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A delicate balance: Psychotropic polypharmacy and anti-cholinergic use are correlated with fall incidence in Australian inpatients with dementia

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Abstract

Background: Persons with dementia commonly experience a range of behavioural and psychological symptoms, including agitation, aggression, perceptual disturbances, and depression. While psychotropic medications are regularly prescribed to mitigate these symptoms, these agents also carry a broad adverse effect profile. This study aimed to characterize psychotropic medication use in patients with dementia, as well as identify prescribing factors associated with falls in this cohort.

Methods: This retrospective study collected longitudinal demographic and medication data from all patients admitted to a neuro-cognitive unit at an Australian metropolitan hospital over a 2-year period. Psychotropic polypharmacy and psychotropic agent use per patient-fortnight were investigated for their association with inpatient falls.

Results: All patients (n = 147) were prescribed at least one psychotropic medication, with 96% receiving anti-psychotic medications and 90% receiving benzodiazepines. Patient fall rate was significantly associated with anticholinergic drug use (Incidence rate ratio: 2.2; $P < .001$), as well as concomitant use of ≥5 daily psychotropic agents (Incidence rate ratio: 3.1; $P = .001$).

Conclusions: Patients with dementia are routinely prescribed a wide variety of psychotropic medications. Use of anticholinergic drugs and psychotropic polypharmacy are correlated with fall incidence in persons with dementia.

KEYWORDS
antidepressant, dementia, falls, neuropsychiatry, psychotropic

1 | INTRODUCTION

Dementia is a highly prevalent and morbid syndrome in the older population.[1-3] 80% of persons with dementia experience neuropsychiatric symptoms (NPS; also known as behavioural and psychological symptoms of dementia, or BPSD), including aggression, agitation, disinhibition, psychotic symptoms, disrupted sleep-wake cycle pattern and mood disorders.[4] NPS are a key contributor

to the overall burden of dementia; they decrease quality of life for patients and carers, and increase rates of admission to long-term care facilities such as nursing homes.[5,6]

Management of NPS in the clinical setting involves a range of strategies, including behavioural interventions, structured therapies, and psychotropic agents.[7] Antipsychotics have demonstrated modest efficacy in the reduction of NPS, particularly for aggression and psychotic symptoms (delusions and hallucinations).[8,9] However, their use is complicated by a variety of adverse effects, including extra-pyramidal symptoms, falls, weight gain and cerebrovascular dysfunction.[4] Benzodiazepines are commonly prescribed to manage agitation, insomnia, and anxiety,[7] though this must be counterbalanced against side effects such as sedation, increased fall risk, and dependence formation.[10] Antidepressants[7] and sleeping adjuncts such as melatonin[11] are often prescribed to relieve behavioural NPS.[12] Notably, conventional anti-dementia drugs such as acetylcholinesterase inhibitors are generally ineffective in the management of NPS.[7,13]

Polypharmacy, defined as the concomitant use of five or more daily medications, is a key contributor to morbidity in the geriatric population.[14] In patients with dementia, polypharmacy is implicated in sentinel events such as falls, respiratory depression, and cardiac arrest.[10,14,15] Additionally, there is evidence that long-term use of anti-psychotics and benzodiazepines in dementia is linked to cognitive decline,[4] reduced mobility,[16] and all-cause mortality, including deaths attributable to falls and fractures.[7] Several harm reduction tools have been identified for prescribing in this vulnerable cohort. The Beers Criteria[17] is an established resource with utility in reducing inappropriate prescribing in the geriatric population. In recent years, the Drug Burden Index[18] has risen as a novel measure capable of capturing the cumulative burden of medications with anticholinergic and sedative activity.

Given this, Japanese and Australian recommendations in dementia outline that atypical antipsychotics be prescribed for a maximum of 12 weeks,[2,19-21] and that benzodiazepines be used sparingly and for short durations.[22,23] However, a review of Australian prescribing data suggests that psychotropic agents continue to be overprescribed for persons with NPS.[7]

Few studies have specifically examined psychotropic use in dementia,[2,24] and the authors were unable to identify any reports that examined this in an inpatient setting. Therefore, this study aimed to (i) describe psychotropic prescribing in an Australian dementia unit over a 2-year period, reporting on medication type, duration, and dose; and (ii) evaluate the relative risks of selected demographic- and medication-related exposures on patient fall rate.

