previously to examine the association of congenital heart defects with antidepressant use in pregnant mothers.[16] Still, to our knowledge, no studies have used a similar design to understand the risk of delirium posed by antimuscarinic drugs in older adults. Therefore, our study chose a case-time-control design to mitigate confounding from unknown time-invariant confounders. In the case-time-control design, a control group can adjust for time trends of antimuscarinic use for OAB. We followed all the recommendations to apply a case-time-control design to our analyses.[17–19] For case-time-control design, the

key assumptions are that occurrence of the event must be acute, and the exposure may vary over time.[18,20]

2 | METHOD

2.1 | Ethics

The Ethical Implications of Research Activity Form (EIRA1-5312) to conduct this study was approved on October 20, 2020, by the University of Bath.

2.2 | Data sources

We used a nationwide inpatient hospital data (2005–2015), National Minimum Data Set (NMDS), maintained by the Ministry of Health, New Zealand, to examine new-onset diagnosis of delirium. We extracted all hospitalisations from the NMDS from 1 January 2005 to 31 December 2015, in which the primary reason was delirium. The NMDS contains clinical (length of hospital stay, diagnosis and procedures) and demographic (age, sex, ethnicity, date of birth and date of event) information for each hospital admission.

2.3 | Study population

Eligible patients were older adults aged 65 at entry into the cohort on 1 January 2006. The cohort attrition table shows the inclusion/exclusion criteria and the final population analysed in the case-control design (Supplementary Table 1). We defined the cohort entry as the date of the first prescription for an antimuscarinic (oxybutynin or solifenacin). We defined incident use as a new prescription for oxybutynin or solifenacin with no previous prescription claims during the 12 months before cohort entry. We censored at new-onset diagnosis of delirium, end of the study period (31 December 2015), discontinuation of oxybutynin and solifenacin (90 days after the end of treatment, cross-over to another antimuscarinic (either oxybutynin or solifenacin).

2.4 | Exposures and effect modifiers

We used dispensing claims data to determine antimuscarinic treatment exposure. We obtained de-identified dispensing claims data for individuals aged 65 years or older for 2005–2015 from the New Zealand (NZ) Ministry of Health (MoH). The Pharms database is a national dispensing claims database maintained by the MoH, which captures subsidised prescriptions dispensed by community pharmacies in NZ. The antimuscarinics included in this study were new users of oxybutynin and solifenacin. These two antimuscarinics are subsidised by the Pharmaceutical Management Agency (PHARMAC) and are the most frequently used antimuscarinic in NZ. In addition, the effect-modifying drugs were sourced from the literature.[21–23] These included antibiotics, antipsychotics (first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs), antidepressants (tricyclics and selective serotonin receptor inhibitors), antiepileptics, weak and strong anticholinergics (Appendix 1). We considered these medication classes as separate covariates and examined them individually in the case-time-control model.

2.5 | Outcomes

The primary outcome was the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian

