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RESEARCH ARTICLE

Discontinuation of antipsychotics treatment for elderly patients within a specialized behavioural unit: a retrospective review

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Abstract

Background Best practice guidelines recommend regular evaluation of antipsychotics in managing behaviours for dementia patients with a view to de-prescribing, given its significant mortality and adverse outcomes (Reus et al. in Am J Psychiatry 173(5):543–546, 2016, Deprescribing Guidelines and Algorithms in https://deprescribing.org/resources/deprescribing-guidelines-algorithms/, 2019). The relationship between the dose of antipsychotic and the probability of discontinuation remains unknown in hospitalized dementia patients. *Objectives* This study aims to examine the relationship between high dose antipsychotic (greater than 62 mg chlorpromazine equivalent daily dose) and antipsychotics discontinuation in hospitalized dementia patients. *Setting* Specialized Dementia Behavioral Health Program in Hamilton, Ontario, Canada. *Method* A retrospective chart review was completed from August to December of 2019. A univariate logistic regression model was applied to antipsychotic doss (in chlorpromazine equivalent) and antipsychotic discontinuation outcome at 60 days (Narayan and Nishtala in Eur J Clin Pharmacol 73(12):1665–1672, 2017). A multivariant model was used to assess potential confounders, including other psychiatric medication exposure and Medicines Comorbidity Index (Luthra in J Gerontol Geriatr Res 4(260):2, 2015). Regression and dose–response models were utilized to identify the threshold dose (maximum daily dose). *Main outcome measures* Antipsychotic discontinuation at 60 days after the last dose. *Results* A total of 42 patients were eligible for outcome analysis. High dose antipsychotic was associated with worse discontinuation outcomes in both unadjusted (odds ratio, 0.09; 95% confidence interval, 0.02–0.37; $p < 0.01$) and adjusted generalized estimation equation models (odds ratio 0.65; 95% confidence interval, 0.59–0.72; $p = 0.01$). There were no statistically significant associations between baseline comorbidities (Medicines Comorbidity Index) ($p = 0.68$), mood stabilizer ($p = 0.14$), benzodiazepines ($p = 0.93$) and antidepressant exposure ($p = 0.68$) with antipsychotic discontinuation. The logistic regression model identified 40.7 mg of quetiapine, 1.7 mg of olanzapine and 0.51 mg of risperidone as the threshold dose, balancing sensitivity and specificity. The dose–response model also identified similar doses of 42 mg of quetiapine, 1.76 mg of olanzapine and 0.53 mg of risperidone. *Conclusion* The use of high dose antipsychotics is associated with worse discontinuation outcomes in hospitalized dementia patients. Therefore, our results suggest not exceeding a daily dose of 50 mg of quetiapine, 1.75 mg of olanzapine and 0.5 mg of risperidone when used for responsive behaviours and reassess the benefits and risks for each patient regularly.

Keywords Antipsychotic · Antipsychotic discontinuation · Canada · Dementia · Elderly

Impacts on Practice

- Antipsychotics are frequently used to manage responsive behaviours in hospitalized patients with dementia.
- Antipsychotics are associated with increased mortality and adverse outcomes in this patient population.
- Clinicians should aim for the lowest effective dose to manage behaviours, while assessing the risk and benefits on a minimum of monthly basis, with a view to deprescribing in the future.

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Introduction

Public Health Agency of Canada (PHAC) (2013–2014) report a prevalence of more than 7.1% or 402,000 seniors (65 years and over) with a diagnosis of dementia in Canada [1]. Despite the limited effectiveness of antipsychotics in managing behavioural and psychological symptoms of dementia (BPSD) and the short duration in clinical trials (less than 12 weeks), the Canadian Institute for Health Information reported in 2014 that 39% of Canadian seniors in long term care (LTC) facilities received at least one antipsychotic agent and 22.4% of Canadian seniors living in LTC are chronic users of antipsychotics [2–7]. These numbers raise concerns as Dementia Antipsychotic Withdrawal Trial (DART-AD) study shown an association between dementia patients who continued antipsychotics with an increased risk of mortality [8]. While Cochrane (2018) reviewed two randomized, placebo-controlled discontinuation studies concluded no worsening of neuropsychiatric symptoms following antipsychotic deprescribing [9]. In summary, both American and Canadian guidelines have strongly recommended the deprescribing of antipsychotics after three months of therapy in managing behaviours in dementia [3, 10].