2 | METHODS

2.1 | Study design

This was a retrospective observational single-site study located at The Prince Charles Hospital (TPCH) in Brisbane, Australia. Ethical approval for this study was granted by the Queensland Metro North Human Research Ethics Committee (HREC/18/QPCH/190).

2.2 | Study participants

This study was conducted at the TPCH Cognitive Assessment and Management (CAM) Unit, a 13-bed unit dedicated to the assessment and management of patients experiencing neuropsychiatric symptoms. Admission criteria for the CAM include all patients with hyperactive delirium, moderate to severe NPS, and/or undifferentiated neuro-cognitive disorders. All patients admitted to the CAM Unit over a 2-year period from January 1, 2015 to December 31, 2016 were included in the study.

2.3 | Data collection

Patient data were collected from electronic records, as well as hospital-supplied prescribing information. Demographic data obtained included age, sex, length of stay, and discharge destination (eg, home, another ward, or an aged care facility). Primary diagnosis was determined by treating consultant specialists, with reference to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V). Additionally, we collected comprehensive psychotropic prescription data, including medication type, dose, and duration of use; and selected clinical measures, including fall events, Body Mass Index (BMI) and patients' Health of the Nation Outcome Scale (HoNOS) scores. Only psychotropic medication data (Appendix 1) was included in this study. As a validated measure of cognitive and social function, the HoNOS is routinely used by neurocognitive and psychiatric units to quantify symptom severity, as well as to evaluate patients' responses to treatment over time.[25] Both BMI and HoNOS scores were collected by trained clinicians at admission and discharge.

2.4 | Data processing and analysis

Depending on their primary indication, each medication was grouped into one of five categories: antipsychotic, anxiolytic (eg, benzodiazepines), antidepressant, anti-dementia (eg, cholinesterase inhibitors), and miscellaneous. Each medication was also assessed as for its clinical anticholinergic activity (see Appendix 1).[26,27] In this study, psychotropic polypharmacy was defined as the concomitant use of ≥5 psychotropic agents. As length of stay varied considerably between patients, prescription data was compared between the first and final fortnight of each patient's admission. Given that medications are often reviewed and altered early in patients' admissions, we elected to assess prescribing data from day 8 (midpoint of first fortnight) and day 15 (endpoint of first fortnight) as representative and stable point-prevalence estimates for use in modelling fall risk.

Statistical analyses were conducted in Stata 15.[28] Descriptive statistics were used to explore patient characteristics and prescription data. Categorical variables were summarised into frequencies and compared between time periods using McNemar's test for paired categorical data. Continuous variables were described as median (interquartile range); as the data were not normally distributed, Wilcoxon's signed-rank test for non-parametric data was used to evaluate differences between patients' initial and final fortnights.

Negative binomial regression was used to model associations between fall incidence and selected exposure variables, including baseline patient characteristics, psychotropic polypharmacy, and administration of any anticholinergic drug in the first fortnight of admission. Variables with univariate P-values <.2 were entered into a multivariate model, before sequentially dropping variables with the highest p-value. Excluded variables were re-entered and tested in a sequential multivariate model, using Akaike's information criteria to select the best-fitting model. In assessing psychotropic polypharmacy, only patients with length of stay ≥8 days were assessed and reported; however, a sensitivity analysis was undertaken with all patients.

3 | RESULTS

3.1 | Patient characteristics and clinical outcomes

A total of 147 patients (mean age 77.6 ± 9.2, 37% F) were included in this study, with the cohort's demographic and clinical characteristics detailed in Table 1. Mixed-type dementia (41%) and Alzheimer's disease (31%) were the most common primary diagnoses.

