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Research Report

Characterizing PRN Use of Psychotropic Medications for Acute Agitation in Canadian Long-Term Care Residents with Dementia Before and During COVID-19

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Abstract.
Background: Agitation is a disabling neuropsychiatric symptom of dementia. Pro re nata (PRN) injections of psychotropics can be administered for severe acute agitation, but little is known about the frequency of their actual use.
Objective: Characterize actual use of injectable PRN psychotropics for severe acute agitation in Canadian long-term care (LTC) residents with dementia and compare use before and during the COVID-19 pandemic.
Methods: Residents from two Canadian LTC facilities with orders for PRN haloperidol, olanzapine, or lorazepam between January 1, 2018–May 1, 2019 (i.e., pre-COVID-19) and January 1, 2020–May 1, 2021 (i.e., COVID-19) were identified. Electronic medical records were reviewed to document PRN injections of psychotropic medications and collect data on reason and demographic characteristics. Descriptive statistics were used to characterize frequency, dose, and indications of use, and multivariate regression models were used to compare use between time periods.
Results: Of the 250 residents, 45 of 103 (44%) people in the pre-COVID-19 period and 85 of 147 (58%) people in the COVID-19 period with standing orders for PRN psychotropics received ≥1 injections. Haloperidol was the most frequently used agent in both time periods (74% (155/209 injections) pre-COVID-19; 81% (323/398 injections) during COVID-19). Residents in the COVID-19 period were almost two times more likely to receive injections compared with those in the pre-COVID-19 period (odds ratio = 1.96; 95% CI = 1.15–3.34; $p = 0.01$).

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Conclusion: Our results suggest that use of PRN injections increased in LTC during the pandemic and contribute to the mounting evidence that agitation worsened during that time.

Keywords: Alzheimer's disease, antipsychotic agents, behavioral symptoms, benzodiazepines, COVID-19, dementia, haloperidol, lorazepam, olanzapine, psychotropic drugs

INTRODUCTION

Dementia is a debilitating syndrome that can be caused by a host of different neurodegenerative disorders, all of which involve progressive decline of cognitive and functional abilities [1]. For patients and their caregivers, non-cognitive disturbances known as neuropsychiatric symptoms (NPS) are some of the most challenging aspects of dementia to manage [2, 3]. Agitation is a particularly taxing NPS that occurs in 30–50% of dementia patients [4, 5], with some studies reporting rates as high as 70% [6]. According to the consensus definition of agitation developed by the International Psychogeriatric Association (IPA), agitated behaviors generally fall under three categories: excessive motor activity, verbal aggression, and physical aggression [7, 8]. These behaviors cannot be attributed to another cause and must be severe enough to impair social functioning or activities of daily living. The most recent update by the IPA acknowledges and defines acute agitation [8]. Unsurprisingly, agitation has been associated with many deleterious health outcomes, including decreased quality of life [9, 10], accelerated cognitive decline [11], earlier transfer to long-term care (LTC) [12], greater caregiver burden [13, 14], and increased mortality [15].

Pro re nata (PRN; "as needed") injections of typical antipsychotics, atypical antipsychotics, and benzodiazepines are sometimes used off-label to treat severe acute agitation where individuals exhibit behaviors that pose risk of harm to themselves or others [16–19]. Under such extreme circumstances, rapid relief is necessary and PRN injectables may be considered after verbal de-escalation and attempts to administer oral psychotropic medications have failed [18–20]. Intramuscular (IM) haloperidol (typical antipsychotic), olanzapine (atypical antipsychotic), and lorazepam (benzodiazepine) are a few of the most widely used agents for treating acute agitation that have demonstrated good efficacy and reasonable safety in frail geriatric populations [21].

Despite a substantial amount of research on antipsychotic and benzodiazepine use for agitation as a whole [22, 23], little is known about PRN use of injectable psychotropic medications for agitation in older adults with dementia [24–27]. In general, the prescription and administration of PRN injections of antipsychotics and benzodiazepines in acutely agitated patients may vary by clinician, institution-specific policies, and availability of pharmacological agents [24, 28]. A pitfall of this, as noted by a recent case study, is that clinicians may give undue preference to older, more familiar medications even in situations where newer agents may be more suitable [29]. As such, further research is needed to clarify some of the ambiguity surrounding current practices in the administration of PRN psychotropics for dementia-associated agitation.

