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Original Study

A Longitudinal Treatment Effect Analysis of Antipsychotics on Behavior of Residents in Long-Term Care

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A B S T R A C T

Objective: The proportion of long-term care (LTC) residents being treated with antipsychotic medication is high, and these medications may exacerbate behavioral symptoms. We used propensity scores to investigate the effect of antipsychotic use on the worsening of behavioral symptoms among residents in LTC facilities.

Design: A retrospective study.

Setting and participants: Residents in LTC in 8 provinces and 1 territory in Canada, without severe aggressive behavior at baseline and reassessed at follow-up, between March 2000 and March 2022.

Methods: We used propensity score matching and weighting to balance baseline covariates and logistic regression to estimate the effect of antipsychotics on the worsening of behavioral symptoms in the original, matched, and weighted cohorts. The treatment variable was use of antipsychotic medication at baseline and the outcome was worsening of behavior at follow-up.

Results: A total of 494,215 participants were included [318,234 women and 175,981 men; mean age 82.8 years (SD 10.1; range 18−112)].130 558 (26.4%) used antipsychotics at baseline and 88,632 (17.9%) had worsening behavior in follow-up. In the matched cohort, there were 249,698 participants, and 124,849 were matched (1:1) in each treatment group. There was a significant association between antipsychotic use at baseline and worsening in behavior at follow-up in the adjusted regression models [OR 1.27 (95% CI 1.25−1.29), <0.0001] as well as in matched [OR 1.20 (95% CI 1.17−1.21), <0.0001] and weighted [OR 1.26 (95% CI 1.24−1.28), <0.0001] cohorts.

Conclusions and implications: This study further evidence to support the cautious use of antipsychotics in LTC facilities. Future research in LTC facilities could include a more granular analyses of behavior change, including bidirectional analyses between different symptom severity classifications.

Antipsychotics are commonly used off-label as first-line agents for pharmacological treatment of behavioral and psychological symptoms of dementia (BPSD) in long-term care (LTC) facilities. Approximately 26% of residents in Canada were treated with these medications outside the approved indications between the 2014-2015 and 2019-2020 periods.[1] Over the past 3 decades, health care agencies have made efforts to change prescription practices to reduce the chronic use of antipsychotics in nursing homes.[2] Furthermore, there has been a major push to reduce the inappropriate use of antipsychotics in the treatment of BPSD due to risk of side effects and concerns about safety and quality of care among persons with dementia.[3,4]

BPSD symptoms include irritability, aggression, agitation, delusions, hallucinations, anxiety, psychosis, depression, sleep or appetite changes, apathy, dysphoria, wandering, repetitive questioning, sexually inappropriate behaviors, and refusal of care.[5-7] BPSDs are frequently experienced in LTC facilities and can be distressing for patients, difficult to manage for caregivers and staff, and can significantly affect the prognosis and management of dementia.[4,6,8,9] Despite

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evidence of small clinical benefits and potential serious adverse effects, some physicians consider antipsychotics to be an efficacious treatment option for BPSD.[10]

A retrospective study with community-dwelling patients diagnosed with dementia being treated with atypical antipsychotics over a period of up to 2 weeks found that more than 40% of the sample had worsening behavioral symptoms.[11] In addition, studies suggest that risks associated with antipsychotic use such as cardiovascular events and death may outweigh the benefits for the treatment of BPSD.[12,13] It should be noted that antipsychotics have shown modest superiority compared with placebo in clinical trials involving older adults with BPSD,[14] and no relevant differences in terms of efficacy have been reported across different compounds.[15]

Although the risks and benefits of these medications are widely discussed in the literature, evidence on the association between the use of antipsychotics and worsening behavior in LTC residents is limited. In addition, clinical trials tend to demonstrate efficacy rather than effectiveness, which limits understanding of the true treatment effect in real-world conditions.[16] Thus, no study has analyzed the effect of antipsychotic use on worsening behavior in a representative sample of LTC residents while accounting for the research strategies to address the methodological gaps.

Therefore, this study aimed to investigate the effect of antipsychotic use on the worsening of behavioral symptoms among a representative sample of residents in LTC facilities. Treatment effect analyses (TEA) with propensity scores (PS) matched and weighted were used to estimate the causal effects of antipsychotic use with existing observational data.