Several studies have attempted to identify predictors of successful deprescribing of antipsychotics in community-dwelling patients. One randomized trial found that for dementia patients living in nursing homes and chronic care homes, individuals who started and continued higher doses of antipsychotics (chlorpromazine equivalent) were more likely to see worsening of behavioural symptoms following deprescribing [11]. However, the study did not report on the definition of high doses. Several cohort studies have also discovered severe baseline symptoms as another predictor of successful antipsychotic deprescribing. One study found that dementia patients with severe baseline hallucinations were associated with a higher risk of relapse following the discontinuation of risperidone treatment [12]. Another study that measured behavioural and psychiatric symptoms using the Neuropsychiatric Inventory (NPI) found that dementia patients with higher baseline NPI scores were more likely to develop marked behavioural problems if discontinued from antipsychotics [13]. To the authors' knowledge, no study has examined the predictors of successful antipsychotic discontinuation in hospitalized patients with dementia.

Aim of the study

To examine the relationship between the dose of antipsychotic (normalized to chlorpromazine equivalent daily dose) and successful antipsychotic discontinuation in hospitalized patients with dementia. The study will also explore the hypothesis of a maximum therapeutic dose of antipsychotics associated with successful antipsychotic discontinuation in this patient population.

Ethics approval

his study was reviewed and approved by the Hamilton Integrated Research Ethics Board (HiREB) (Final approval letter: 7202).

Method

Study design and population

A retrospective chart review was conducted on patients admitted to the Behavioural Health Program (BHP), St. Peter's Hospital, within Hamilton Health Sciences, Ontario, Canada. BHP is a specialized geriatric behavioural unit for dementia patients who are exhibiting responsive behaviours with high levels of risk, which cannot be safely managed in their respective institutions. The diagnosis of dementia was confirmed by the geriatric psychiatrist and nurse case manager based on previous documentation and clinical examination. All inpatients of BHP between August to December 2019 were screened for enrollment into the study. Exclusion criteria included length of stay of fewer than 60 days, requiring antipsychotics for other psychiatric comorbidities (schizophrenia, mood disorder, severe depression, and psychotic symptoms), and patients admitted without antipsychotics. The follow-up time of 60 days was based on the time to relapse after antipsychotic deprescribing; 6.8 weeks to relapse in a randomized study and 80% of patients are stable by 60 days following antipsychotic discontinuation with marginal gains by 95 and 190 days in an observational study [9, 14].

Upon admission, all patients underwent a standardized discontinuation schedule of tapering by 25% of the total daily dose every 5 days until complete discontinuation unless an escalation of responsive behaviours occurred, requiring the continuation of antipsychotics. After screening, patients were assigned to the discontinued group if antipsychotics were discontinued and remained antipsychotic-free for 60 days from the last dose given. Patients who required the continuation of antipsychotics, as evidenced by a return to previous antipsychotic doses or an increase in antipsychotic doses above baseline, were assigned to the continued group.

Data collection and statistical methods

Baseline demographic characteristics were collected from previous health records, including age, sex, admission medications per class, antipsychotics, and daily doses.