Further complicating matters, there is an ever-expanding body of research showing that the ongoing coronavirus disease 2019 (COVID-19) pandemic has had serious negative effects on the psychological well-being of populations worldwide, including that of older adults [30, 31]. Agitation was commonly reported to have worsened overall in dementia patients since the emergence of COVID-19 [32, 33], which some studies suggest could be an inadvertent consequence of social contact restrictions [34, 35]. For LTC homes in Canada and elsewhere, this included measures such as isolating residents in their rooms during outbreaks, suspending in-person activity programs, and prohibiting or greatly limiting visits from family and friends [36–38]. During the first year of COVID-19 in Canada, residents also received fewer visits from physicians and more than half of LTC facilities reported critical shortages in direct-care staff (e.g., nurses, personal support workers), who play key roles in maintaining the quality of resident care [36, 39]. In light of these challenges, dementia patients residing in LTC may have been particularly vulnerable to poorer neuropsychiatric outcomes.

Moreover, there have been concerns that exacerbations of NPS combined with constraints such as staffing shortages may have led to a greater reliance on and use of psychotropic medications during the pandemic [40]. Data published by the National Health

Service in the United Kingdom showed that rates of antipsychotic drug prescribing among dementia patients were significantly higher in March, April, and May of 2020 as compared to the same months in 2018 and 2019 [41]. Conversely, a Dutch study by Sizoo et al. found that psychotropic drug use among LTC residents with dementia did not change significantly throughout the first wave of the pandemic [42]. However, very little focus has been given to psychotropic drugs that are administered on an as needed basis, which may explain these mixed findings. Specifically, it is unclear whether use of PRN psychotropic drugs for managing acute agitation changed after the emergence of COVID-19. To address this research gap, the present study aimed to 1) document the actual use of injectable PRN haloperidol, olanzapine, and lorazepam for severe acute agitation in dementia patients at two Canadian LTC facilities and 2) compare use of these psychotropic medications before and during the COVID-19 pandemic.

METHODS

Study design

A retrospective chart review was performed to document actual use of injectable PRN psychotropic medications in LTC residents with dementia and to compare use before and during the COVID-19 pandemic. We defined the pre-COVID-19 period as January 1, 2018–May 1, 2019 and the COVID-19 period as January 1, 2020–May 1, 2021 given that the first case of COVID-19 in Canada was reported on January 25, 2020 [43]. For each of the two 16-month periods, we reviewed the charts of all LTC patients with orders for PRN haloperidol, olanzapine, or lorazepam administered via subcutaneous or IM routes for agitation. Only patients diagnosed with dementia were included in the analysis. Ethics approval was received from the Research Ethics Board of Sunnybrook Health Sciences Centre as the Board of Record and accepted by Villa Colombo Toronto.

Setting

This study was conducted at two LTC facilities: Sunnybrook Health Sciences Centre (SHSC) and Villa Colombo Toronto (VC). SHSC is an academic research hospital affiliated with the University of Toronto [44]. The Veterans Program at SHSC provides long-term and complex care to over 300 veterans of World War II and the Korean War. Resident care units are located in two adjoined wings on the same campus as the acute care hospital and are characterized as: 1) Cognitive support to accommodate veterans with diagnoses of dementia and other challenging medical needs, 2) Physical support for residents with physical disabilities and chronic conditions, and 3) Palliative care catered to patients with advanced disease who are at the end-of-life stage [45]. For this study, patients on palliative floors were excluded. In addition, we included patients from the Dorothy Macham Home at SHSC, a specialized behavioral support unit that was established to manage dementia patients with the most challenging behavioral needs [46]. VC is a non-profit LTC home that primarily services Italian-Canadian seniors, providing 24-hour nursing and medical services to over 350 residents [47]. VC also offers behavioral support and restorative care programs to residents with impairments and behavioral needs.