Methods

Study Design, Data Collection, and Participants

This longitudinal study used data collected in LTC facilities in Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Nova Scotia, Ontario, Saskatchewan, and Yukon territory provinces from Canada between March 2000 and March 2022. Data were deidentified and collected quarterly throughout the year using the interRAI Minimum Data Set 2.0,[9] which is standardized clinical person-centered assessment mandated in LTC facilities. These assessments are completed by a trained assessor (usually nurses). The interRAI suite of assessments has been shown to be reliable across 12 countries and across health care sectors. With respect to data quality, there is evidence to demonstrate high-quality health care data.[17]

We included individuals aged 18 years or older at baseline with 2 assessments in which their first assessment (baseline) and the next closest assessment (follow-up) were used. Only residents who were alive at the follow-up assessment were included in this analysis. Individuals experiencing severe aggressive behaviors, as measured by a score of 5 or higher on the Aggressive Behavior scale (ABS) at baseline were excluded.[18]

Research Ethics approval was obtained (ORE# 30173). Written informed consent was not required from each participant, following national legislation and institutional requirements in Canada.

Outcome and Treatment Variables

Behavior symptoms were measured using the ABS scale, a 12-point scale with higher scores indicating a higher frequency and combination of aggressive behaviors. The ABS scale consists of items that capture abuse (verbal and physical), resisting care, and socially inappropriate or disruptive behaviors.[18] The outcome variable behavior change was dichotomized as follows: *same* that included those participants classified as not having an increase in the frequency and intensity of aggressive behavior at baseline and whose status had not changed at follow-up (ABS scale score <5); *worse* that included those participants with an ABS score of 0 to 4 at baseline and a score of 5+ at their follow-up assessment. This cutoff for behavior change was based on previous literature that used interRAI data.[19,20] The treatment examined in this study was the use of antipsychotic medications in the 7 days before the assessment at baseline, a specific item of the interRAI Minimum Data Set 2.0. The variable antipsychotic use at baseline was based on information extracted from physician order sheets and medication administration records. Antipsychotic use was dichotomized as "yes" if they have taken antipsychotic medications and "no" if they have not taken antipsychotic medications at baseline.

Covariates

We used demographic and social variables, such as age group and sex assigned at birth collected by the staff (male or female). Social engagement was examined using the Index of Social Engagement (ISE). The ISE describes the person's sense of initiative and social involvement in the LTC facility, and higher scores are indicative of higher levels of social participation. The ISE variable was categorized into 2 groups (0–2 and 3+).[18,21]

We included clinical variables, such as the modified version of the Armstrong frailty index. The modified version contains 43 items that were all available in the MDS 2.0 assessment used for these analyses. The following cutoffs were used in this study: <0.2 was assigned to non-frail, ≥ 0.2 and ≤ 0.3 for pre-frail, and >0.3 for frail. These cutoffs are consistent with previous literature in supportive living environments.[22] Fall risks were assessed through the interRAI falls risk Clinical Assessment Protocol (CAP), which assesses the risk of falling in an LTC facility (no falls risk, medium risk, and high risk).[23] The interRAI pain scale captures the frequency and intensity of pain, and higher scores are indicative of higher pain.[24] The Changes in Health, End-Stage Disease and Signs and Symptoms (CHESS) scale detects health instability. Higher scores on the CHESS scale are associated with adverse health outcomes. The CHESS scale was categorized as 0, 1 to 2, and 3 to 5.[25,26] The Activities of Daily Living Self-Performance Hierarchy Scale (ADL-S) was also used; higher scores indicate loss greater functional loss across areas of self-care (eg, toileting, locomotion, hygiene, and eating).[27]

Mental health and neurological variables were included such as Alzheimer's disease or dementia (Yes or No), diagnosis of psychosis (Yes or No), and delirium (Not triggered and triggered) as captured using the delirium CAP.[28] We also used the Cognitive Performance Scale (CPS), an observational scale with higher scores indicating more severe cognitive impairment. The CPS variable was categorized into groups: 0, 1, 2–3, and 4–6.[29] The Depression Rating Scale (DRS) was used to measure signs and symptoms of depression. DRS scores range from 0 to 14, and scores of 3 and higher indicate potential problems with depression.[30]

Propensity Score

TEA was used to examine the effect of antipsychotic use on the worsening of behavioral symptoms. Specifically, we used PS matching and PS weighting. PS represents the probability of receiving a treatment when considering a set of baseline characteristics. Creating a PS is done to mimic the randomization process in an experimentally designed study, which allows us to estimate the effect of the treatment in an observational study.[31]

For PS matching, the logit of the PS was used to match those receiving the treatment to those who did not receive the treatment. One-to-one, nearest neighbor matching was used with a conservative caliper of 0.2. PS matching can be applied with or without replacement (one-to-one matching) and the latter is more common in the literature.[32] Furthermore, there is evidence to support a caliper width