Luthra's Behavioral Assessment and Intervention Response (LuBAIR™) Inventory was used to record the clusters of responsive behaviours at baseline [15]. Total scores on the Medicines Comorbidity Index (MCI) was used to standardize the patient's baseline medical comorbidities [16]. Admission antipsychotics daily doses were normalized to chlorpromazine equivalent, based on published international consensus dosing guidelines [17]. Pharmacoepidemiology studies on elderly dementia patients in Ontario have identified high dose antipsychotics as 62–74 mg of chlorpromazine equivalent daily dose [18, 19]. We chose the lower end of the dose range (62 mg) as the cut off for this study. Continuous data were expressed as mean ± standard deviation, and categorical data were expressed as proportions. Baseline demographics were compared with the paired *t* test and Pearson's Chi square test, and statistical significance was set to a *p* value of 0.05. Statistical tests were carried out by the R project [20].

In addition to an unweighed univariant logistic regression, a weighted generalized estimating equation (GEE) model, adjusted with the stabilized inverse probability weighting (IPTW) method, was also used to examine the high dose antipsychotics and discontinuation outcomes. A weighted multivariant model was also used to assess other potential confounding medication classes, namely mood stabilizers, antidepressants and benzodiazepines. A maximum daily dose that would facilitate antipsychotics discontinuation was determined using two approaches, balancing sensitivity, specificity and accuracy: (1) utilizing the threshold of dose–response model fitting with regards to chlorpromazine equivalent daily dose and discontinuation outcomes, known as lethal dose 50 (LD50), (2) A non-weighted logistic regression model-fitting approach between chlorpromazine equivalent daily dose and discontinuation outcome.

Results

Baseline characteristics

This retrospective chart review screened 65 patient charts and excluded 23 patients. Four patients had a length of stay of fewer than 60 days at the time review. Four patients were not exposed to scheduled antipsychotics before admission. The other 15 patients did not qualify due to documented histories of other psychiatric diagnoses. These include six patients with a prior diagnosis of mood disorder, 5 patients had a previous diagnosis of schizophrenia, two patients with a documented history of psychotic symptoms and the other two patients with severe depression (Table 1).

After screening, the final analysis included 42 patients with 19 patients in the discontinued group and 23 in the continued group. Baseline characteristics were compared using the Chi square and student t-tests. The discontinued group was significantly older (84.1 vs. 79.0, $p=0.04$), while the gender distribution was similar to the continued group (% female: 47.4 vs. 30.4, $p=0.33$). The two groups had similar baseline MCI scores (2.87 vs. 3.05, $p=0.70$). Both groups had a similar percentage of patients for each type of behaviour at baseline, including physically aggressive behaviour (89.5 vs. 70, $p=0.23$), oppositional behaviours (89.5 vs. 82.6, $p=0.85$), and vocal behaviours (57.9 vs. 69.6, $p=0.64$). Although the continued group showed higher proportions of patients on antidepressants (73.9 vs. 57.9), the difference was not statistically significant ($p=0.44$). Mood stabilizers, mainly valproic acid (15.8 vs. 9.7, $p=0.82$), and benzodiazepine (21.1 vs. 21.7, $p=1$) exposures, were also similar in the two groups. For antipsychotics at admission, the continued group had significantly higher doses of antipsychotics at baseline (chlorpromazine equivalent daily dose (mg/day): 139.2 vs. 52.3, $p<0.01$). Within individual antipsychotics agents, continued and discontinued groups had a significantly higher dose in the risperidone group (112.5 vs. 60.9, $p=0.04$) and quetiapine group (117.2 vs. 20.6, $p=0.02$) at baseline. Trifluoperazine, haloperidol and olanzapine were not able to be compared statistically due to a lack of sufficient numbers in either group.