Overall, 42% of patients experienced at least one fall during their stay. Mean BMI was 24.0 (SD: 4.7) at admission and 24.5 (SD: 5.0) at discharge. Mean HoNOS decreased from 32.2 (SD: 8.0) on admission to 28.9 (SD: 9.5) at discharge.

3.2 | Medication frequency and duration

Table 2 describes the prescribing frequency for each medication category, as well as each medication's mean daily dose and duration of use. All patients were prescribed at least one psychotropic medication during their admission.

In this study cohort, 96% of patients received antipsychotic medications during their stay. The most common antipsychotic agents were risperidone (64%; median dose: 0.8 mg; IQR: 0.5-1.1) and olanzapine (29%; median dose: 6.7 mg; IQR: 5.0-9.0). Similarly, 90% of patients were prescribed at least one benzodiazepine, most commonly oxazepam (88%; median dose: 15.8 mg; IQR: 13.3-24.8).

Antidepressants were prescribed to 60% of patients, most commonly citalopram (23%; median dose: 17.7 mg; IQR: 10.0-20.0) or mirtazapine (22%; median dose: 15.0 mg; IQR: 14.0-25.7). Anti-dementia medications were prescribed to 35% of patients, including

TABLE 1 Cohort characteristics and clinical outcomes

Characteristic	Patients (n = 147)
Patient demographics	
Mean age (years ± SD)	77.6 ± 9.2
Males	92 (63%)
Females	55 (37%)
Median days of stay (IQR)	44 (24-89)
Primary diagnosis	
Mixed-type dementia	60 (41%)
Alzheimer's disease	45 (31%)
Vascular dementia	14 (10%)
Fronto-temporal dementia	7 (5%)
Alcohol-related dementia	6 (4%)
Parkinson's disease	6 (4%)
Lewy body dementia	4 (3%)
Acquired brain injury	2 (1%)
Bipolar disorder	1 (1%)
Limbic encephalitis	1 (1%)
Schizophrenia	1 (1%)
Discharge destination	
Residential aged care facility	105 (71%)
Patient's home	30 (20%)
Hospital ward	5 (3%)
Mortality	6 (4%)
Clinical outcomes	
Patients on ≥1 anti-cholinergic medication	65 (44%)
Total falls	153
Patients with ≥1 fall	62 (42%)
Median falls (IQR)	0.0 (0.0-1.0)
BMI at admission (±SD)	24.0 ± 4.7
BMI at discharge (±SD)	24.5 ± 5.0
HoNOS at admission (±SD)	32.2 ± 8.0
HoNOS at discharge (±SD)	29.0 + 9.5

Note: All figures are reported as n (%) unless otherwise stated.
Abbreviations: BMI, Body Mass Index; HoNOS, Health of the Nation Outcome Scale.

4 (3%) instances of levodopa for Parkinson's disease. Miscellaneous medications were prescribed to 22% of patients, most prominently melatonin (16%; median dose: 2.0 mg; IQR: 2.0-2.2).

Table 3 demonstrates temporal trends in prescribing frequency for the 122 patients with a length of stay ≥15 days. Patients were prescribed a median of 3 unique medications (IQR: 2-4) during their first fortnight of admission. This increased to a median of 4 unique medications (IQR: 3-5) in their last fortnight of admission (P < .001). This was largely due to statistically significant increases in anxiolytic (P = .006), antidepressant (P < .001), anti-dementia (P < .001), and miscellaneous (P = .001) medication prescribing from the initial