Table 1
Baseline Characteristics Before Matching

Characteristics	Total (n = 494,215)	Antipsychotic Use: No (n = 363,657)	Antipsychotic Use: Yes (n = 130,558)	SMD*
Age groups, n (%)				
18–64	28,735 (5.8)	18,520 (5.1)	10,215 (7.8)	−0.28
65–74	53,844 (10.9)	34,904 (9.6)	18,940 (14.5)	
75–84	158,069 (32.0)	110,738 (30.5)	47,331 (36.3)	
85–94	216,283 (43.8)	168,145 (46.2)	48,138 (36.9)	
≥95	37,284 (7.5)	31,350 (8.6)	5934 (4.5)	
Sex, n (%)				
Male	175,981 (35.6)	125,558 (34.5)	50,423 (38.6)	−0.08
Female	318,234 (64.4)	238,099 (65.5)	80,135 (61.4)	
ISE, n (%)				
≤2	204,739 (41.4)	140,886 (38.7)	63,853 (48.9)	−0.20
≥3	289,476 (58.6)	222,771 (61.3)	66,705 (51.1)	
ADRD, n (%)				
No	210,944 (42.7)	174,683 (48.0)	36,261 (27.8)	0.45
Yes	283,271 (57.3)	188,974 (52.0)	94,297 (72.2)	
Psychosis, n (%)				
No	472,564 (95.6)	356,776 (98.1)	115,788 (88.7)	0.29
Yes	21,651 (4.4)	6881 (1.9)	14,770 (11.3)	
Delirium, n (%)				
Not triggered	464,455 (94.0)	344,292 (94.7)	120,163 (92.0)	0.09
Triggered	29,760 (6.0)	19,365 (5.3)	10,395 (8.0)	
Falls risk, n (%)				
No falls risk	397,857 (80.5)	294,960 (81.1)	102,897 (78.8)	0.04
Medium risk	63,847 (12.9)	45,379 (12.5)	18,468 (14.2)	
High risk	32,511 (6.6)	23,318 (6.4)	9193 (7.0)	
CHESS, n (%)				
0	267,594 (54.2)	194,038 (53.4)	73,556 (56.3)	−0.01
1–2	206,692 (41.8)	154,721 (42.5)	51,971 (39.8)	
3–5	19,929 (4.0)	14,898 (4.1)	5031 (3.9)	
CPS, n (%)				
0	61,793 (12.5)	54,222 (14.9)	7571 (5.8)	0.40
1	68,716 (13.9)	55,799 (15.3)	12,917 (9.9)	
2–3	273,513 (55.3)	198,155 (54.5)	75,358 (57.7)	
4–6	90,193 (18.3)	55,481 (15.3)	34,712 (26.6)	
Pain, n (%)				
0	292,905 (59.3)	210,905 (58.0)	82,000 (62.8)	−0.11
1	125,523 (25.4)	94,048 (25.9)	31,475 (24.1)	
2	65,137 (13.2)	50,175 (13.8)	14,962 (11.5)	
3	10,650 (2.1)	8529 (2.3)	2121 (1.6)	
ADL-S, n (%)				
0	31,383 (6.3)	23,499 (6.5)	7884 (6.0)	−0.00
1–2	130,283 (26.4)	94,764 (26.0)	35,519 (27.2)	
3–6	332,549 (67.3)	245,394 (67.5)	87,155 (66.8)	
DRS, n (%)				
≤2	395,098 (80.0)	299,659 (82.4)	95,439 (73.1)	0.20
≥3	99,117 (20.0)	63,998 (17.6)	35,119 (26.9)	
Frailty, n (%)				
Non-frail	171,374 (34.7)	128,727 (35.4)	42,647 (32.7)	0.09
Pre-frail	219,154 (44.3)	162,626 (44.7)	56,528 (43.3)	
Frail	103,687 (21.0)	72,304 (19.9)	31,383 (24.0)	

*SMD, Standardized mean difference statistic was used before PS matching to verify the balance of the covariate distribution by antipsychotic use categories. An SMD value of < 0.1 of the absolute value is considered the cut point for a small imbalance.

equal to 0.2 of the standard deviation of the logit of the PS. A caliber of 0.2 can minimize the mean squared error of the estimated effect.[31]

The PS matching approach generates an average treatment effect for those who were treated (ATT). For PS weighting, weights derived from PS were created as the inverse of the probability of receiving or not receiving treatment, resulting in a balanced pseudo-population. The advantage of the weighting technique is that all participants are retained for analyses compared with matching, wherein the unmatched are not retained. This approach can generate the average treatment effect (ATE), which is the average difference in the score between the treated and the controls. The ATT and the ATE are both generated using logistic regression models that account for the PS and thus a more robust analytic approach compared with logistic regression alone.[31,33] The absolute standardized mean differences were used to assess the balance of the covariates before and after PS matching and weighting. A standardized mean difference of <0.1 of the absolute value was used because this is considered the cut point for a small imbalance,[34] and the results were expressed in absolute numbers and through the love plot.