While LTC is not listed as an insured health service under the *Canada Health Act*, LTC facilities in Canada are still partially or fully financed by public funding from provincial and territorial governments [48, 49]. In some jurisdictions, residents are required to contribute to the cost of accommodations and meals through co-payment fees [50]. According to the National Institute on Ageing, Canada spent CAD $27 billion on LTC in 2018; approximately 75% of the costs were publicly funded and the remaining 25% were paid for privately [51]. With this funding model, LTC is available to the majority of Canadians [51].

Data sources and outcomes

LTC file numbers with orders for injectable PRN haloperidol, olanzapine, or lorazepam in the pre-COVID-19 and COVID-19 periods were obtained from pharmacy records at SHSC and VC. For each chart, we reviewed consultation notes, discharge summaries, patient assessments, and progress notes on electronic medical records (EMR), and medication use on electronic Medication Administration Records (eMARs) used by clinical care staff at both sites. Data were extracted on time period (before or during COVID-19), site (SHSC or VC), age, sex, dementia diagnosis (type and severity), days of observation, care type (physical, cognitive, behavioral, or mixed), number of comorbidities, number of concomitant medications, and injection use (frequency, dose, indication).

Presence of dementia was established based on medical history and corroborated with cognitive assessment scores from the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), or Rowland Universal Dementia Assessment Scale (RUDAS). We checked LTC charts to confirm that all orders were written for agitation. We measured days of observation to capture the window of time during which a resident could potentially receive an injection. In other words, we considered the number of days that had elapsed from the beginning of the specified time period or the patient's date of admission (whichever came later) to the end of the specified time period or the patient's date of death (whichever came first). To characterize the specific manifestations of agitation for which PRN injections were given, we examined progress notes describing the events that occurred immediately before or during acute agitation episodes and categorized the patient's behavior according to the three domains of agitation specified by the IPA criteria (e.g., pacing would be classified as excessive motor activity, screaming as verbal aggression, kicking as physical aggression) [7, 8].

Statistical analysis

Data were analyzed with IBM SPSS statistical software version 28.0 (IBM Corporation, Armonk, NY) and SAS version 9.4 (SAS Institute, Inc., Cary, NC). Descriptive statistics with mean (standard deviation, SD), median (interquartile range, IQR), frequencies, and proportions were used to characterize our study sample. Comparative analyses between the pre-COVID-19 and COVID-19 groups were performed using Chi-square test for categorical variables and Mann-Whitney U test for continuous variables.

A multivariate logistic regression model with time period, age, sex, care type, and days of observation as covariates was constructed using generalized estimating equations (GEEs) to assess whether the probability of patients receiving PRN injections changed after the onset of the COVID-19 pandemic. To compare counts of PRN administrations per patient before and during COVID-19, a Poisson regression model via GEEs was fitted to the number of total injections received by each patient with time period, age, sex, and care type as covariates and days of observation as the offset variable. Results from the analyses are presented in the form of odds ratios (ORs) or incidence rate ratio (IRRs) with 95% confidence intervals (CIs) and corresponding p values. Prior to multivariate analyses, independent variables were assessed for multicollinearity (tolerance statistic <0.40).

RESULTS

Patient characteristics

Using census data on occupancy rates provided by LTC staff, we determined that 658 and 621 residents stayed at the two facilities in the pre-COVID-19 and COVID-19 time periods, respectively, for a total of 1,279 residents. Of these, 326 patients had orders for PRN injections of haloperidol, olanzapine, or lorazepam and their charts were reviewed. Of those, 250 patients had dementia and were included in the analysis. A comparison of patient characteristics between the two cohorts is shown in Table 1.

During the pre-COVID-19 period, 103 of 658 patients (16%) had active orders for haloperidol, olanzapine, or lorazepam. The mean age was 94.4 ± 3.8 years and the vast majority of patients were male (86%) and from SHSC (90%). On average, patients were observed for 274 ± 165 days. Of the patients whose dementia subtype and severity were specified, 23 of 51 (45%) had Alzheimer's disease and 56 of 83 (68%) were at the advanced stages of the disease. Within SHSC, over 60% of patients were located on cognitive support units while the rest resided on physical support units (20%) and behavioral support units (8%). Because VC does not make that distinction, we classified the 10 patients (10%) from that site as having received mixed care (Table 1).