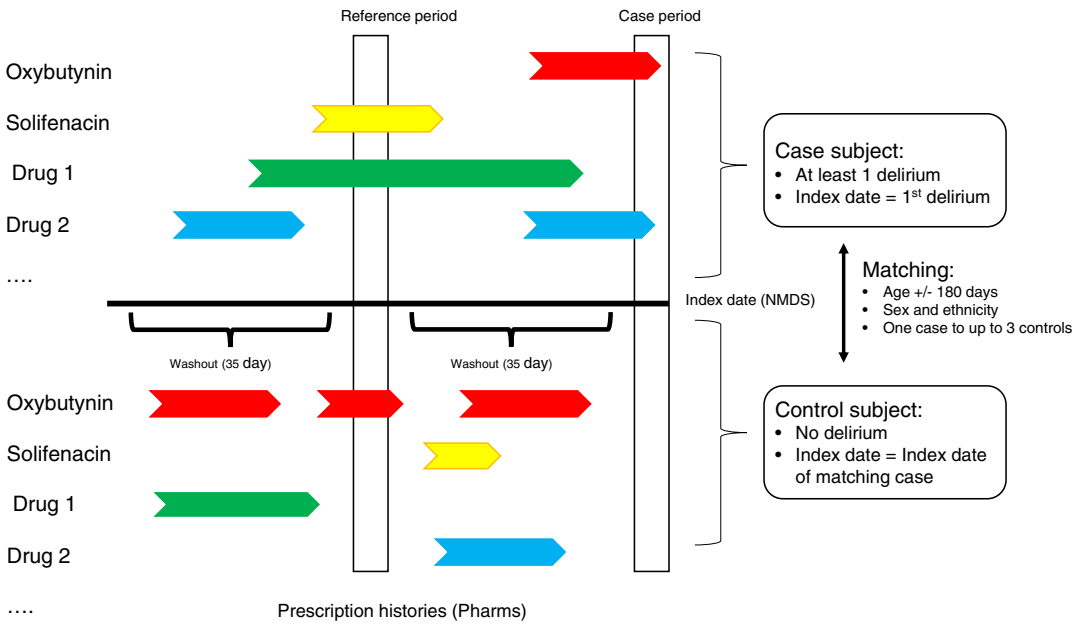

FIGURE 1 Case-time-control cohort

Modification (ICD-10-AM) code for a new inpatient diagnosis of delirium. We used the ICD-10-AM codes to identify delirium diagnosis (F050, F051, F058 and F059). We excluded patients with the first-time diagnosis of delirium within 180 days after 1 January 2005.

TABLE 1 Characteristics of the study population according to the antimuscarinic type

Characteristic	Oxybutynin	Solifenacin
Age		
65–69	0	6
70–74	11	50
75–79	44	172
80–84	107	272
85–89	100	372
90+	71	265
Sex		
Male	190	664
Female	143	473
Ethnicity		
NZ European	310	1062
Māori	6	18
Asian	4	12
Pacific people	0	8
MELAA	0	3
Other	13	34
Calendar year of the incident event		
2005–2009	0	395
2010–2014	333	742

Abbreviation: MELAA- Middle Eastern, Latin American and African.

2.6 | Statistical analyses

2.6.1 | Case- time-control cohort

We created a case-time-control cohort for medication exposures, with 5-day observation periods and two 5-week (35 days) washout periods, summed up to an 80-day study period. Case-period is the 5 days before the index date. The reference period is 45–41 days before the index date (Figure 1). We chose two 5-week washout periods based on our previous study and the need to minimise carry-over effects and misclassification of medication exposure. First, we calculated the duration of each prescription by dividing the total dose supplied by the daily dose. Next, we determined whether an individual had non-intermittent exposure to the medications of interest within the case and the reference period with the prescription dates.

We compared antimuscarinic use in the case and the control periods, in individuals with delirium (cases) and without a delirium diagnosis (control). First, we calculated the odds ratio in the cases (OR_{cases}) by dividing the number of older adults prescribed antimuscarinics in the case period by the number of older adults prescribed antimuscarinics in the reference period. Similarly, we calculated the odds ratio for controls ($OR_{controls}$) to adjust the time trend of exposure. Finally, we derived the MORcase-time-control by dividing the ratio of OR_{cases} by $OR_{controls}$. Each individual with a delirium diagnosis was matched to three individuals without a delirium diagnosis based on age (at cohort entry ± 180 days), gender, and

TABLE 2 The matched odds ratio (MOR) for delirium diagnosed in older adults (65 years and above) who used antimuscarinics in a case-time-control study

