

# Management of Agitation in Dementia and Effects on Inpatient Length of Stay



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## ABSTRACT

### Background

Agitation associated with dementia impacts delivery of medical care and is a major reason for institutionalization in dementia patients. This study examines the association of medication use and other clinical factors with patients' 'dischargeability' (i.e., amount of time until a patient is considered dischargeable from an inpatient unit).

### Methods

This study was a retrospective chart review examining 200 patients with dementia and agitation, hospitalized at a Canadian acute care geriatric ward between November 2007 and November 2018. The main outcome measure was time until a patient was deemed dischargeable. Univariate linear regression analyses, followed by multiple linear regression analyses, were used.

### Results

Risperidone and quetiapine were the most commonly prescribed medications, but were not associated with time until dischargeable. Olanzapine (40.9 vs. 16.2 days until dischargeable,  $\beta = 0.23$ ,  $p = .001$ ), regular benzodiazepine (32.7 vs. 16.5 days until dischargeable,  $\beta = 0.15$ ,  $p = .027$ ), and as-needed ('PRN') benzodiazepine use (31.7 vs. 15.9 days until dischargeable,  $\beta = 0.19$ ,  $p = .006$ ) were independently associated with prolonging time until dischargeable.

### Conclusions

Olanzapine, benzodiazepine, and PRN benzodiazepine use were associated with longer time until patients with dementia and agitation were considered ready for discharge. This raises the question as to whether the risks of these medications outweigh the benefits in a hospital setting.

**Key words:** agitation, dementia, geriatric inpatient unit, length of stay, time until dischargeable

## INTRODUCTION

Globally, an estimated 47 million people are affected by dementia.<sup>(1)</sup> The number of people living with dementia worldwide is expected to double approximately every 20 years.<sup>(2)</sup> Agitation is a form of neuropsychiatric symptom (NPS) that has been defined as 'inappropriate verbal, vocal, or motor activity' that is judged by an outside observer to not result directly from the needs or confusion of the agitated individual.<sup>(3)</sup> A systematic review reports that agitation occurs in 5–88% of patients in Alzheimer's disease and other forms of dementia, with one study reporting 44% prevalence in a hospital setting.<sup>(4)</sup> Agitation frequently interferes with the delivery of medical care, causes frustration for family members, and often limits the capacity for home care, thus resulting in institutionalization.<sup>(5)</sup>

One major driver of costs related to agitation in dementia is inpatient hospitalizations.<sup>(6)</sup> Identifying potential predictors of inpatient hospitalization length of stay could ultimately inform strategies to reduce costs in this population. However, there is only one previous study that examined predictors of hospitalization outcomes in dementia patients with agitation, focusing on psychosocial factors predicting number of visits to the emergency room and length of stay in hospital.<sup>(7)</sup> There are a number of unanswered questions in this field, such as whether certain pharmacotherapies or other clinical/demographic variables can predict length of stay. Based on previous clinical trials using symptom rating scales, risperidone is expected to be more efficacious than other pharmacological treatments.<sup>(8)</sup> Risperidone is the only atypical antipsychotic approved to treat behavioural symptoms of dementia in Canada, specifically in Alzheimer's disease,<sup>(8)</sup> and meta-analyses have shown that patients on risperidone experience significant improvements in aggression and psychosis.<sup>(9)</sup> However, data have also showed that 74% of patients received off-label antipsychotics rather than FDA-approved medications to treat Alzheimer's disease or other forms of dementia.<sup>(6)</sup> Furthermore, it is not clear whether these results are reflected in a real-world setting,

and more data would be helpful to clinicians. A literature review found that only one previous study included time until dischargeable as an outcome measure, by examining the waiting time for dischargeable patients in the somatic department compared to the geropsychiatric department.<sup>(10)</sup> Using time until dischargeable as an outcome measure may help clarify whether medication use translates into a clinically meaningful aid.