During the COVID-19 period, 147 of 621 patients (24%) had orders for injectable PRN haloperidol, olanzapine, or lorazepam. This was a significant increase from the pre-COVID-19 period (Table 1). Demographic characteristics related to site, age, sex, days of observation, and care type did not change significantly (Table 1). Similarly to the pre-COVID period, cognitive support was the most common care type, followed by physical support, mixed care, and behavioral support. While there were differences in terms of dementia subtype and dementia severity before and during COVID-19, Alzheimer's disease and severe dementia remained the most prevalent categories, respectively, among cases that could be determined. Additionally, the mean number of concomitant medications increased from 5.0 ± 4.8 to 8.8 ± 5.7 medications, while the mean number of comorbidities decreased from 11.2 ± 3.6 to 8.9 ± 5.0 conditions (Table 1).

Table 1
Characteristics of patients in the pre-COVID-19 and COVID-19 periods

Variable	Pre-COVID-19 ($n = 103$)	COVID-19 ($n = 147$)	p
Age (mean ± SD)	94.4 ± 3.8	93.9 ± 5.7	0.5[b]
Sex (n, % male)	89 (86)	119 (81)	0.3[a]
Days of observation (mean ± SD)	274 ± 165	255 ± 158	0.4[b]
Site			0.2[a]
Sunnybrook	93 (90)	125 (85)	
Villa Colombo	10 (10)	22 (15)	
Dementia subtype (n, %)			0.04[a]
Alzheimer's disease	23 (22)	24 (16)	
Vascular	16 (16)	9 (6)	
Mixed	11 (11)	13 (9)	
Other	1 (1)	4 (3)	
Unspecified	52 (51)	97 (66)	
Dementia severity (n, %)			0.009[a]
Mild	12 (12)	22 (15)	
Moderate	15 (15)	18 (12)	
Severe	56 (54)	53 (36)	
Unspecified	20 (19)	54 (37)	
Care type (n, %)			0.1[a]
Physical support	21 (20)	40 (27)	
Cognitive support	64 (62)	68 (46)	
Behavioral support	8 (8)	17 (12)	
Mixed	10 (10)	22 (15)	
Concomitant medications (mean ± SD)	5.0 ± 4.8	8.8 ± 5.7	<0.001[b]
Conditions in medical history (mean ± SD)	11.2 ± 3.6	8.9 ± 5.0	<0.001[b]
Prevalence of PRN orders (%)[c]	16	24	<0.001[a]

[a]Chi-square test for categorical variables. [b]Mann-Whitney U test for continuous variables. [c]Prevalence was calculated using census data on total occupancy.

Frequency of use

Among the 103 patients with active orders for haloperidol, olanzapine, or lorazepam between January 1, 2018 and May 1, 2019, 45 patients (44%) received at least one injection for a total of 209 injections. Table 2 shows the distribution of orders and injection administrations stratified by type of psychotropic medication. Overall, 38 out of 85 patients (45%) with orders for haloperidol received one or more haloperidol injections and 13 out of 33 patients (39%) with orders for lorazepam received lorazepam injections. Only one patient had an order for olanzapine but did not require any PRN administrations during the duration of the study. Of the 209 injections administered in total, 155 (74%) were haloperidol and 54 (26%) were lorazepam (Table 2).

During the COVID-19 period, PRN injections were administered to 85 out of 147 dementia patients (58%) with active orders. Specifically, 75 of 117 patients (64%) with orders for haloperidol, 22 of 61 patients (36%) with orders for lorazepam, and 2 of 3 patients (67%) with orders for olanzapine received their prescribed PRN agitation medications. Similarly to the pre-COVID-19 period, haloperidol (81%) made up the majority of injections, and only a small number of lorazepam (14%) and olanzapine injections (4.5%) were used (Table 2). Eleven of 398 injections in the COVID-19 period were administered within 14 days of a positive COVID-19 test.

Doses of injections

Across both time periods, the median doses of haloperidol and lorazepam were both 0.5 mg. For olanzapine, no data were available for the pre-COVID-19 period as it was not used; during the COVID-19 period, the median dose was 5.0 mg. Other details on the mean doses and total use of haloperidol, olanzapine, and lorazepam can be found in Table 3.

