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Trends in Psychotropic Dispensing Among Older Adults with Dementia Living in Long-Term Care Facilities: 2004-2013.

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Objective: *Guidelines worldwide have cautioned against the use of antipsychotics as first-line agents to treat neuropsychiatric symptoms of dementia. We aimed to investigate the changes over time in the dispensing of antipsychotics and other psychotropics among older adults with dementia living in long-term care facilities.* **Methods:** *We used drug claims data from Ontario, Canada, to calculate quarterly rates of prescription dispensing of six psychotropic drug classes among all elderly (≥65 years of age) long-term care residents with dementia from January 1, 2004, to March 31, 2013. Psychotropic drugs were classified into the following categories: atypical and conventional antipsychotics, non-sedative and sedative antidepressants, anti-epileptics, and benzodiazepines. We used time-series analysis to assess trends over time.* **Results:** *The study sample increased by 21% over the 10-year study period, from 49,251 patients to 59,785 patients. The majority of patients (within the range of 75%–79%) were dispensed at least one psychotropic medication. At the beginning of the study period atypical antipsychotics (38%) were the most frequently dispensed psychotropic, followed by benzodiazepines (28%), non-sedative antidepressants (27%), sedative antidepressants (17%), anti-epileptics (7%), and conventional antipsychotics (3%). Dispensing of anti-epileptics (2% increase) and conventional antipsychotics (1% decrease) displayed modest changes over time, but we observed more pronounced changes in dispensing of benzodiazepines (11% decrease) and atypical antipsychotics (4% decrease). Concurrently, we observed a substantial growth in the dispensing of both sedative (15% increase) and non-sedative (9% increase) antidepressants. The proportion of patients dispensed two or more psychotropic drug classes increased from 42% in 2004 to 50% in 2013.* **Conclusions:** *Utilization patterns of*

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psychotropic drugs in institutionalized patients with dementia have changed over the past decade. Although their use declined slightly over the study period, atypical antipsychotics continue to be used at a high rate. A decline in the use of benzodiazepines along with an increased use of sedative and non-sedative antidepressants suggests that the latter class of drugs is being substituted for the former in the management of neuropsychiatric symptoms. Psychotropic polypharmacy continues to be highly prevalent in these patient samples. (Am J Geriatr Psychiatry 2015; 23:1259–1269)

Key Words: Dispensing, antipsychotics, psychotropics, dementia, long-term care

Two out of three elderly long-term care residents suffer from dementia[1,2]; of these patients, approximately 80%[3] present with neuropsychiatric symptoms (NPS) such as anxiety, depression, agitation, psychological distress, psychosis, and/or insomnia.[4] Psychotropic medications are often used to manage such symptoms.[5]

In the past decade, numerous drug regulatory agencies and clinical guidelines have cautioned against the use of antipsychotics, either conventional or atypical, to manage NPS; these warnings are based on findings of increased risks with these medications of cerebrovascular events and death.[6–12] Nonetheless, they continue to be prescribed and dispensed with varying rates around the world (from 7% to 40%).[13–19] The Canadian dementia guidelines have identified other classes of psychotropics that may be considered instead for the management of NPS; these include antidepressants (sedative and non-sedative), benzodiazepines, anti-epileptics and cognitive enhancers.[10] These guidelines, however, as well as those from other countries, highlight the variable evidence base for the use of these agents.[5,20] It may be that each class of psychotropic is being differentially used to target specific NPS. Though not recommended, physicians may prescribe a combination of more than one psychotropic drug class in an attempt to manage the NPS, although the evidence base for this practice is even more limited.[21,22]

Although the dispensing rates of psychotropics in patients with dementia are well documented in the community setting,[23,24] there are limited reports of their use in the long-term care setting. When compared with dementia patients in the community setting, long-term care patients are older, more frail, and at increased risk of the adverse effects of psychotropic medications; these include potentially dangerous drug interactions between co-dispensed psychotropic medications.

Physicians have become increasingly aware of the risks associated with the use of antipsychotics in the elderly and may be shifting their prescribing to other psychotropics, as single agents or in combination, to manage the NPS in older patients with dementia in long-term care facilities. We assessed the dispensing rate of antipsychotics and other classes of psychotropics in older adults with dementia living in long-term care facilities from 2004 to 2013.

METHODS

This study was approved by the Sunnybrook Health Sciences Centre research ethics board in Toronto, Ontario.

Study Design and Setting

We conducted a cross-sectional time-series analysis in Ontario, Canada. Ontario is the most populous province of Canada; at the beginning of 2004 approximately 1.3 million Ontarians were 65 years of age or older. By the end of 2017 this population is expected to grow to over 1.6 million.[25]

Data Source and Study Outcomes

We used data from a number of linked healthcare databases housed at the Institute of Clinical Evaluative Sciences, Ontario, Canada. These databases included the Registered Persons Database, which contains demographic information on all Ontario residents; the Ontario Health Insurance Plan

database, which contains information on physician billing claims for inpatient procedures and outpatient physician visits; the Canadian Institutes of Health Information—Discharge Abstract Database, which contains information about hospitalizations; and the Ontario Drug Benefits (ODB) database, which contains information on all medications dispensed for those aged 65 years or older, and identifies whether a patient resides in a long-term care facility. The ODB database has been found to have an error rate of less than 1%.[26]