In this study, our primary objective was to examine whether psychotropic pharmacological treatments often used to treat agitation and other clinical variables are independently associated with time until dischargeable in a multiple linear regression analysis. We hypothesized that risperidone will be associated with a shorter dischargeable time compared to non-risperidone use, and we reported other associations between medication and baseline variables with time until dischargeable. Our secondary objective was to investigate whether medication use, demographic variables, and clinical factors are associated with length of stay. We also conducted exploratory analyses to compare the associations of different antipsychotic medications with time until dischargeable and to identify risk factors for institutionalization after discharge.

## METHODS

### Study Design & Study Population

We conducted a retrospective chart review of patients admitted to the 32-bed acute geriatric inpatient unit at the tertiary care Jewish General Hospital (JGH) in Montreal, Canada. The patients were admitted directly from the emergency room for agitation in the context of dementia between November 1st, 2007 and November 1st, 2018. We randomly assessed charts from a list of 5,792 patients aged 50 to 100 who were admitted to geriatric inpatient unit during this period. The first 200 patient charts meeting the following inclusion and exclusion criteria were then included in the study.

The charts were screened for potential inclusion based on the hospital discharge summary and were reviewed in further detail if the main diagnosis included behavioural problems in the context of Alzheimer's, mixed, or vascular dementia. Patients were included if 'agitation' appeared in the nursing and medical progress notes of the first seven days of their admission or in the discharge summary. This timeline was chosen because the pharmacological and behavioral interventions in the first seven days tend to be indicative of the course of treatment throughout hospitalization. Additionally, this ensures standardization of medication exposure assessment in all patients, and allows enough time to pass to see the effects of these psychotropic medication exposures on clinical outcomes, such as time until dischargeability and length of stay.

Patients were excluded if: 1) agitation was caused by an identifiable medical problem (i.e., agitation induced by medications, infections); 2) the patient had Parkinson's disease and/or Lewy body dementia (antipsychotics can worsen symptoms of these conditions).<sup>(11,12)</sup>

A total of 2,199 patient charts were assessed; 1,999 charts were excluded because they did not meet the inclusion criteria. This study had received research ethics approval from the Jewish General Hospital.

### Outcome Measures

The main outcome measure was length of time from admission until the patient was dischargeable in the geriatric inpatient unit (e.g., awaiting long-term care). A patient was deemed dischargeable when key terms in the chart suggested 'awaiting placement or discharge', written by the physician, usually in the Plan/Disposition. The goal of using dischargeability as an outcome measure was to mitigate the social and organizational factors that may influence a patient's length of stay in hospital (e.g., extended length of stay because of unavailable placement, even if agitation has been controlled).<sup>(13)</sup>

The secondary outcome was the length of stay in the geriatric inpatient unit.

### Potential Predictor Variables

We examined medications used to address agitation during the first seven days of hospitalization. Psychotropic drugs of interest included: antipsychotics (e.g., risperidone, olanzapine, quetiapine, haloperidol),<sup>(14)</sup> cholinesterase inhibitors,<sup>(15)</sup> memantine,<sup>(16)</sup> antidepressants (e.g., citalopram, sertraline, mirtazapine),<sup>(17)</sup> anticonvulsants (valproic acid, pregabalin),<sup>(17)</sup> and benzodiazepines,<sup>(14)</sup> as well as any of these medications that were taken 'as needed' (PRN – pro re nata). The medication administration chart was used to identify which medications of which patients received at least one dose. PRN medications that were prescribed but not administered were excluded.

Furthermore, we investigated other baseline socio-demographic variables that potentially predict an increased length of stay in an inpatient unit: older age,<sup>(18)</sup> male gender,<sup>(19)</sup> higher number of medications prior to admission,<sup>(20)</sup> increased number of medical comorbidities,<sup>(21)</sup> and living in a supervised environment (institutionalization) before hospitalization.<sup>(19)</sup>

### Statistical Analysis

Descriptive statistics were used to characterize the study sample; mean ( $\pm$ SD), median (IQR), and % (n) were applied where appropriate. The normality of continuous variables was determined with the Shapiro-Wilk test.

For the primary outcome, length of stay until dischargeable, univariate linear analyses were performed on each predictor variable. All variables with statistical significance  $p < .10$  were subsequently included in the multiple linear regression model. For all multiple linear regressions, a two-tailed  $p < .05$  was considered statistically significant. Collinearity diagnostics were applied to ensure minimal multicollinearity between predictor variables in the multiple linear regression model. The secondary outcome, length of stay, was also assessed using univariate linear regression, followed by multiple linear regression for predictor variables with  $p < .10$  in univariate models.