Indications for use

Overall, 159 injections in the pre-COVID-19 period and 354 injections in the COVID-19 period had corresponding progress notes that were sufficiently detailed such that the incidents could be categorized according to IPA criteria. In both time periods, most PRN administrations were for behav-

Table 2
Number of patients who received ≥1 PRN injections of those with orders

	Number of patients with orders (*n*, % of Total)	Number of patients who received ≥1 injections (*n*, % of Total)	Number of injections (*n*, % of Total)
	Pre-COVID-19		
Haloperidol	85 (83)	38 (84)	155 (74)
Olanzapine	1 (1.0)	0 (0)	0 (0)
Lorazepam	33 (32)	13 (29)	54 (26)
Total	103	45	209
	COVID-19		
Haloperidol	117 (80)	75 (88)	323 (81)
Olanzapine	3 (2.0)	2 (2.4)	18 (4.5)
Lorazepam	61 (41)	22 (26)	57 (14)
Total	147	85	398**

*Frequencies displayed are not mutually exclusive as some patients had orders for and received two or more different agents. **11 of 398 injections in the COVID-19 period were administered within 14 days of a positive COVID-19 test.

Table 3
Mean and median doses of injections and total consumption (mg)

	Pre-COVID-19			COVID-19		
	Mean ± SD	Median (IQR)	Total consumption	Mean ± SD	Median (IQR)	Total consumption
Haloperidol	1.02 ± 1.18	0.5 (0.5–1.0)	157.4	0.64 ± 0.47	0.5 (0.5–0.5)	208.1
Olanzapine*			0	4.17 ± 1.21	5.0 (2.5–5.0)	75.0
Lorazepam	0.63 ± 0.23	0.5 (0.5–1.0)	34.3	0.68 ± 0.64	0.5 (0.5–0.5)	38.5

*No olanzapine injections were administered during the pre-COVID-19 period.

iors presenting as excessive motor activity (e.g., pacing, general restlessness), followed by verbal aggression (e.g., cursing, screaming), and lastly physical aggression (e.g., punching, kicking), as shown in Table 4.

Regression analyses

Results from the multivariate logistic regression model are presented in Table 5. ORs greater than 1 indicate higher likelihood of receiving at least one PRN agitation medication injection whereas ORs less than 1 indicate a decreased likelihood of receiving injections. Overall, time period was significant such that patients in the COVID-19 period were almost two times more likely to receive a PRN agitation medication injection than patients in the pre-COVID-19 period (OR = 1.96; 95% CI = 1.15–3.34; $p = 0.01$). Compared to patients who received mixed care at VC, patients in specialized care at SHSC were also more likely to receive one or more PRN agitation medication injections. Specifically, SHSC patients who resided in cognitive support units, physical support units, and behavioral support units had ORs of 3.22 (95% CI = 1.24–8.36, $p = 0.02$), 3.50 (95% CI = 1.21–10.13, $p = 0.02$), and 4.95 (95% CI = 1.59–15.45, $p = 0.006$), respectively (Table 5). There was no evidence of multicollinearity in covariates.

As shown in Table 6, none of the variables in the multivariate Poisson regression model were significant. Time period had an IRR of 1.35 (95% CI = 0.78–2.33), which would imply a 35% higher count of injections in the COVID-19 period compared to the pre-COVID-19 period, but this association failed to achieve statistical significance ($p = 0.3$) (Table 6).

DISCUSSION

Little is known about the actual frequency of PRN use of psychotropics for acute agitation in dementia. This retrospective chart review sought to characterize actual use of PRN haloperidol, olanzapine, and lorazepam injections for treating severe acute agitation in dementia patients and to compare use before and during the COVID-19 pandemic. Of those who resided in LTC during the pre-COVID-19 period, 103 people (16%) had standing orders for injectable PRN haloperidol, olanzapine, or lorazepam and 45 (44%) of them received one or more administrations. In the COVID-19 period, 147 residents (24%) had

Table 4
IPA indications of use of injections

	Pre-COVID-19 (*n*, % of Total)	COVID-19 (*n*, % of Total)
Excessive motor activity	135 (85)	282 (80)
Verbal aggression	64 (40)	153 (43)
Physical aggression	50 (31)	125 (35)
Total	159	354

Categories are not mutually exclusive as an episode of acute agitation may involve two or more IPA domains.