Covariates considered in the creation of the PS included age groups, sex, delirium, ADL-S, a diagnosis of Alzheimer's disease or dementia, a diagnosis of psychosis, frailty, falls risk, pain, the CHESS scale, the DRS scale, and ISE. These variables were selected based on existing literature and included because of their simultaneous relationship with the treatment and the outcome variables (confounders) or their relationship only with the outcome.[3,5,9,33] To this end, directed acyclic graphs (DAG) via the hill-climbing (HC) algorithm were used.[35] We estimated the DAG models for all covariates and we also created separate graphs to better visualize the relationships between variables. The identified confounders were age, sex, ISE, falls, CHESS, pain, ADL-S, CPS, psychosis, and Alzheimer's disease or related dementia (ADRD), whereas frailty was related to the outcome. Only the DRS and delirium covariates did not influence the treatment and/or outcome variable. However, these covariates were retained for PS analysis as

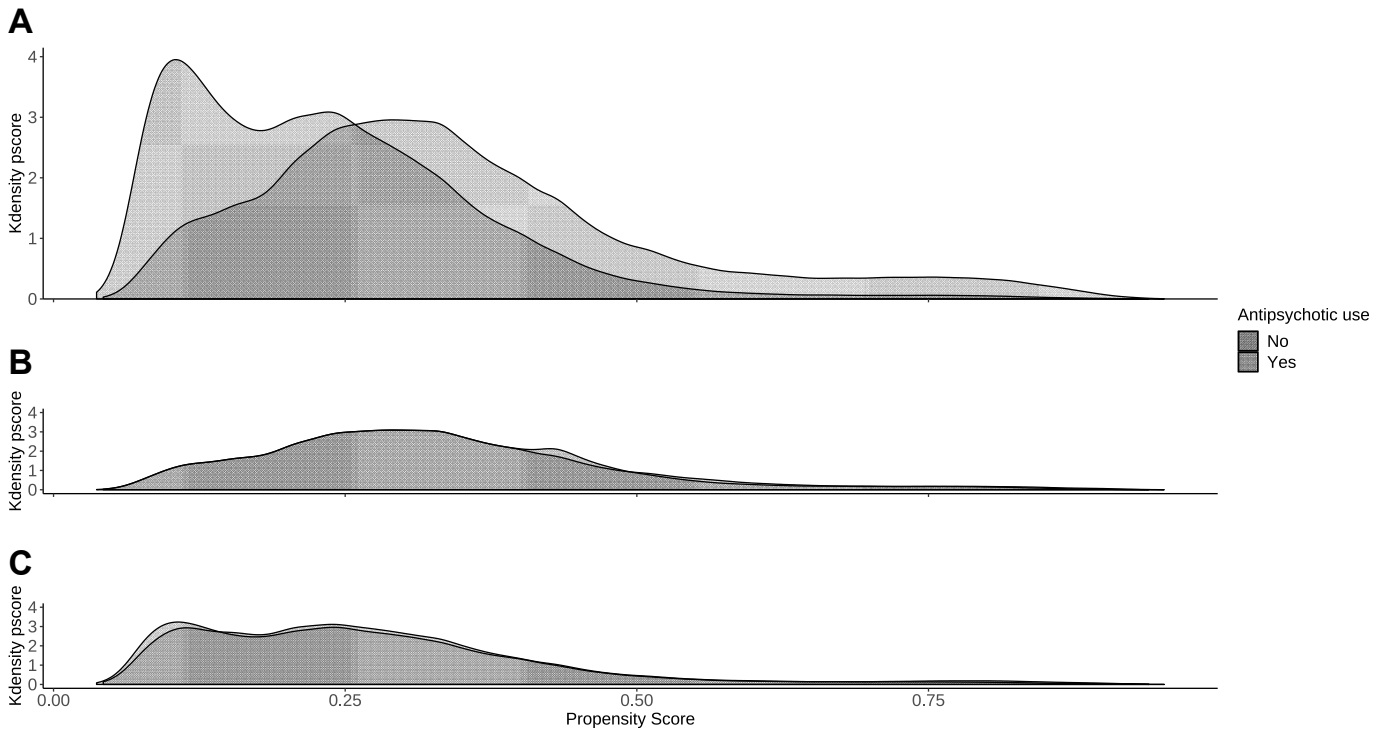

Fig. 1. Distribution of PS in the antipsychotic use groups in original (A), matched (B), and weighted (C) samples. Note: The x-axis shows the probability of receiving or not receiving antipsychotics, that is, PS values. The y-axis shows the distribution of PS values. The blue color density plot represents the PS values for the Yes category and the red color for the No category of the antipsychotic use variable.

both are clinically important (Supplementary Figure 1). The relationships between covariates, treatment, and outcome also were investigated through the χ^2 test (Supplementary Tables 1 and 2).