Exploratory analyses were also performed to compare the relation between individual antipsychotics (risperidone, olanzapine, and quetiapine) and time to dischargeability. A Mann-Whitney U test was performed to compare the number of days until dischargeable between patients given risperidone and patients using any other antipsychotic. One-way ANOVA was performed to compare patients given risperidone vs. quetiapine vs. olanzapine, with dischargeability as the outcome measure (patients with multiple antipsychotics were excluded from this analysis). We also explored whether baseline variables (e.g., gender, number of medications prior to admission) and medication use were associated with institutionalization after discharge (i.e., from home to a “supervised environment” such as foster home or long-term care). Possible predictor variables of institutionalization were assessed using simple logistic regression, then multivariable logistic regression was conducted for predictor variables with  $p < .10$ .

All data analysis was completed with SPSS (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. IBM Corp., Armonk, NY).

## RESULTS

Two-hundred patient charts were examined. The median age of patients was 84.0 (IQR=79-89) years, with 56.5% (n=113) being female. Mini-Mental State Examination (MMSE) scores<sup>(22)</sup> were available in 65% of the charts and the mean score in those patients was 14.21 ( $\pm 5.50$ ). Severity of agitation (e.g., Cohen-Mansfield Agitation Inventory)<sup>(23)</sup> was not systematically documented in the charts. Other demographic and clinical characteristics are listed in Table 1.

Antipsychotics were the most common class of psychotropic drug given to patients during the first seven days of stay in the inpatient geriatric unit, with 63.7% (n=127) of patients receiving an antipsychotic: 33.0% (n=66) received quetiapine, 25.5% (n=51) received risperidone, and 8.0% (n=16) received olanzapine. Other frequently administered psychotropic drugs include SSRIs (selective serotonin reuptake inhibitors) (21%, n=42), ACHEIs (acetylcholinesterase inhibitors) (30.0%, n=60), and benzodiazepines (10.5%, n=21). 69.5% (n=139) of patients received at least one dose of a PRN psychotropic medication (administered as needed) within the first seven days.

### Primary Outcome: Length of Time Until Dischargeable

The median length of time until dischargeable (awaiting placement) was 10.0 days (IQR=6-22) (mean=18.16  $\pm$  25.90 days). Univariate regression showed that age, antipsychotics, olanzapine, benzodiazepine, and benzodiazepine PRN were associated with a longer time until dischargeable (Table 2), while other variables such as gender, living in a supervised environment before admission, number of medical comorbidities, number of medications prior admission, and other psychotropic medications were not. Subsequently, a

multiple linear regression model including age, antipsychotics, olanzapine, benzodiazepine, and benzodiazepine PRN found that only olanzapine (40.9 vs. 16.7 days,  $\beta = 0.23$ ,  $p = .001$ ), benzodiazepines (32.7 vs. 16.5 days,  $\beta = 0.15$ ,  $p = .027$ ), and benzodiazepine PRNs (31.7 vs. 15.9 days,  $\beta = 0.19$ ,  $p = .006$ ) were independently associated with longer time until discharge with a significance of  $p < .05$ , while age ( $\beta = -0.48$ ,  $p = .48$ ) and general antipsychotic use ( $\beta = 0.08$ ,  $p = .28$ ) were not (Table 2).

### Secondary Outcome: Length of Stay

The median length of stay in the hospital was 34.0 days (IQR=16-68.75) (=49.8  $\pm$  49 days). Univariate analysis found that the following predictor variables for length of stay (days) were significant with  $p < .10$ : age, number of medications before hospitalization, antipsychotics, benzodiazepines, mirtazapine, and haloperidol PRN (Table 3). The following predictor variables were subsequently shown to be significantly associated with increased length of stay in the multiple linear regression model: benzodiazepines ( $\beta = 0.17$ ,

TABLE 1.  
Baseline demographic and clinical characteristics of hospitalized patients with dementia and agitation (n=200)