Medication	Patients (n = 147) [n (%)][b]	Median daily dose prescribed, in mg (IQR)
Antipsychotic medications	141 (96%)	
Risperidone	94 (64%)	0.8 (0.5-1.1)
Olanzapine	42 (29%)	6.7 (5-9.0)
Haloperidol	26 (18%)	0.9 (0.5-1.2)
Quetiapine	26 (18%)	46.3 (25.2-74.0)
Chlorpromazine	3 (2%)	32.2[a]
Aripiprazole	1 (1%)	6.1[a]
Anxiolytic medications	132 (90%)	
Oxazepam	130 (88%)	15.8 (13.3-24.8)
Midazolam	17 (12%)	3.3 (2.5-5.0)
Temazepam	12 (8%)	10.0 (10.0-10.0)
Clonazepam	11 (7%)	0.7 (0.5-1.2)
Diazepam	9 (6%)	6.0 (5.0-7.0)
Lorazepam	8 (5%)	1.0 (0.8-1.2)
Clobazam	1 (1%)	10.0[a]
Antidepressant medications	88 (60%)	
Citalopram	34 (23%)	17.7 (10.0-20.0)
Mirtazapine	32 (22%)	15.0 (14.0-25.7)
Sertraline	9 (6%)	86.9 (77.0-100.0)
Escitalopram	6 (4%)	13.9 (11.5-18.8)
Venlafaxine	6 (4%)	174.7 (152.3-225.6)
Fluoxetine	4 (3%)	33.1[a]
Duloxetine	3 (2%)	41.0[a]
Paroxetine	3 (2%)	10.0[a]
Amitriptyline	1 (1%)	10.0[a]
Dothiepin	1 (1%)	25.0[a]
Nortriptyline	1 (1%)	21.9[a]
Anti-dementia medications	52 (35%)	
Donepezil	26 (18%)	6.2 (5.0-10.0)
Rivastigmine	9 (6%)	4.6 (4.6-6.1)
Galantamine	8 (5%)	15.7 (12.7-16.6)
Memantine	8 (5%)	16.6 (10.0-20.0)
Levodopa	4 (3%)	171.2[a]
Miscellaneous medications	32 (22%)	
Melatonin	23 (16%)	2.0 (2.0-2.2)
Sodium valproate	8 (5%)	650.0 (400.0-1422.7)
Carbamazepine	3 (2%)	660.6[a]
Lithium	2 (1%)	689.2[a]
Pregabalin	2 (1%)	92.8[a]
Levetiracetam	1 (1%)	1.0[a]
Phenytoin	1 (1%)	400.0[a]

TABLE 2 Psychotropic prescribing frequency and dose by medication category

[a]Interquartile range (IQR) only reported for categories with n ≥ 5.

[b]As some patients were either on multiple medications in the same category or had medication changes during their admission, percentages in each category do not add up to 100%.

TABLE 3 Selected psychotropic prescribing data for initial and final fortnight of admission for 122 patients with length of stay ≥15 days

	Patients (n = 122)		
	Initial fortnight	Final fortnight	P-value
Median unique prescriptions (IQR)	3 (2-4)	4 (3-4)	<0.001[a]
≥1 antipsychotic drugs [n (%)]	116 (95%)	116 (95%)	1.0[b]
≥1 anxiolytic drugs [n (%)]	103 (84%)	113 (93%)	0.006[b]
≥1 antidepressant drugs [n (%)]	65 (53%)	79 (65%)	<0.001[b]
≥1 anti-dementia drugs [n (%)]	31 (25%)	48 (39%)	<0.001[b]
≥1 miscellaneous drugs [n (%)]	20 (16%)	31 (25%)	0.001[b]

Note: P-values calculated using [a]Wilcoxon's signed-rank test and [b]McNemar's test.

Abbreviations: LoS, Length of Stay.

fortnight to the final fortnight. On both day 8 and day 15 of each patient's respective admission, 6% of patients were prescribed ≥5 unique medications.

3.3 | Factors associated with fall occurrence

Table 4 demonstrates the associations between variables of interest and fall rate for the 138 patients with a length of stay ≥8 days. After multivariate adjustment, the incidence of falls was approximately 120% greater in patients receiving anticholinergic medications (IRR: 2.2; 95% CI: 1.4-3.6; *P* = .001). Patients on ≥5 daily unique psychotropic medications on day 8 of their admission were at substantially greater risk of falls (IRR: 3.1; 95% CI: 1.4-6.6; *P* = .001). A sensitivity analysis on all patients, including those with length of stay <8 days, indicated consistent results.