High dose antipsychotics and antipsychotic discontinuation

The unadjusted model reported a significantly lower likelihood of successful discontinuation at 60 days with high dose antipsychotics (odds ratio (OR), 0.09; 95% confidence interval (CI), 0.02 to 0.37; $p<0.01$) (Table 2). After adjustments for baseline characteristics, including age, sex, medical comorbidities, and categories of responsive behaviours using the IPTW method, the generalized estimating equation (GEE) model also reported a significantly lower likelihood of successful discontinuation at 60 days when high dose antipsychotics were used (OR 0.65; 95% CI, 0.59–0.72; $p=0.01$). As part of the post hoc analysis for potential confounders, baseline MCI score, mood stabilizer, benzodiazepine and antidepressant exposure were also assessed. While high dose antipsychotics were similar to the adjusted model (OR, 0.65; 95% CI 0.46–0.9; $p=0.01$), MCI scores (OR, 0.98; 95% CI 0.88–1.09; $p=0.68$), as well as mood stabilizers (OR, 1.39; 95% CI, 0.88–2.17; $p=0.14$), benzodiazepines (OR, 0.98; 95% CI, 0.62–1.55; $p=0.93$) antidepressant (OR, 0.94; 95% CI 0.69–1.28; $p=0.68$) exposures were not associated with successful antipsychotic discontinuation in this study.

Maximum daily dose

To investigate the threshold daily dose that would maximize the likelihood of successful antipsychotics discontinuation,

Table 1 Baseline characteristics

	Total (n = 42)	Discontinued group (n = 19)	Continued group (n = 23)	*p* value
Age (years)	81.1 ± 8.75	84.1 ± 5.46	79.0 ± 10.2	0.04
Sex (% female)	38.2 (n = 16)	47.4 (n = 9)	30.4 (n = 7)	0.33
Medicines Comorbidity Index	2.95 ± 0.23	2.87 ± 0.32	3.05 ± 0.33	0.70
Physically aggressive behaviour (%)	78.6 (percent, n = 33)	89.5 (n = 17)	70.0 (n = 16)	0.23
Oppositional behaviour (%)	85.7 (n = 36)	89.5 (n = 17)	82.6 (n = 19)	0.85
Vocal behaviour (%)	64.2 (n = 27)	57.9 (n = 11)	69.6 (n = 16)	0.64
Other psychotropic medications at admission				
Antidepressant (%)	66.7 (n = 28)	57.9 (n = 11)	73.9 (n = 17)	0.44
Benzodiazepine (%)	21.4 (n = 9)	21.1 (n = 4)	21.7 (n = 5)	1
Mood stabilizer (Divalproex) (%)	11.9 (n = 5)	5.8 (n = 3)	8.70 (n = 2)	0.82
*Antipsychotics at admission**				
Total (mg/day)	100 ± 95.8	139.2 ± 20.4	52.3 ± 15.9	< 0.01
Risperidone (mg/day)	86.7 ± 12.6 (n = 16)	112.5 ± 16.4 (n = 8)	60.9 ± 14.8 (n = 8)	0.04
Quetiapine (mg/day)	66.4 ± 19.2 (n = 19)	117.2 ± 33.4 (n = 9)	20.6 ± 4.3 (n = 10)	0.02
Olanzapine (mg/day)	236.3 (n = 6)	223.5 (n = 5)	300 (n = 1)	
Trifluoperazine** (mg/day)	1 (n = 1)		1 (n = 1)	
Haloperidol (mg/day)	130 (n = 1)		130 (n = 1)	

*Normalized and expressed in chlorpromazine equivalent mg per day

**One patient was treated with a combination of trifluoperazine and olanzapine

Table 2 Logistic regression model summary

	Odds ratio	95% confidence interval (lower bound, upper bound)	*p* value
Unweighted univariant model			
High dose antipsychotics*	0.09	0.02, 0.37	< 0.01
IPTW weighted univariant model			
High dose antipsychotics*	0.65	0.59, 0.72	< 0.01
IPTW weighted multivariant model			
High dose antipsychotics*	0.65	0.46, 0.91	0.014
Medicines Comorbidity Index (MCI)	0.98	0.88, 1.09	0.68
Mood stabilizer	1.39	0.88, 2.17	0.14
Benzodiazepines	0.98	0.62, 1.55	0.93
Antidepressants	0.94	0.69, 1.28	0.68