	Mean ( $\pm$ SD), Median (IQR), or % (n)
<i>Demographics</i>	
Age (yrs)	84.0 (79-89)
Female	56.5% (n=113)
Supervised environment before admission	34.5% (n=69)
# Medical comorbidities	4.0 (3-6)
# Medications before admission	7.0 (5-9)
<i>Medications Prior to Admission</i>	
<i>Antipsychotics</i>	
Quetiapine	23.5% (n=47)
Risperidone	15.5% (n=31)
Olanzapine	5.0% (n=10)
<i>Antidepressants</i>	
Citalopram	16.0% (n=32)
Sertraline	2.0% (n=4)
Mirtazapine	6.0% (n=12)
<i>Anticonvulsants</i>	
Pregabalin	3.5% (n=7)
Sodium Valproate	2.0% (n=4)
<i>ACHEI</i>	
Memantine	5.5% (n=11)
Benzodiazepines	12.5% (n=25)
<i>PRNs</i>	
Quetiapine PRN	6.5% (n=13)
Haloperidol PRN	9.0% (n=18)
Risperidone PRN	3.0% (n=6)
Benzodiazepines PRN	14.5% (n=29)

TABLE 2.  
Univariate analyses and multiple linear regression models for time until dischargeable (days) (n=200)

Predictor Variables	Univariate Analysis				Multiple Linear Regression Model	
	Medication Received Mean (days) ± SD	Medication Not Received Mean (days) ± SD	β	p value	β	p value
Age (years)			-0.053	<.001	-0.48	.48
Antipsychotics	20.88±30.74	13.41±12.82	0.14	.049	0.08	.28
Olanzapine	40.94±57.73	16.17±20.17	0.26	<.001	0.23	.001
Benzodiazepines	32.71±36.09	16.45±23.99	0.19	.006	0.15	.027
Benzodiazepine PRN	31.69±52.10	15.86±17.36	0.22	.002	0.19	.006

SD = standard deviation;  $R^2 = 0.14$ ;  $\beta$  = standardized coefficient.

TABLE 3.  
Univariate analyses and multiple linear regression models for length of stay in geriatric inpatient unit (days) (n=200)

Predictor Variables	Univariate Analysis				Multiple Linear Regression Model	
	Medication Received Mean (days) ± SD	Medication Not Received Mean (days) ± SD	β	p value	β	p value
Age (years)			-0.082	.031	-0.056	.43
# of medications prior to admission			-0.007	.055	-0.042	.56
Antipsychotics	56.09±54.00	38.59±36.32	0.17	.015	0.13	.056
Benzodiazepines	75.14±51.42	46.72±46.56	0.18	.011	0.17	.016
Mirtazapine	82.30±62.45	47.98±47.71	0.15	.030	0.15	.037
Haloperidol PRN	58.07±55.19	42.85±42.19	0.16	.028	0.17	.016

SD = standard deviation;  $R^2 = 0.14$ ;  $\beta$  = standardized coefficient.

$p = .016$ ), mirtazapine ( $\beta = 0.15$ ,  $p = .037$ ) and haloperidol PRN ( $\beta = 0.17$ ,  $p = .016$ ) (Table 3). Antipsychotics approached statistical significance ( $\beta = 0.13$ ,  $p = .056$ ), while number of medications before hospitalization ( $\beta = -0.042$ ,  $p = .56$ ) and age were not significant ( $\beta = -0.056$ ,  $p = .43$ ).

### Exploratory Analyses

#### *Risperidone vs. Other Antipsychotics*

A Mann-Whitney U test indicated no significant difference in the number of days until dischargeable between patients using risperidone (Mdn = 11.5) and patients using other antipsychotics (either quetiapine or olanzapine) (Mdn = 10.0),  $U=1575$ ,  $p = .86$ ,  $r = -.012$ .