After the variable selection stage, we estimated a regression model to regress the antipsychotic use variable on all covariates in order to obtain the distribution of PS between groups of the treatment variable. This step is important to verify if there is an overlap in the probability of receiving the treatment between treatment groups, that is, "common support." Once sufficient overlap is identified, it is possible to find correspondence between groups and therefore proceed to the next stages.[33]

Statistical Analysis

Chi-square tests were used in the descriptive analyses at baseline. Frequencies and proportions of baseline characteristics of individuals included in this study were shown with standardized mean difference from PS analysis. We considered a *P* value of less than .05 to be significant.

The effect of antipsychotic use on the outcome behavior change was verified in 3 different samples: the original sample without covariate balance, as well as matched and weighted samples. Thus, we fit 3 logistic regression models with behavior change as a dependent variable and antipsychotic use as the main independent variable. In the first crude logistic regression model, only the effect of the independent variable antipsychotic use on behavior change with the original sample was verified. In the second model, we adjusted this treatment effect for all confounders. This second model also was fitted with the original sample. Finally, we fit 2 logistic regression models with antipsychotic use as an independent variable on the outcome with the matched and weighted samples. In logistic regression with the original sample, the treatment effect can be interpreted as a traditional analysis (ie, the effect of the independent variable on the dependent variable crude and after adjustment for all confounders). In the regression model for the matched sample, the average effect was verified only in the treatment group or ATT, considering the participants who were expected to receive and not to receive treatment. In the regression model for the weighted sample, the average effect was verified both in the treatment and comparison groups (ATE), considering the participants who were expected to receive and expected not to receive treatment. Listwise deletion was applied in all analyses. R version 4.2.2 (R Core Team, 2021) was used for all the data analyses. (Supplementary Figure 2).

Results

A total of 532,981 LTC residents 18 years or older were identified; 38,608 (7.2%) were excluded because they experienced severe behavioral symptoms at baseline. The number of days between assessments ranged from 0 to 200 and the average number of days between assessments was 84.9 days. Missing data across key scales and CAPs were also excluded from analyses. A total of 158 (0.03%) participants were excluded because they had missing data (Supplementary Figure 3). A total of 494,215 participants were included in this study [mean age 82.8 years (SD 10.1; range 18−112)]. Of these, 318,234 (64.4%) were women, 158,069 (43.7%) were aged between 75 and 84 years, and 130,558 (26.4%) used antipsychotics at baseline. Differences in proportions in the baseline characteristics were observed according to treatment groups. Specifically, compared with individuals who did not use antipsychotics, those who used antipsychotics tended to be younger with a higher proportion of ADRDs (72.2% vs 51.7%), psychosis (11.3% vs 1.9%), high risk of future falls (7.0% vs 6.4%), cognitive impairment by a CPS score of 4 to 6 (26.5% vs 15.2%), depressive symptoms by a DRS score of 3 or greater (26.9% vs 17.6%), delirium (7.9% vs 5.3%), and frailty (24.0% vs 19.8%). Standardized differences ranged from −0.28 to 0.45, showing the