*Defined as greater than 62 mg of chlorpromazine equivalent daily dose

we used logistic regression and dose–response models. For the regression model, we used a receiver operating characteristic (ROC) curve to examine the effect of various probability thresholds (Fig. 1). The model reached its maximum sensitivity of 0.79 and specificity of 0.83 with a threshold of 0.59. In addition to the ROC curve, we have also used

a maximum accuracy model, revealing the same threshold of 0.59 with an accuracy of 0.81, which is higher than the baseline predictability of 0.45. The predicted probability of 0.59 corresponds to 50.9 mg in chlorpromazine equivalent daily dose. When translated back to the commonly used antipsychotics seen in this population, the dose is equivalent to 40.7 mg of quetiapine, 1.7 mg of olanzapine and 0.51 mg of risperidone. The dose–response model was also applied to explore the hypothesis of a potential maximum daily dose (Fig. 2). The model showed the lethal dose 50 of 52.76 mg chlorpromazine equivalent daily dose (95% CI 25.93, 79.60), equivalent to 42 mg of quetiapine, 1.76 mg of olanzapine and 0.53 mg of risperidone.

Discussion

European Federation of Neurological Societies and the American Psychiatric Association (APA) have published guidelines for the use of antipsychotics in dementia patients. However, both guidelines lack consensus on adequate dosing, which would lead to successful deprescribing [3, 21]. One consensus guideline on the use of antipsychotics in managing agitated and delusions in dementia patients recommends 0.5–2 mg/day of risperidone, 50–150 mg/day of quetiapine, and 5–7.5 mg/day of olanzapine. While another expert group has recommended titrating to a target and maximum dose of risperidone 1–2 mg, aripiprazole 10–12.5 mg and quetiapine 100–150 mg [22, 23]. Finally, the CATIE-AD

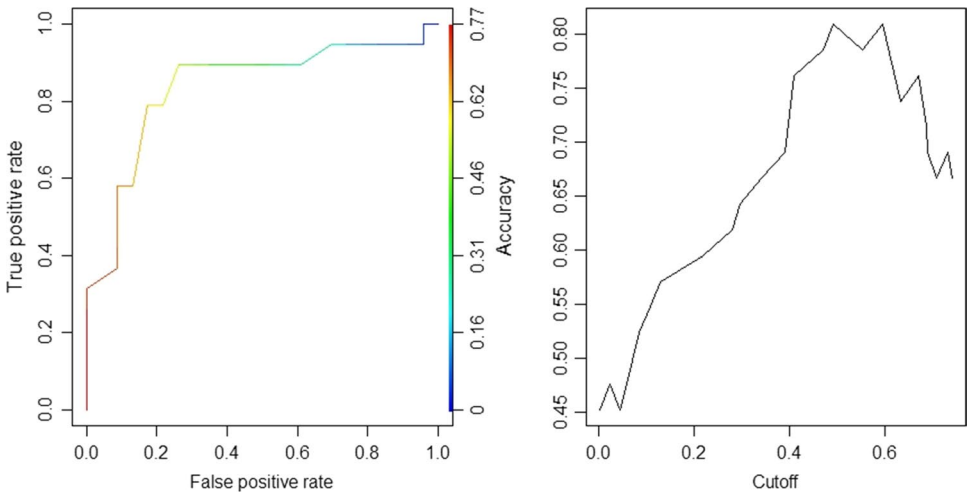

Fig. 1 Measures used to explore the threshold of unweighted logistic regression model between chlorpromazine equivalent daily dose and antipsychotic discontinuation outcomes at 60 days post-admission. Left: Receiver operator characteristics (ROC) of true positive and false negative rates between the spectrum of potential threshold (right column). Right: accuracy plot of cutoff points