Table 5
Multivariate logistic regression analysis of factors associated with likelihood of receiving an injection

Predictors	OR	SE	Wald's χ^2	95% CI		*p*
				Lower	Upper	
Days of observation	1.001	0.0008	0.8	0.999	1.002	0.4
Age	0.96	0.029	1.9	0.90	1.02	0.2
Sex						
Male	1.000					
Female	0.70	0.27	0.9	0.33	1.48	0.4
Care type						
Mixed	1.000					
Physical support	3.50	1.9	5.3	1.21	10.13	0.02
Cognitive support	3.22	1.6	5.8	1.24	8.36	0.02
Behavioral support	4.95	2.9	7.6	1.59	15.45	0.006
Time period						
Pre-COVID-19	1.000					
COVID-19	1.96	0.53	6.2	1.15	3.34	0.01

OR, odds ratio; SE, standard error; CI, confidence interval.

Table 6
Multivariate Poisson regression analysis of factors associated with injection count

Predictors	IRR	SE	Wald's χ^2	95% CI		*p*
				Lower	Upper	
Age	1.01	0.031	0.2	0.95	1.08	0.7
Sex						
Male	1.000					
Female	0.50	0.21	2.7	0.21	1.15	0.1
Care type						
Mixed	1.000					
Physical support	0.86	0.54	0.1	0.25	2.92	0.8
Cognitive support	0.62	0.38	0.6	0.19	2.05	0.4
Behavioral support	1.10	0.68	0.0	0.33	3.72	0.9
Time period						
Pre-COVID-19	1.000					
COVID-19	1.35	0.38	1.2	0.78	2.33	0.3

IRR, incidence rate ratio; SE, standard error; CI, confidence interval.

orders, which was a significant increase from the pre-COVID-19 period, and 85 (58%) received at least one injection of their prescribed medication. Only a small proportion of injections in the COVID-19 period were administered within 14 days of a positive COVID-19 test. Haloperidol, a typical antipsychotic, was by far the most frequently used agent for treating acute agitation in both time periods. In our study, we found that residents in the COVID-19 period were two times more likely to receive PRN injections than residents in the pre-COVID-19 period. As well, we found that those who lived in specialized care units were more likely to receive PRN administrations than residents who received mixed (i.e., generalized) care. However, the mean count of injections per patient did not differ significantly before and after the emergence of COVID-19.

Overall, our findings were consistent with the limited literature that currently exists, which suggests that psychotropic drug use has increased since the start of COVID-19. Among Canadian LTC residents in particular, an early report published by the Cana-

dian Institute for Health Information found a modest increase in antipsychotic prescriptions among LTC residents with dementia between March and August of 2020 compared to the analogous period in 2019 [36]. Likewise, another population-based study by Stall et al. concluded that increases in the prescription of psychotropic drugs from March to September 2020 were larger than the projected trends over time and distinct from prescribing changes in other drug classes [52]. Internationally, recent studies investigating psychotropic drug use for the treatment of NPS in LTC settings have produced mixed findings with some reporting significant increases during the pandemic [40, 41, 53, 54], and others reporting unchanged or even decreased rates of prescribing [42, 55]. In some cases, increases in psychotropic drug use did not necessarily correspond to worsened NPS [40, 42, 53]. Moreover, rates of psychotropic drug use may have appeared to remain stable due to high heterogeneity in the development and resolution of different NPS, which also varied on an individual basis [42]. Nonetheless, it is likely that overall use of psychotropic medications during the pandemic was still underestimated, as most studies did not consider PRN administrations [40, 52, 53].

From a broader perspective, our results are a reflection of the mental health challenges that have been amplified by the COVID-19 pandemic and have been suggested to be associated with serious and potentially irreversible harm to older adults [32, 56, 57]. Since the onset of the pandemic, numerous studies have identified agitation as one of the most common NPS to have worsened in dementia patients, with approximately 20% to 30% of patients experiencing such exacerbations [32, 34, 35, 58, 59]. Our findings indicating an increased likelihood of injection administration in the COVID-19 period could be interpreted to mean that a greater proportion of patients experienced episodes of acute agitation severe enough to warrant immediate treatment with PRN medications during COVID-19 compared to pre-COVID-19 times. In line with previous research, this supports the view that there was indeed a collective worsening of agitation among LTC residents with dementia.