Table 2
Baseline Characteristics After Matching

Characteristics	Total (n = 249,698)	Antipsychotic Use: No (n = 124,849)	Antipsychotic Use: Yes (n = 124,849)	SMD*
Age groups, n (%)				
18–64	17,116 (6.9)	8506 (6.8)	8610 (6.9)	−0.01
65–74	34,087 (13.7)	16,645 (13.3)	17,442 (14.9)	
75–84	91,255 (36.5)	45,700 (36.6)	45,555 (36.4)	
85–94	95,466 (38.2)	48,123 (38.8)	47,343 (37.5)	
≥95	11,774 (4.7)	5875 (4.5)	5899 (4.3)	
Sex, n (%)				
Male	95,419 (38.2)	47,493 (38.1)	47,926 (38.4)	−0.00
Female	154,279 (61.8)	77,356 (61.9)	76,923 (61.6)	
ISE, n (%)				
≤2	121,664 (48.7)	61,000 (48.8)	60,664 (48.6)	0.00
≥3	128,034 (51.3)	63,849 (51.2)	64,185 (51.4)	
ADRD, n (%)				
No	65,487 (26.4)	31,547 (25.3)	34,310 (27.5)	−0.05
Yes	183,841 (73.6)	93,302 (74.7)	90,539 (72.5)	
Psychosis, n (%)				
No	233,551 (93.5)	118,126 (94.6)	115,425 (92.5)	0.06
Yes	16,147 (6.5)	6723 (5.4)	9424 (7.5)	
Delirium, n (%)				
Not triggered	230,081 (92.3)	115,239 (92.3)	114,842 (92.0)	0.01
Triggered	19,617 (7.7)	9610 (7.7)	10,007 (8.0)	
Falls risk, n (%)				
No falls risk	196,876 (79.3)	98,740 (79.1)	98,136 (78.6)	0.00
Medium risk	35,115 (13.6)	17,223 (13.8)	17,892 (14.3)	
High risk	17,707 (7.1)	8886 (7.1)	8821 (7.1)	
CHESS, n (%)				
0	139,042 (55.7)	69,271 (55.5)	69,771 (55.9)	0.00
1–2	101,082 (40.5)	50,908 (40.8)	50,174 (40.2)	
3–5	9574 (3.8)	4670 (3.7)	4904 (3.9)	
CPS, n (%)				
0	14,324 (5.8)	6904 (5.5)	7420 (5.9)	−0.03
1	23,554 (9.4)	11,071 (8.9)	12,483 (10.0)	
2–3	144,599 (57.9)	72,660 (58.2)	71,939 (57.7)	
4–6	67,221 (26.9)	34,214 (27.4)	33,007 (26.4)	
Pain, n (%)				
0	156,603 (62.7)	78,829 (63.1)	77,774 (62.3)	0.02
1	60,323 (24.2)	29,967 (24.0)	30,356 (24.3)	
2	28,759 (11.5)	14,104 (11.3)	14,655 (11.7)	
3	4013 (1.6)	1949 (1.6)	2064 (1.7)	
ADL-S, n (%)				
0	14,545 (5.6)	7003 (5.6)	7542 (6.1)	−0.01
1–2	66,815 (26.6)	33,163 (26.5)	33,652 (26.9)	
3–6	168,338 (67.8)	84,683 (67.8)	83,655 (67.0)	
DRS, n (%)				
≤2	183,284 (73.4)	91,804 (73.5)	91,480 (73.3)	0.00
≥3	66,414 (26.6)	33,045 (26.5)	33,369 (26.7)	
Frailty, n (%)				
Non-frail	79,644 (31.9)	39,752 (32.4)	40,433 (32.4)	−0.01
Pre-frail	109,157 (43.7)	54,930 (43.4)	54,238 (43.4)	
Frail	60,897 (24.4)	30,037 (24.2)	30,178 (24.2)	

*SMD, Standardized mean difference statistic was used after propensity score matching to verify the balance of the covariate distribution by antipsychotic use categories. An SMD value of < 0.1 of the absolute value is considered the cut point for a small imbalance.

imbalance of covariates between treatment and comparison groups in the unadjusted sample (Table 1).

Sufficient overlap in PS distribution was observed when comparing the 2 groups of the antipsychotic use variable (Figure 1A). A high degree of balance for both PS matching and weighting suggested no substantial difference between these 2 approaches in terms of the probability of receiving the treatment for the adjusted sample (Figure 1B and C). In the PS matching analysis, 244,517 individuals were unmatched, of whom 238,808 (97.6%) were from the untreated group and 5709 (2.4%) were from the treated group. The matched cohort included 249,698 participants. No baseline covariates were unbalanced after matching (absolute standardized mean values close to zero) (Table 2).

For both PS matching and weighting methods, the initial imbalance of demographic, social, and clinical characteristics at baseline between the treatment and comparison was within the recommended limit of 10% and below (Figure 2). The odds of worsening in behavior symptoms at follow-up were greater in participants who used antipsychotics than those who did not use antipsychotics at baseline in the crude analysis [odds ratio (OR), 1.52; 95% CI, 1.50–1.54; $P < .0001$]. After adjustment for confounders, the odds of worsening behavior symptoms were still greater among those using antipsychotics (adjusted OR, 1.27; 95% CI, 1.25–1.29; $P < .0001$) in the original sample. The association between antipsychotic use at baseline and worsening in behavior at follow-up was also evidenced in the regression models that used dataset after PS matching (OR, 1.20; 95% CI, 1.17–1.21; $P < .0001$) and weighing (OR, 1.26; 95% CI, 1.24–1.28; $P < .0001$) (Table 3).