Drug	Delirium at index date	Exposures within 5-day observation periods					Exposures within 3-day observation periods				
		Neither	Case	Control	Both	MOR	Neither	Case	Control	Both	MOR
Oxybutynin	Yes	4485	85	57	191	2.06 (1.07–3.96)	4487	86	53	192	2.24 (1.16–4.33)
	No (Reference)	13 275	21	29	30		13 276	21	29	29	
Solifenacin	Yes	3681	212	230	695	0.89 (0.64–1.23)	3680	227	231	680	1.00 (0.72–1.39)
	No (Reference)	13 013	110	106	126		13 020	105	107	123	
Antibiotics	Yes	4607	79	45	87	1.96 (1.27–3.03)	4610	79	49	80	1.78 (1.16–2.73)
	No (Reference)	12 868	130	145	212		12 869	132	146	208	
Antiepileptics	Yes	4745	10	16	47	0.62 (0.22–1.81)	4744	12	17	45	0.85 (0.28–2.59)
	No (Reference)	13 273	15	15	52		13 274	10	12	59	
Antipsychotics	Yes	4550	77	64	127	1.09 (0.74–1.62)	4564	63	64	127	0.94 (0.63–1.42)
	No (Reference)	12 735	177	161	282		12 738	166	159	292	
Antidepressants	Yes	4380	105	74	259	1.43 (0.98 2.11)	4379	105	76	258	1.44 (0.99–2.11)
	No (Reference)	12 547	136	138	534		12 545	132	128	550	
Weak anticholinergics	Yes	3263	265	214	716	1.24 (1.00–1.53)	3613	258	224	723	1.13 (0.91–1.39)
	No (Reference)	10 117	571	570	2097		10 103	569	556	2127	
Strong anticholinergics	Yes	4813	1	1	3	1.00 (0.02–50.4)	4814	1	1	2	1.00 (0.02–50.4)
	No (Reference)	13 351	1	1	2		13 351	1	1	2	

TABLE 3 The effect sizes with 95% CI of the dose–response change in the risk of delirium for oxybutynin and solifenacin using case-time-control study design

Variable	Oxybutynin	Solifenacin
	0.047 (0.016–0.077)	−0.011 (−0.028–0.005)
Age groups: 70–74 yr	−0.051 (−0.479–0.377)	−0.051 (−0.478–0.377)
Age groups: 75–79 yr	−0.096 (−0.507–0.315)	−0.095 (−0.506–0.315)
Age groups: 80–84 yr	−0.064 (−0.472–0.344)	−0.065 (−0.472–0.343)
Age groups: 85–89 yr	−0.144 (−0.551–0.263)	−0.143 (−0.550–0.264)
Age groups: 90 yr +	−0.292 (−0.701–0.116)	−0.290 (−0.699–0.118)
Sex: Female	−0.015 (−0.082–0.053)	−0.016 (−0.083–0.052)
Ethnicity: Māori	−0.179 (−0.413–0.056)	−0.179 (−0.413–0.056)
Ethnicity: Pacific	0.066 (−0.277–0.408)	0.064 (−0.278–0.407)
Ethnicity: Asian	0.101 (−0.172–0.374)	0.099 (−0.174–0.372)
Ethnicity: MELAA	0.469 (−0.219–1.158)	0.463 (−0.226–1.152)
Ethnicity: Other	0.388 (0.215–0.561)	0.389 (0.216–0.562)
Antibiotics exposed: case period	0.615 (0.336–0.894)	0.627 (0.349–0.906)
Antibiotics exposed: control period	0.008 (−0.295–0.312)	-6e-04 (−0.304–0.303)
Antibiotics exposed: both periods	0.030 (−0.207–0.266)	0.030 (−0.206–0.266)
Antiepileptics exposed: case period	1.474 (0.536–2.412)	1.493 (0.554–2.432)
Antiepileptics exposed: control period	0.675 (−0.325–1.675)	0.654 (−0.347–1.656)
Antiepileptics exposed: both periods	0.861 (0.503–1.220)	0.861 (0.503–1.219)
Antipsychotics exposed: case period	0.280 (0.041–0.519)	0.278 (0.040–0.517)
Antipsychotics exposed: control period	0.075 (−0.180–0.330)	0.075 (−0.180–0.330)
Antipsychotics exposed: both periods	0.155 (−0.046–0.356)	0.152 (−0.049–0.353)
Antidepressants exposed: case period	0.768 (0.485–1.052)	0.772 (0.489–1.055)
Antidepressants exposed: control period	0.439 (0.130–0.747)	0.436 (0.128–0.744)
Antidepressants exposed: both periods	0.302 (0.1561–0.4483)	0.302 (0.156–0.449)
Weak anticholinergics exposed: case period	0.028 (−0.140–0.196)	0.039 (−0.129–0.207)
Weak anticholinergics exposed: control period	0.021 (−0.153–0.195)	0.010 (−0.164–0.185)
Weak anticholinergics exposed: both periods	−0.116 (−0.209 - -0.024)	−0.116 (−0.208–0.024)
Strong anticholinergics exposed: case period	1.237 (−1.537–4.011)	1.142 (−1.632–3.916)
Strong anticholinergics exposed: control period	1.065 (−1.709–3.838)	1.064 (−1.710–3.837)
Strong anticholinergics exposed: both periods	1.246 (−0.582–3.074)	1.245 (−0.584–3.073)
Dementia diagnosis before index-date	1.361 (0.798–1.925)	1.369 (0.805–1.932)