#### *Risperidone vs. Olanzapine vs. Quetiapine*

Antipsychotics were the most commonly prescribed psychotropic medication to target agitation in the first seven days of hospitalization. After removing patients who received multiple antipsychotics (n=11), we compared patients who received quetiapine (n=59), olanzapine (n=13), and risperidone (n=44). There was a statistically significant difference between patients who received quetiapine vs. olanzapine vs. risperidone, as determined by a one-way ANOVA ( $F(2,113)=4.8$ ,  $p = .01$ ). A

Tukey post hoc test found that the time until dischargeable was statistically significantly shorter for patients given quetiapine ( $16.34 \pm 20.56$  days,  $p = .009$ ) or risperidone ( $17.23 \pm 17.15$  days,  $p = .015$ ), compared to patients given olanzapine ( $41.77 \pm 63.45$  days). There was no statistically significant difference between patients who received quetiapine and patients who received risperidone ( $p = .986$ ).

#### *Change in Supervised Environment*

34.5% (n=69) of patients lived in a supervised environment (e.g., long-term care) prior to admission, whereas 84.5% (n=169) of patients lived in a supervised environment following discharge from the geriatric inpatient unit. 69.5% (n=139) of patients transitioned to a more supervised environment, 29.5% (n=59) patients returned to the same living arrangement, one patient transitioned to a less supervised environment, and one patient died while hospitalized.

The logistic regression model for change in level of supervision of living environment—which included gender, supervised environment before admission, and number of medications before admission—was statistically significant,  $\chi^2(6) = 19.50$ ,  $p < .001$ . The model explained 13.2% (Nagelkerke  $R^2$ ) of the variance in level of supervision.

Patients who lived in a non-supervised environment prior to admission were 3.05 times more likely to transition to a more supervised environment after discharge.

## DISCUSSION

Our results suggest that the use of olanzapine, regular benzodiazepines, and PRN benzodiazepines were independently associated with a prolongation of time needed for a patient to be considered dischargeable. With olanzapine, the mean length of time to be dischargeable was 2.5 times greater than non-olanzapine users (40.94 vs. 16.17 days) and remained significant in multiple linear regression analyses. Olanzapine was also associated with a significantly increased time until dischargeable compared to risperidone and quetiapine users. Both regular benzodiazepines (32.71 vs. 16.45 days) and as-needed benzodiazepines (31.69 vs. 15.86 days) were independently associated with a two-fold increase in time until dischargeable. This poses the question as to whether prescribing these medications is more beneficial or more harmful to patients with dementia and agitation.

To our knowledge, our study is the second article that examines predictors of hospitalization outcomes in dementia patients with agitation.<sup>(7)</sup> The study by Nejtek *et al.* examined psychosocial factors, number of visits to the emergency room, and length of stay in hospital as the main outcome measures.<sup>(7)</sup> Among their results, it was found that nursing homes located in impoverished areas transferred patients to the psychiatric emergency center significantly more often than those in affluent areas.<sup>(7)</sup> A recent review of pharmacological interventions on treatment of agitation in dementia revealed that most studies have used rating scales for their primary outcomes.<sup>(24,25)</sup> Our study adds to the current literature by looking at two clinically relevant factors: 1) the impact of pharmacological agents, and 2) the dischargeability of a patient as an outcome measure. Our results suggest that there is a possible association between the time it takes for a patient to be deemed dischargeable and the medications they receive in the first seven days of hospitalization.

Analyses revealed that risperidone was not statistically significantly associated with time until dischargeable. This is surprising, as a recently published algorithm for agitation in the inpatient setting suggests risperidone as a first-line treatment.<sup>(8)</sup>

Along similar lines, it is intriguing that olanzapine was associated with an increased length of stay until dischargeable, while none of the other antipsychotics (quetiapine and risperidone) were found to be a significant predictor of time until dischargeable. The Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer’s Disease (CATIE–AD) study had previously compared the effectiveness of atypical antipsychotics (quetiapine, olanzapine, risperidone) for patients with Alzheimer’s and agitation, aggression, or psychosis.<sup>(26)</sup> The CATIE-AD study found that olanzapine and risperidone had a statistically significant longer time until discontinuation due to lack of efficacy compared to quetiapine and a placebo,<sup>(26)</sup> suggesting that olanzapine is an

effective treatment for agitation. However, in the CATIE–AD study, no significant differences were noted among the groups with regard to improvement on clinical global improvement between groups (e.g., 32% of patients assigned to olanzapine, 29% assigned to risperidone, 26% assigned to quetiapine, and 21% of patients assigned to placebo).<sup>(26)</sup> Another study in dementia patients found that quetiapine, olanzapine, and risperidone all have similar number needed to treat (NNT), but all three atypical antipsychotics showed a significant relationship between mortality and dose.<sup>(8)</sup>