4 | DISCUSSION

In this descriptive study of an inpatient neuro-cognitive unit, we documented psychotropic medication use over a 2-year period, and identified several factors associated with fall rate in this setting. Patients were prescribed a median of 3 unique medications during their first fortnight in the unit, comprising a combination of pre-existing and new medications. The majority of patients received both antipsychotic and anxiolytic medications. Furthermore, patients accrued more unique prescriptions and greater drug burden the longer they stayed in hospital. Factors associated with in-hospital falls included

TABLE 4 Associations between fall incidence and baseline variables of interest for 138 patients with length of stay ≥8 days

	Univariate model		Multivariate model	
Factor	IRR (95% CI)	P-value[a]	IRR (95% CI)	P-value[a]
Use of anticholinergic drugs in first fortnight	2.6 (1.6-4.3)	<0.001	2.2 (1.4-3.6)	0.001
Use of ≥5 unique medications on day 8	5.7 (2.5-13.2)	<0.001	3.1 (1.4-6.6)	0.001
Diagnosis		0.08		0.03
Mixed-type dementia	Ref		Ref	
Alzheimer's disease	0.6 (0.3-1.1)	0.08	0.5 (0.3-0.9)	0.03
Other dementia	0.4 (0.2-1.1)	0.07	0.4 (0.2-0.9)	0.03
Vascular dementia	1.5 (0.7-3.4)	0.32	1.0 (0.5-2.1)	0.99
Parkinson's disease	0.9 (0.2-3.5)	0.90	0.5 (0.2-1.7)	0.27
Other	0.2 (0.0-2.0)	0.18	0.1 (0.0-0.9)	0.40
Female gender	0.4 (0.2-0.8)	0.004	0.5 (0.3-0.9)	0.011
Baseline HoNoS (per 10 units)	1.3 (0.9-1.8)	0.16		
Age category		0.57		
<70	Ref			
70-84	0.8 (0.4-1.5)	0.40		
≥85	0.7 (0.3-1.4)	0.31		
BMI category		0.25		
<20 kg/m^2	Ref			
20-30	1.8 (0.9-3.6)	0.11		
≥30	1.3 (0.5-3.8)	0.61		

Abbreviations: CI, confidence interval; DBI, Drug Burden Index; HoNOS, Health of the Nation Outcome Scale; IRR, incidence rate ratio; Ref, Reference.

[a]*P*-values calculated using negative binomial regression.

benzodiazepine prescription, as well as increased administration of medications with an anticholinergic effect, including antipsychotics and antidepressants. Patients' mean HoNOS score decreased by a mean of 3.3 points from admission to discharge; this modest but significant reduction highlights both the progressive course of dementia as well as inpatient benefits to NPS management.

By recording prescription data over time, we were able to capture medication use longitudinally instead of cross-sectionally, allowing us to evaluate temporal trends in medication burden. The use of patient-fortnights also permits valid analysis of patient data over differing lengths of stay, avoiding the inherent inaccuracy in ad hoc comparisons of collapsed cross-sectional data.[29] Notably, there was a significant increase in total unique prescriptions from patients' initial fortnight to their last fortnight in the unit. This is largely attributable to increases in median benzodiazepine, antidepressant, and anti-dementia medication usage over this period, indicating that patients' medication burden generally increases with greater length of stay. We note that this method of measuring prescription data also captures medication changes; while these are also associated with patient morbidity, they are distinct from true concomitant medication use.[30] Therefore, we elected to assess psychotropic polypharmacy as a point prevalence of total unique medications on days 8 of admission.

Overall, our study has several implications for prescribing practice in dementia, with the primary goals of reducing concomitant anticholinergic medication use. While these medications have a demonstrated role in reducing NPS,[7-9] our data indicates that (1) falls are a common event in dementia units, (2) use of psychotropic agents is correlated with greater fall incidence, and (3) psychotropic polypharmacy is associated with the highest fall rate of all assessed risk factors in this cohort. Therefore, clinical decision making needs to balance the therapeutic benefit of anticholinergic agents with this greater risk profile. In this context, integrated chart warnings may represent a useful stratification tool to mitigate fall incidence; for example, patients with ≥5 unique psychotropic medications or ≥12 weeks of antipsychotic use could receive more frequent medication reviews[2,19] as well as prophylactic physiotherapy and occupational therapy interventions.[31]