ethnicity. The index date is the day the individual was diagnosed with delirium for the first time. We used shorter, 3-day case and control periods in the sensitivity analyses and compared antimuscarinic use in the risk and reference periods.

2.6.2 | Subgroup analysis

We were interested to understand the risk of delirium posed by anti-muscarinics in the study population with and without dementia. We hypothesised that dementia status might be a potential effect modifier/interaction to explore. We identified dementia cases using ICD-10-AM codes G308, G309, F002, F009, F019, acetylcholinesterase inhibitors, donepezil and rivastigmine subsidised by PHARMAC for the treatment of dementia.

2.6.3 | Dose–response analysis

The dose–response analysis (Table 3) was done using a case-time-control design. The total dosages of drugs exposed within observation periods were computed as continuous variables instead of binary exposure indicators. For this reason, longer, 7-day case and control periods were used.

To calculate the total dosage exposed within the case and the control periods for each prescription, we counted the number of days the prescription overlapped within the case period, multiplied by the daily dose specified, summed all prescriptions and repeated the calculation for the control period. Then, we computed the increase in total dosage exposed from the control to the case period.

We used the multivariate binary logistic regression model to adjust for covariates (age, gender, ethnicity, any use of effect modifiers, etc.), the change of log(OR) of incident delirium at the end of the

case period (i.e. the index date), in response to one unit increase in total dosage exposed from the control to the case period. In Table 3, we report a change in log (odds ratio) with 95% CI with one unit increase in dosage. For effect modifying drugs, these are changes in log(odds ratio) compared to non-exposure.

The pharmaceutical collections (Pharms) and NMDS data were made available as annual, CSV-formatted datasets. The filtering mentioned above and cohort-construction procedures were performed using a computer program written in R (3.4.2, R Core Team, 2016). All analyses were performed using the R software, version 3.2.1.5.[24]

3 | RESULTS

3.1 | Study participants

We identified 4818 individuals (mean age 82.14) from 2005 to 2015 with incident delirium and exposed to at least one of the antimuscarinic of interest, with or without co-exposures to any of the effect-modifying drugs of interest. Of these, 333 had at least one prescription record of the oxybutynin, and 1137 had at least one prescription record of solifenacin within the 80-day study period. The distribution of ages was slightly skewed towards the higher age group, and there were more males than females. However, most of them were NZ Europeans, and only a few belonged to the Māori ethnic group (Table 1).