Discussion

We analyzed the effect of antipsychotic use on the worsening of behavioral symptoms in a representative sample of LTC residents from multiple provinces and territories across Canada. To our knowledge, this is the first national longitudinal observational study that has used

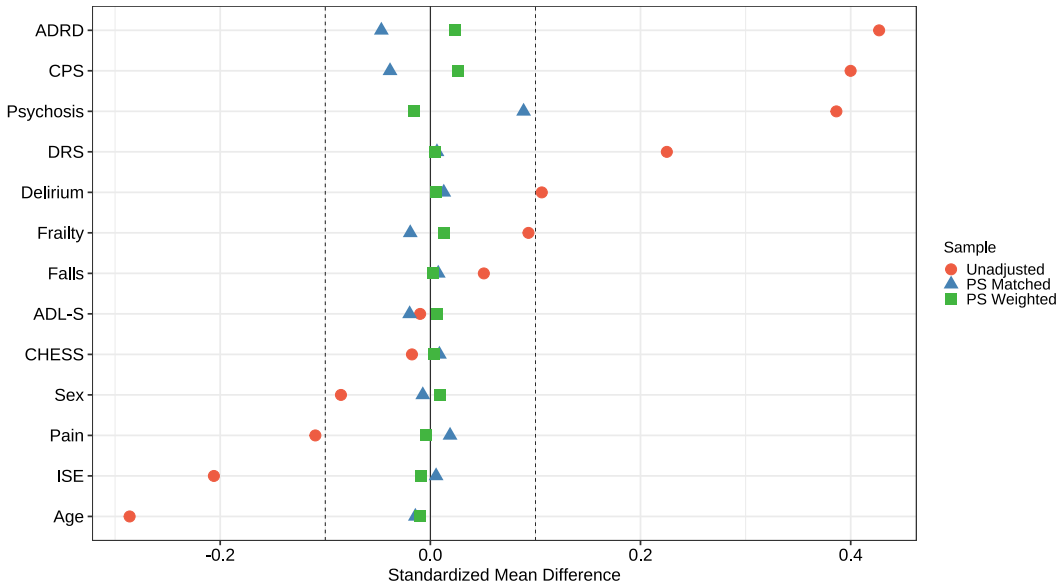

Fig. 2. Balancing covariates before and after PS matching and weighting by selected individuals' characteristics. Note: Black dotted lines represent standardized mean differences between – 0.10 and 0.10 indicating adequate balance. Red objects represent the standardized mean difference before PS. Blue and green objects represent the standardized mean difference after PS matching and weighting, respectively.

PS methods to explore this relationship. Irrespective of the statistical methods used (logistic regression, PS matching, PS weighting), the association between antipsychotic use and worsening behavior was consistent. Higher accuracy is achieved with PS methods because the approach reduces the sampling bias that is common in observational studies where the randomization process is not possible.[31]

This study extends our current understanding of pharmacological interventions beyond efficacy. Consistent with existing literature, similar characteristics were observed in the current study among those taking antipsychotics as having a diagnosis of dementia,[36] being frail, experiencing more severe cognitive impairment, and having a high risk of falls.[37]

The findings from the current study also indicate that antipsychotics are minimally effective for behavior change. In fact, our analyses show they contribute to a 27% increase in the odds of worsening behavior among those who take them. Extrapyramidal symptoms (eg, tremor, rigidity, painful dystonia, inability to stand and walk, and akathisia) are common side effects of antipsychotics that could also exacerbate BPSD.[38] Further, adverse effects related to the anticholinergic activity of antipsychotics, such as sedation, delirium, and worsened cognitive function, can influence the emergence of new behavioral and psychotic symptoms or worsen those already present.[39]

Despite the risks associated with off-label antipsychotic use, they are frequently prescribed in LTC facilities.[1] Some reports suggest that off-label antipsychotic prescriptions may be used to combat stress during the transition from the community to LTC facilities.[40] Even with little effectiveness and restricted recommendations, the prescription of antipsychotics in the treatment of BPSD was more frequent than the prescription of antidepressants, even when behavioral symptoms were associated with depression, and pharmacological treatment was used more than non-pharmacological treatment.[41] Off-label antipsychotic use also presents risks that can range in severity from drowsiness to cerebrovascular diseases and death.[42] Our findings support the importance of focusing on non-pharmacological approaches to care, especially in the setting of those experiencing BPSD.

Non-pharmacological treatment is an effective option in the treatment of BPSD. Effective interventions include real or simulated social contact, behavioral therapy, reality orientation, multisensory therapy, music therapy, art therapy, age-appropriate exercise, walking activities, and functional exercises to reduce behavioral symptoms (eg, agitation and aggression) in LTC facilities.[43,44] Other indirect interventions include training or approaches with caregivers and multidisciplinary teams and modifying environmental factors that may be related to behavioral symptoms. A randomized controlled trial analyzed the effectiveness of person-centered care and psychosocial interventions among people with dementia living in nursing homes. The findings demonstrated that interventions such as person-centered care training, social interactions, and education about antipsychotic medications were associated with improved quality of life, reduced agitation, and general neuropsychiatric symptoms.[45] Although the positive effects of non-pharmacological treatment are widely discussed in the literature, these approaches are infrequently and inconsistently implemented.[46]