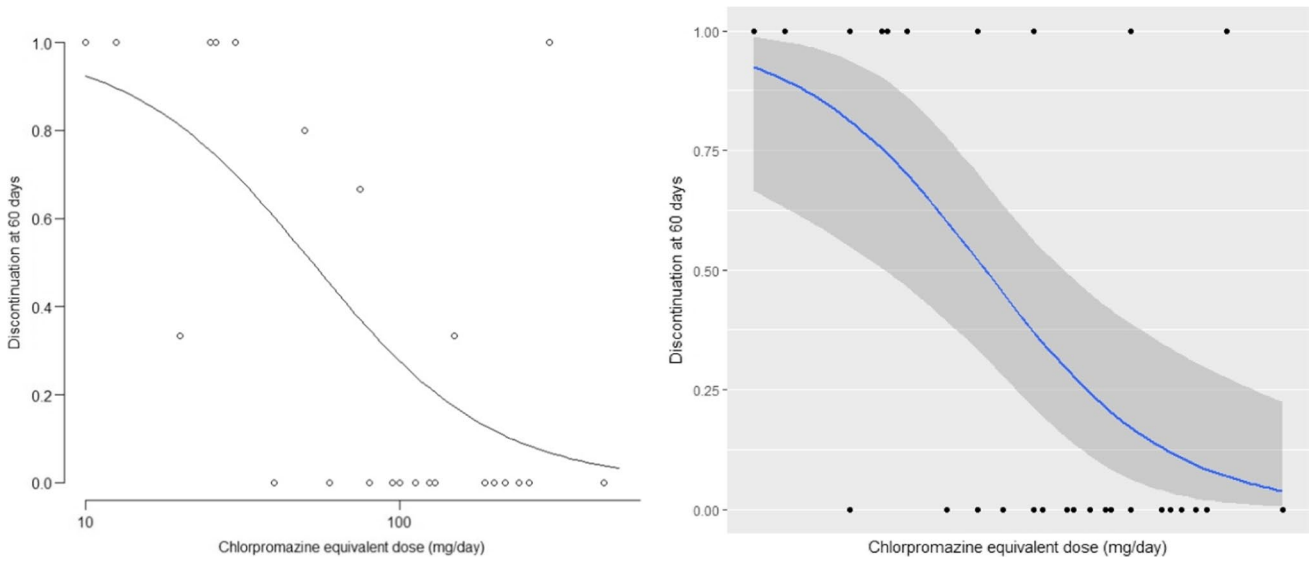

Fig. 2 Unweighted regression models of chlorpromazine equivalent daily dose and the probability of successful discontinuation at 60 days from-last antipsychotic dose. Left: dose–response model. Right: unweighted univariant logistic regression model

study had reported mean antipsychotic doses (risperidone: 1 mg per day, olanzapine: 5.5 mg per day and quetiapine: 56.5 mg per day) for dementia patients [24]. In summary, current literature had reported higher daily doses of antipsychotics than the doses identified in this retrospective study.

However, randomized studies have not consistently demonstrated that higher doses of antipsychotics are more effective than lower doses. In a fixed-doses study on the use of olanzapine in dementia patients with behavioural disturbances, all five doses (1, 2.5, 5, or 7.5 mg/day) showed significant improvement in the Neuropsychiatric Inventory Nursing Home version (NPI-NH) Psychosis total scores (sum of delusion and hallucination items) when compared to placebo ($p < 0.001$) [4]. Notably, 2.5 mg showed the most improvement in clinical global impression scale (CGI-C) ($p = 0.03$) [4]. In another fixed-dose study of olanzapine in dementia patients with behavioural disturbances, low doses of olanzapine (5, 10 mg/day) had significant improvement compared with placebo in agitation/aggression, hallucination and delusion items of the NPI-NH ($p = 0.006$). In contrast, patients in high dose group (15 mg/day) were not significantly different from placebo [5].

A fixed-dose study on the use of risperidone (0.5 mg, 1 mg and 2 mg daily dose) in managing behaviours in dementia patients found a greater reduction in Behavioural Pathology in Alzheimer's Disease rating scale (BEHAVE-AD) than placebo at 12 weeks ($p = 0.005, < 0.01$, 0,02) [6]. However, there were no significant inter-dose differences in the reduction of BEHAVE-AD rating scale scores amongst the three groups. Similarly, quetiapine used at 100 mg and 200 mg daily dose did not demonstrate statistically significant different results under the last observation carried forward method but was statistically significant with the observed case method [7]. Additionally, all secondary outcomes in this study were not statistically significant from placebo except for CGI-C scores in the 200 mg group, which was not specific to agitation in dementia [7].