3.2 | Primary analyses

The case-time-control matched odds ratio (MOR) for delirium with oxybutynin was (2.06, 95% confidence interval 1.07–3.96). Solifenacin was not associated with delirium (0.89, 95% CI 0.64–1.23) (Table 2).

3.3 | Sensitivity analyses

The case-time-control MOR for delirium using a shorter risk period (0–3 days) did not change the results. The MOR for delirium with oxybutynin was (2.24, 95% confidence interval 1.16–4.33). Solifenacin was also not associated with delirium (1.00, 95% CI 0.72–1.39) (Table 2).

3.4 | Secondary analyses

The dose–response risk of delirium was significant for oxybutynin (0.05, 95%CI 0.02–0.08) but not for solifenacin (−0.01, 95%CI −0.03 to 0.00). (Table 3).

3.5 | Subgroup analyses

A statistically significant association was found for oxybutynin in the non-dementia cohort (2.11, 95% CI 1.08–4.13) and the dementia cohort (1.25, 95%CI 0.05–26.9). On the other hand, solifenacin was

TABLE 4 The matched odds ratio (MOR) for delirium diagnosed in older adults (65 years and above) by dementia status who used antimuscarinics in a case-time-control study

		No dementia					Dementia				
		Exposures within 5-day observation periods					Exposures within 5-day observation periods				
Drug	Delirium at index date	Neither	Case	Control	Both	MOR	Neither	Case	Control	Both	MOR
Oxybutynin	Yes	4336	80	53	177	2.11 (1.08–4.13)	149	5	4	14	1.25 (0.05–26.9)
	No (Reference)	13 112	20	28	28		163	1	1	2	
Solifenacin	Yes	3539	203	223	681	0.89 (0.64–1.23)	142	9	7	14	0.64 (0.04–8.62)
	No (Reference)	12 853	108	105	122		160	2	1	4	
Antibiotics	Yes	4442	76	45	83	1.96 (1.26–3.05)	165	3	0	4	N/A
	No (Reference)	12 710	124	144	210		158	6	1	2	
Antiepileptics	Yes	4576	9	15	46	0.60 (0.20–1.79)	169	1	1	1	N/A
	No (Reference)	13 107	15	15	51		166	0	0	1	
Antipsychotics	Yes	4386	73	62	125	1.07 (0.72–1.60)	164	4	2	2	2.00 (0.15–26.7)
	No (Reference)	12 575	175	159	279		160	2	2	3	
Antidepressants	Yes	4228	97	71	250	1.43 (0.97–2.11)	152	8	3	9	0.53 (0.04–6.67)
	No (Reference)	12 404	131	137	516		143	5	1	18	
Weak anticholinergics	Yes	3135	249	209	693	1.19 (0.96–1.48)	128	16	5	23	2.80 (0.67–11.7)
	No (Reference)	9992	563	563	2070		125	8	7	27	
Strong anticholinergics	Yes	4641	1	1	3	1.00 (0.02–50.4)	172	0	0	0	N/A
	No (Reference)	13 184	1	1	2		167	0	0	0	

not associated with delirium in non-dementia (0.89, 95%CI 0.64–1.23) as well as dementia cohort (0.64, 95%CI 0.04–8.62) (Table 4).

4 | DISCUSSION

Case-time-control analyses conducted on a population of older adults showed that oxybutynin increased the risk of new-onset delirium.