A recurring explanation for this is that agitation and other NPS have worsened due to protracted isolation caused by social contact restrictions [32, 34, 35, 60]. For example, Cagnin et al. argued that quarantine could be viewed as a form of "deprivation syndrome" that exacerbates NPS via concurrent reductions in social, physical, and cognitive stimulation [35]. Relatedly, Wei et al. observed that dementia patients in LTC were at greater risk of experiencing worsened NPS compared to community-dwelling individuals [34]. The authors explained that this difference may be partly attributed to the implementation of visitation bans in LTC homes, which decreased the amount of meaningful contact between residents and their friends and family. During the first wave of COVID-19 in Canada, for instance, LTC facilities imposed strict "no visitor" policies in an effort to contain viral spread [37, 61]. As a result, residents were isolated from their regular support systems and denied invaluable social support that can be critical to their psychosocial well-being [62]. Thus, loss of contact with informal caregivers may be one explanation for our findings, which indirectly show that more patients experienced severe acute agitation during COVID-19. However, it is important to consider that there could be substantial interindividual differences with regard to the effects of visitor restrictions, which may not always be negative. In fact, one study found that LTC residents in the lockdown group demonstrated decreased levels of conflict with other residents compared to those in the control group [63].

Another potential reason patients were more likely to receive PRN administrations during COVID-19 may be that many non-pharmacological interventions for managing NPS in dementia patients were temporarily suspended in accordance with social distancing guidelines [60, 64]. At the height of pandemic restrictions in Canada, all in-person group activities were canceled, communal dining was stopped, and residents were not allowed to leave their facilities [65]. It is possible that even simple non-pharmacological interventions such as regularly scheduled walks provided some level of maintenance therapy for dementia patients with agitation and that discontinuation of these beneficial activities led to more occurrences of breakthrough agitation. Another factor to consider is that LTC staff were facing a myriad of new stressors from staffing shortages and COVID-19 protocols that increased their daily workload [66]. This likely had a detrimental effect on their ability to provide routine care and acted as a barrier to the delivery and efficacy of non-pharmacological strategies.

Looking at care type, we found that residents living in the behavioral support unit at SHSC had the highest odds of receiving an injection. This makes intuitive sense because the behavioral support unit was specifically designed to care for veterans with dementia who exhibit challenging NPS, such as aggression. Accordingly, the residents who were most likely to

demonstrate behaviors that pose risk of harm and require PRN injections were concentrated in this unit. Our inability to detect a significant association between time period and injection count may be due to the high variability of the data, with some patients receiving no injections and others receiving over 30. As well, there may have been additional confounding factors that we did not account for in our regression models.

It is worth highlighting that a large proportion of patients with orders for haloperidol, olanzapine, or lorazepam did not actually receive any injections, both before and during COVID-19. This could be because the PRN medications were prescribed in advance as precautionary measures and reserved for severe breakthrough agitation, which some patients never experienced. Prior to and during the pandemic, haloperidol was the most frequently used agitation medication while olanzapine was very rarely administered. On one hand, there is an extensive evidence base built from decades of clinical trials and experience showing that haloperidol is generally effective for acute agitation [67–69]. However, the fact that olanzapine was almost never used was surprising; a sizable number of studies have found that atypical antipsychotics offer many advantages over typical agents, including a lower risk of extrapyramidal side effects [24]. In a recent Delphi study, for example, 97% of expert respondents agreed that oral and parenteral preparations of atypical antipsychotics are better tolerated and safer than typical antipsychotics for treating NPS in dementia patients [70]. Practical reasons for this incongruence may be that olanzapine is not always available in its injectable form and is more expensive than haloperidol [24]. Additionally, olanzapine cannot be dispensed in very low doses at the Veterans Centre (SHSC), while haloperidol does not have this limitation and allows for greater flexibility in dosing. With respect to lorazepam, previous studies have suggested that the drug is as effective as haloperidol but poses numerous risks to patients [17, 71]. Specifically, IM lorazepam has been associated with respiratory depression and may cause hypotension when used together with IM olanzapine [17, 72]. Moreover, both lorazepam and olanzapine appear to carry greater risks of sedation than haloperidol [17, 24, 73]. This may explain why lorazepam and olanzapine were occasionally used in our study, but not nearly as frequently as haloperidol.