In contrast, evidence suggests a consistent dose–response between antipsychotics and adverse events, including mortality. One retrospective cohort study found a significant dose-gradient between the use of second-generation antipsychotics and serious events (hospital admission or death within 30 days after antipsychotic initiation) [25]. Another retrospective case–control study found that the use of high doses of second-generation antipsychotics (haloperidol equivalent of greater than 3 mg/day) reported 3.5% (95% CI 0.5–6.5%, $p = 0.02$) higher mortality in comparison to the lower dose group (haloperidol equivalent of less than 1.5 mg/day) [26]. In addition to mortality, falls in elderly patients can lead to significant morbidity and complications. Antipsychotics are associated with a significant dose–response relationship of a higher incidence of falls in elderly patients (hazards ratio, 2.78; 95% CI 1.49–5.17) [27]. It is also worth noting that even at lower doses (25% of defined daily dose), antipsychotics are associated with higher risks of falls (0.32%; 95% CI (0.23–0.44%) to 0.55%; 95% CI (0.38–0.79%)) [27]. Lastly, 2 mg per day of risperidone increases the risk of extrapyramidal symptoms, somnolence and mild peripheral edema compared to 1 mg per day in a dose-dependent fashion. [6].

The results of this retrospective study can be used as general guidance to inform clinicians of the optimal use of antipsychotics in managing behaviours for hospitalized dementia patients. Deprescribing of antipsychotics should always remain the ultimate goal, and a lowered likelihood of successful discontinuation is associated with high dose antipsychotics (greater than 62 mg chlorpromazine equivalent daily dose). This article is the first to propose a maximum daily dose for the commonly used antipsychotics in managing behaviours in dementia, which is lower than the results reported in the current literature. Clinicians should carefully balance the risks of side effects and benefits of the antipsychotics, given the frailty of the population that is often complicated by dementia. Thus extreme caution is warranted when considering prescribing antipsychotics for behaviours in dementia. The results from this study can also serve as a cautionary checkpoint when clinicians consider a higher than the proposed maximum daily doses. The results of this study suggest an evaluation of the benefits and risks if the doses are escalated higher than the total daily dose equivalence of 50 mg of quetiapine, 1.75 mg of olanzapine and 0.5 mg of risperidone.

Limitations

There were several limitations to generalizing the results of this study. This study included a small sample size of patients. The results will need to be further validated in future prospective studies. Also, while possible selection bias could narrow the sample population, antipsychotic deprescribing and a discontinuation plan are standard practices in BHP. The study's scope was limited to agents initiated before admission to minimize selection bias, and all patients received standardized antipsychotic discontinuation. Also, the care team, including nurses and other allied health professionals, was consistent throughout the review period, and the care assignments were rotated amongst nurses daily.

Furthermore, due to the retrospective nature of the study, the patients' baseline severity of responsive behaviours before admission was not reported. However, the definition of "severity" for dementia behaviours would vary based on different institutions. As previously described, BHP is a specialized unit that admits patients with severe baseline responsive behaviours that could not have been managed at other facilities. The incidence of the patient's baseline

behaviours was also compared between the two groups and was not significantly different. A future prospectively controlled study is needed to validate the results of this study.

Conclusion

This study is the first to individually examine the relationship between antipsychotics dose and discontinuation outcomes and propose a maximum daily dose approach in hospitalized elderly patients with dementia. Clinicians, patients and their families can consider the results of this study and weigh the relative potential benefit and harm when making an informed decision in the use of antipsychotics.

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Conflicts of interest All authors declare no conflict of interest in the writing of this manuscript.

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