It is also well established that off-label antipsychotic use is an important national quality indicator in LTC facilities in Canada.[20,47] Interventions including education, training, and tailored strategies, have previously been effective in reducing the potentially inappropriate use of antipsychotics. A 30% reduction in the odds of remaining on antipsychotics was observed among Canadian adult nursing home residents in the intervention homes compared with the controlled homes between 2014 and 2016.[20] Early identification of LTC facilities whereby rates of inappropriate antipsychotic use are high could benefit from the aforementioned interventions and residents could be monitored for behavioral symptoms.[47] Monitoring both resident-level and facility-level indicators of off-label antipsychotic use and subsequent behaviors could be critical in optimizing care quality, in addition to staff and resident safety. The aforementioned client-level and facility-level interventions related to holistic interdisciplinary non-pharmacological approaches are all potential options to proactively manage BPSD and prevent potential care quality issues.

This study does have limitations. First, there is the possibility of additional confounding factors that were not included in the analyses and/or not captured within the assessment. However, both PS methods demonstrated an excellent balance between relevant covariates and confounders that were carefully selected based on the literature, suggesting that the sample was well-matched. Second, we

Table 3
Regression Models of Association Between Antipsychotic Use and Behavior Change

Logistic Regression model*	OR (95% CI)	*P* value
Crude		
Antipsychotic use	1.52 (1.50−1.54)	<.001
Adjusted for confounders†		
Antipsychotic use	1.27 (1.25−1.29)	<.001
Age, y		
18−64	Ref.	
65−74	0.91 (0.87−0.94)	.022
75−84	0.84 (0.81−0.87)	<.001
85−94	0.75 (0.73−0.78)	<.001
≥95	0.70 (0.65−0.73)	<.001
Female	0.82 (0.81−0.83)	<.001
ISE equal or higher 3	0.95 (0.93−0.97)	<.001
ADRD	1.50 (1.46−1.51)	<.001
Psychosis	1.01 (0.98−1.05)	.35
Falls risk		
No falls risk	Ref.	
Medium risk	1.06 (1.04−1.08)	<.001
High risk	1.09 (1.06−1.12)	<.001
CHESS		
0	Ref.	
1−2	1.09 (1.07−1.11)	<.001
3−5	1.16 (1.12−1.20)	<.001
CPS		
0	Ref.	
1	1.20 (1.16−1.25)	<.001
2−3	1.65 (1.60−1.70)	<.001
4−6	1.93 (1.86−1.99)	<.001
Pain		
0	Ref.	
1	1.01 (0.98−1.02)	.59
2	0.96 (0.94−0.99)	.011
3	1.07 (1.02−1.13)	.005
ADL-S		
0	Ref.	
1−2	1.14 (1.09−1.17)	<.001
3−6	1.22 (1.18−1.26)	<.001
PS matching‡		
Antipsychotic use	1.20 (1.17−1.21)	<.001
PS weighting		
Antipsychotic use	1.26 (1.24−1.28)	<.001

The goodness-of-fit of the adjusted model χ^2 9030 (20 degrees of freedom; $P <$ .0001).

*A total of 494,215 participants were included in the logistic regression model crude and adjusted for confounders; 130,558 of whom used antipsychotics and 88,632 had worsening behavior.

†The confounding factors considered in the adjusted analysis were extracted from the DAG causal models to compare with the crude treatment effect and treatment effect after PS analysis.

‡A total of 249,698 participants were included in the matched dataset; 124,849 of whom used antipsychotics and 53,202 had worsening behavior.

did not obtain information on whether residents were chronic users or new users of antipsychotics at baseline. The duration of treatment, the specific compounds that were prescribed, dosages, and frequency of use were not captured. Further, it was not feasible to thoroughly investigate issues of adherence to drug treatment; however, it is reasonable to expect high adherence within a supervised institutional setting. Last, randomization cannot be replaced and future pragmatic randomized studies that address these clinical conditions remain relevant. That said, our findings suggest that the onus is now on proponents of off-label use of antipsychotics to unequivocally demonstrate, with either TEA or clinical trials in frail older nursing home residents, that the use of these medications actually results in improved behavior.

A strength of our study was the large number of participants available in the period analyzed across several provinces/territories, reducing potential bias. Standardized assessments provided consistent data with minimized loss during follow-up. The assessment also allowed for the inclusion of psychosocial factors as covariates in the study, which are often overlooked in pharmacological controlled trials, and typically not considered inthe LTC facility environment.

Conclusions and Implications

Our findings provide evidence for caution in the correct use of antipsychotic medications in LTC facilities and promote the implementation of non-pharmacological interventions in the treatment of BPSD. Future research in LTC facilities could include a more granular analyses of behavior change, including bidirectional analyses between different symptom severity classifications.

Disclosures

The authors declare no conflicts of interest.

Supplementary Data

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.jamda.2024.105255.

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