This is the first known study to explore psychotropic medication usage and fall risk in an inpatient neuro-cognitive setting. Our patient characteristics were comparable to outpatient cohorts of persons with a dementia diagnosis in the literature,[24,25,32] including similar age and gender profiles; predominant primary diagnoses of mixed-type dementia and Alzheimer's disease; and high rates of polypharmacy. However, rates of antipsychotic (96%) and benzodiazepine (90%) prescribing were significantly higher in this population than in corresponding studies: for example, a Swedish study on outpatients with dementia reported an antipsychotic prevalence of 22% and a benzodiazepine prevalence of 37%,[33] while a Japanese study reported 14% and 11% respectively.[20] This may be due to the inpatient nature of this study: patients hospitalized for dementia are likely to have more severe and frequent NPS than patients able to be managed in an outpatient setting.

However, this study's data should be interpreted in the context of several limitations. Firstly, we did not collect data on physiological co-morbidities, mental wellbeing, or dementia severity, preventing inclusion of these factors in our multivariate analysis. This is pertinent because neuropsychiatric symptoms are themselves associated with impaired mobility, and NPS severity may thus represent a drug-independent contributor to fall risk.[5] Additionally, we did not collect data on the use of non-psychotropic medications (eg, opioid analgesics); as some of these have anticholinergic effects, this may have caused under-estimation of patients' medication burden. Secondly, as this was an observational and single-site study, any prescribing patterns and outcomes reflect the treatment practices of a small group of clinicians, as well as a specific treatment setting. Therefore, these results may not necessarily be generalizable to all inpatients with dementia. Thirdly, the retrospective nature of this study precludes any causal inferences from being drawn, especially given that our method of collection does not account for inter-patient variation in pharmacokinetics or pharmacodynamics.[34]

Overall, management of dementia-associated NPS represents a substantial clinical challenge, and patients are often prescribed multiple psychotropic agents with the aim of mitigating their symptoms. This study found that patients admitted to an Australian dementia unit were invariably prescribed at least one psychotropic medication, with the median number of unique medications rising over length of stay. 6% of patients received at least five unique psychotropic medications on day 8 of their admission, with a corresponding 210% increase in fall incidence. Antipsychotics and benzodiazepines were the most commonly prescribed medication classes. Over-prescription of anxiolytic medications was found to correlate with fall incidence, and thus represents an important goal for harm reduction when clinically managing this cohort. Further primary research is necessary to evaluate the prospective benefits of tapering polypharmacy and long-term medication use in at-risk persons with dementia.

CONFLICTS OF INTEREST
The authors confirm that this manuscript is original, and has not previously been published in part or wholly. The authors have no competing interests to declare with regards to this study or manuscript, including any financial interests or support.

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APPENDIX 1

Medication classification and minimum dose by category

Category	Medications	Anticholinergic activity[25,26]
Antipsychotic medications	Aripiprazole	No
	Chlorpromazine	Yes
	Haloperidol	No
	Olanzapine	Yes
	Risperidone	No
	Quetiapine	Yes
Anxiolytic medications	Clobazam	No
	Clonazepam	No
	Diazepam	No
	Lorazepam	No
	Midazolam	No
	Oxazepam	No
	Temazepam	No

Category	Medications	Anticholinergic activity[25,26]
Antidepressant medications	Amitriptyline	Yes
	Citalopram	No
	Dothiepin	Yes
	Duloxetine	No
	Escitalopram	No
	Fluoxetine	No
	Mirtazapine	No
	Nortriptyline	Yes
	Paroxetine	Yes
	Sertraline	No
	Venlafaxine	No
Anti-dementia medications	Donepezil	No
	Galantamine	No
	Levodopa	No
	Memantine	No
	Rivastigmine	No
Miscellaneous medications	Carbamazepine	Yes
	Levetiracetam	No
	Lithium	No
	Melatonin	No
	Phenytoin	No
	Pregabalin	No
	Sodium valproate	No