The safety profiles of antimuscarinics vary because of their dissimilarities to muscarinic receptor-subtype affinities. The five subtypes of muscarinic receptors (M1–M5) are widely distributed within the human body.[25] M3 receptors, mainly located in human detrusor muscle, are primarily responsible for normal micturition contraction. M1 receptors are widely distributed in the neocortex, hippocampus, and neostriatum. M2 receptors are relatively less common than M1 and play a significant role in memory and cognitive function.[26] Therefore, it is postulated that muscarinic receptor selectivity and permeability to the BBB are pivotal to expressing central anticholinergic adverse effects of antimuscarinics. Tertiary-amine antimuscarinics such as solifenacin have relatively fewer cognitive adverse effects than tertiary-amine antimuscarinics such as oxybutynin because the hydrophilic properties are less likely to cross the BBB.[27] Oxybutynin has a relatively higher affinity for M1 and M2 receptors over M3 subtype muscarinic receptors. Due to the higher blockade of M1 and M2 receptors, oxybutynin is more likely to contribute to delirium than solifenacin, as solifenacin is highly selective for the M3 receptor subtype found in the detrusor muscle of the urinary bladder.[28,29] Therefore, it is biologically plausible that oxybutynin, compared to solifenacin, is more likely to contribute to delirium. Our findings are plausible with this biological mechanism, and the dose–response risk of delirium being greater with oxybutynin than solifenacin is plausible too. The impact of antimuscarinics on delirium must be evaluated in frail older adults, and the treatment choice with an M3 selective agent must be given due consideration, particularly in those with pre-existing cognitive impairment.[30]

Interestingly, our study found differences in dose–response risk of delirium by type of antimuscarinic. A higher risk of delirium is associated with oxybutynin but not with solifenacin.

In both dementia and non-dementia subcohorts, a positive association was found with oxybutynin, and a negative association was found with solifenacin. Oxybutynin is a tertiary amine with a neutral charge, lipophilic, and low molecular weight, and hence can readily cross the blood–brain barrier and induce delirium.[31] In contrast, solifenacin is also a tertiary amine but has a relatively higher molecular weight, is less lipophilic than oxybutynin, and its muscarinic receptor selectivity is higher for the M_3 than M_1. It is also suggested that comorbid dementia may compromise the BBB function; however, due to the small sample size in our study, the confidence interval for the association of delirium with oxybutynin is wide in the dementia subcohort. Hence, the results must be interpreted with caution.

4.1 | Strengths

This study has several strengths, including its large size, nationwide coverage of older adults in NZ, and a case-time-control design to control for confounding of time-invariant confounders and adjustment for the time-trend bias antimuscarinics use in OAB. The new user design eliminated the bias likely to be introduced by including prevalent users of antimuscarinics. We also demonstrated a dose–response relationship between antimuscarinic exposure and the risk of new-onset delirium. The majority of validity assumptions of the case-control design were fulfilled in this study, including the indication is stable over time.[17,18,32] We applied a 5-week washout period considering the differences in half-lives of individual antimuscarinics.

4.2 | Limitations

In our analyses, we extracted the exposures and the outcomes from the administrative datasets. Hence, exposure misclassification due to the lack of information on medication consumption, self-medication and over-the-counter drugs such as NSAIDs linked to delirium may have biased the findings. In addition, we did not validate the ICD-10-AM codes for delirium to confirm a diagnosis, which could have impacted our findings by misclassifying the cases. Previous studies have reported a low sensitivity of 9–28%[33,34] but high 85–99% specificity[35,36] of ICD codes for delirium. Literature has also identified the potential for under-reporting and under-recognising delirium in older hospitalised patients.[37,38] The retrospective nature of our study design does introduce selection bias. The shortcomings of both the case-crossover and case–control designs are carried into the case-time-control design, including bias created by selecting the case and control windows, a control group, and inadequate adjustment for time-varying confounders.

5 | CONCLUSION

The study found that oxybutynin but not solifenacin is associated with a risk of new-onset delirium in older adults. The higher blockade of M1 and M2 receptors by oxybutynin is likely to contribute to delirium than solifenacin, which is highly selective for the M3 receptor subtype. Therefore, the treatment choice with an M3 selective agent must be given due consideration, particularly in those with pre-existing cognitive impairment.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

We obtained ethical approval from the Human Research Committee. The Ethical Implications of Research Activity Form (EIRA1-5312) to conduct this study was approved on October 20, 2020, by the University of Bath.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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