In terms of IPA indications of use, we found that the rank order did not change between the two time periods. Most injections were administered for behaviors best categorized as excessive motor activity, followed by verbal aggression and physical aggression. Given the increased odds of injection use in the COVID-19 group, it was interesting that physical aggression remained the least prevalent indication. After all, acute treatments for agitation are usually administered when there is imminent risk of harm to the patient or others [16, 17]. One possible explanation for our observation is that there was a lower tolerance for non-aggressive agitated behaviors during the pandemic stemming from the need to prevent COVID-19 transmission. For example, PRN psychotropics may have been administered to prevent physically agitated residents from wandering during lock downs and unwittingly being exposed to or spreading COVID-19, and not necessarily because these patients were actively violent.

Strengths and limitations

The greatest strength of our chart review is that we were able to capture actual medication use unlike past studies that have relied on prescriptions or drug claims as proxy measures [36, 52]. Consequently, we were able to document the exact date and time of each PRN administration and, in most cases, obtain detailed information about the frequency, dose, and indication of use. Nonetheless, our results should be interpreted with some limitations in mind. First, of 1279 LTC residents in a Canadian setting, a relatively small number of those with dementia received PRN injections, and they were predominantly male and of very advanced age. This diminishes the generalizability of our findings as our patient sample is not representative of all institutionalized older adults with dementia-associated agitation. In particular, the "oldest-old" (i.e., individuals aged 85 and older) constitute only 7% of older adults over the age of 65 [74, 75]. Another limitation of this study is that we did not include covariates related to dementia severity, dementia subtype, staffing, or rates of illness as explanatory variables in our regression models, which could have influenced the results. Evidence from the literature suggests that the prevalence of agitation may vary depending on the type and severity of dementia [76], but these characteristics were not determined for a large proportion of patients in our study and could not be used for adjustment in the analysis. Additionally, delirium associated with COVID-19 and staffing shortages are additional factors that could have contributed to worsening agitation and increased rates of psychotropic drug use

[66, 77]. It should also be noted that because our study focused on severe acute agitation, we did not address use of oral PRN psychotropics, which may be used to treat mild to moderate cases [71]. Lastly, due to the observational nature of the study, we cannot infer any causality between the independent and outcome variables.

Implications and conclusion

While many social distancing and lockdown measures have been gradually lifted, the possibility that restrictions could be re-introduced in the future cannot be discounted as COVID-19 continues to spread around the world [78]. It is now evident that the outbreak management protocols enforced by LTC homes during the early stages of the pandemic had many regrettable shortcomings. As detailed in position statements by the Canadian Academy of Geriatric Psychiatry (CAGP) and Canadian Coalition for Seniors Mental Health (CCMSH), many of these measures were not designed to be implemented for extended periods of time and thus did not sufficiently consider the psychological impact of prolonged isolation [66]. Consequently, an important implication of the current study is that the need for PRN rescue medications may have increased during the COVID-19 pandemic as an indirect consequence of restrictions on socialization.

To summarize, the present retrospective chart review found that LTC residents with dementia were twice as likely to receive PRN administrations of psychotropic medications for acute agitation during the COVID-19 period relative to the pre-COVID-19 period. Our findings contribute to the growing body of evidence demonstrating that there has been an overall escalation of behavioral disturbances in dementia patients during the pandemic. By focusing on PRN administrations and acute agitation, we provide an important perspective distinct from that of previous studies which have examined psychotropic drug use for NPS more broadly. The insights gained from this study on frequency, dose, and indication of use of PRN haloperidol, olanzapine, and lorazepam could aid in the development of more comprehensive treatment algorithms specific to acute agitation. Nonetheless, our study represents a small step towards this goal and further research is needed to replicate and extend these findings in "younger" samples of dementia patients and in other countries.

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CONFLICT OF INTEREST

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DATA AVAILABILITY

The data supporting the findings of this study are not publicly available due to privacy or ethical restrictions. The authors will provide additional analyses upon reasonable request.

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