In our study, one of the most striking findings of the exploratory analyses was the result of comparing the different antipsychotic groups (quetiapine vs. olanzapine vs. risperidone) with dischargeability as the outcome measure. There were statistically significant differences between olanzapine and the other antipsychotics, but there was no statistical difference between quetiapine and risperidone. This brings about the question as to why olanzapine, specifically, is associated with a 2.5 times higher time until dischargeable compared to the other antipsychotics.

One possibility is that olanzapine is ineffective as a treatment for agitation in dementia patients and thus prolongs time until dischargeable. Another reason (perhaps more likely) could be that olanzapine was prescribed to patients in our unit with more severe cases of agitation, and the higher baseline agitation is what results in the association with an increased length of time until dischargeable. Also, the strong anticholinergic profile of olanzapine may be one factor (quetiapine is considered relatively less anticholinergic<sup>(27)</sup>), leading to more side effects (e.g., confusion) and thereby prolonging the time until a patient is deemed dischargeable.

It is also surprising to find that benzodiazepines given on a PRN basis were associated with a prolonged time until dischargeable. Benzodiazepines given on a PRN basis are considered one of the first-line agents for managing agitation in the inpatient setting, based on an expert-made and evidence-based treatment algorithm.<sup>(13)</sup> There have been no previous studies examining the possible association between as-needed benzodiazepine prescription and length of stay or time until dischargeable in dementia patients with agitation. The fact that benzodiazepines given regularly are associated with prolonging the time of dischargeability is consistent with previous literature that has found benzodiazepines to be a risky treatment for the geriatric population<sup>(28)</sup> and results in increased length of hospital stay.<sup>(29)</sup>

## Strengths and Limitations

This study has several important strengths. This was the first study to examine predictors of a patient’s dischargeability in the context of agitation in dementia in a real-world setting. We included a longitudinal study design. We also used a clinically relevant hard outcome with cost implications: length of time until dischargeable.

Limitations include the fact that this was a retrospective study. There are certain additional factors not examined that could have influence a patient’s dischargeability:

non-psychotropic medications and medical comorbidities are two examples. Additional prospective studies to clarify this association would be helpful. For example, patient's baseline agitation could be assessed and controlled for in the analyses. Randomized control trials (RCTs) could help evaluate causality (e.g., benzodiazepine discontinuation trial in hospitalized agitated patients with dementia; or olanzapine vs. risperidone RCT using the outcome measure of time until dischargeability). Another limitation is that medications prescribed in the first seven days may be different from the medications that were eventually effective in treating agitation, since patient length of stay was, on average, much longer than one week (mean = 50.02 days). However, we chose this timeline to ensure standardization of medication exposure assessments in patients with varying lengths of hospitalization. This approach of measuring exposure during the first seven days, followed by a longer follow-up period, has been used in other studies.<sup>(30)</sup> Additionally, although we pre-specified our primary analyses, exploratory analyses may not have been adequately powered after controlling for multiple comparisons. These exploratory analyses, although some of which have a *p* value less than .05, are less reliable than our primary a priori analyses, and require further confirmation. We nonetheless think of this paper as an exciting hypothesis-generating study.

## CONCLUSIONS

Overall, regular benzodiazepine use, PRN benzodiazepine use, and olanzapine use are associated with a longer time until a patient is deemed dischargeable. Olanzapine had longer time until dischargeability compared to risperidone and quetiapine. Future randomized controlled trials could assess pharmacotherapy effects on time until dischargeability. Nonetheless, these findings raise a question as to whether the risks of benzodiazepines and certain antipsychotics (e.g., olanzapine) outweigh the benefits in the hospital setting.

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## CONFLICT OF INTEREST DISCLOSURES

The authors declare that no conflicts of interest exist.

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