Cohort Formation

For the purpose of this study, we divided each calendar year into four quarters (three-month periods; quarter 1 [Q1]: January to March, Q2: April to June, Q3: July to September, Q4: October to December). Data collection occurred from January 1, 2004, through March 31, 2013, generating a total of 37 quarters. For each quarter, the study sample comprised all residents of Ontario aged 66 years and above living in a long-term care home with a diagnosis of dementia. Patients were identified as having dementia if in the 5 years prior to the start of the interval they had a hospitalization involving a diagnosis of dementia (International Classification of Diseases, Tenth Revision [ICD-10] codes: F00, F01, F02, F03, F05.1, F06.5, F06.6, F06.8, F06.9, G30, G31, R54) or a physician-documented outpatient diagnosis for dementia (ICD-9 codes: 290, 331, 797). We selected a combination of both inpatient and outpatient codes to maximize the sensitivity of diagnoses; these codes have been used in previous large-scale database studies.[27–29] To determine long-term care residency status, we reviewed data from the most recently filled prescription in the one year prior to the start of each quarter. We did not include patients in their first year of prescription-drug coverage (65 years of age) to allow for a one-year look-back. Figure 1 outlines additional exclusion criteria and an example of how each cohort was developed.

Cohort Characteristics

Three quarters were selected a priori to examine patient characteristics at the beginning (January to March, 2004), middle (January to March, 2009) and end (January to March 2013) of the study period. In addition to demographic characteristics, we used hospitalization records from the five years prior to the start of each quarter to characterize their dementia diagnosis and generate a Charlson comorbidity index[30] validated for administrative claims databases[31] (list of comorbidities presented in Table 1).

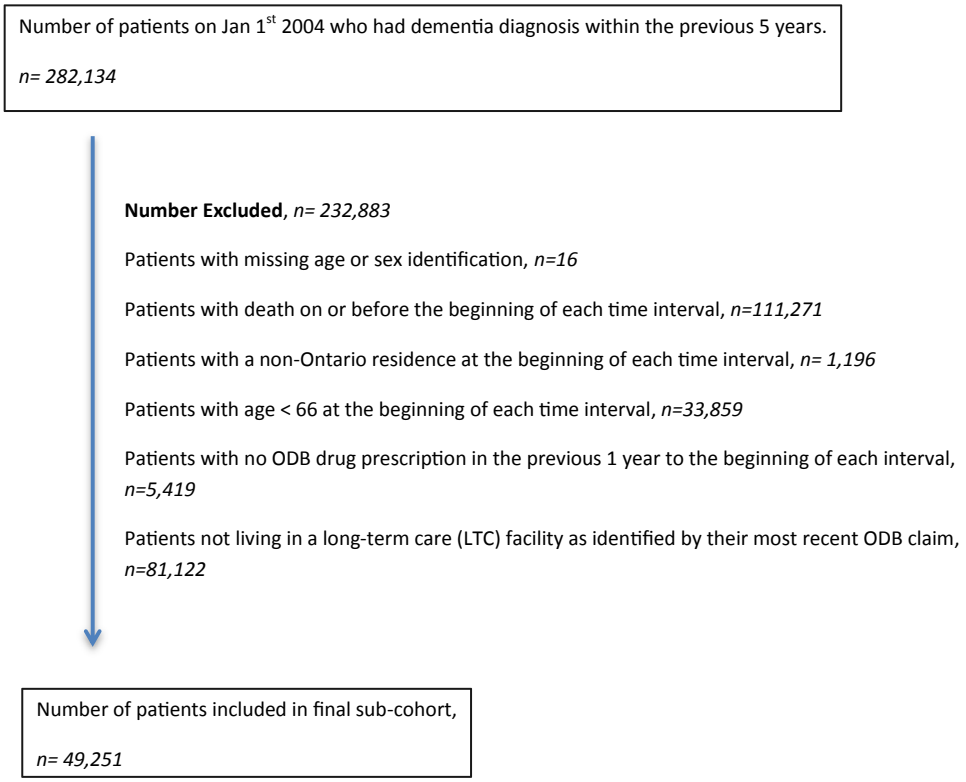
Prescription-Level Monitoring

For every quarter, we identified all prescriptions for the following psychotropic drug classes: atypical and conventional antipsychotics, non-sedative and sedative antidepressants, anti-epileptics, and benzodiazepines (specific drugs are listed in Appendix 1). We selected these medications as they are frequently dispensed for the management of the NPS of dementia. The rate of dispensing of each drug class was calculated quarterly by summing the number of patients dispensed a prescription for that drug class divided by the total number of patients in that quarter. Similarly, the rate of dispensing combination psychotropics was assessed by counting the number of patients who were dispensed with two or more unique psychotropic drug classes in the quarter being studied divided by the total number of patients in that quarter. Medications that did not have universal provincial coverage throughout the study period, or where the total count of prescriptions for the sample was less than 5, were excluded.

Statistical Analysis

To assess trends in the use of psychotropics, data was analyzed through time-series analysis[32] using exponential smoothing models. Time-series analyses are well-established methods that use a collection of techniques for modeling autocorrelations in temporally sequenced data.[32] Schwarz-Bayesian criteria were used to assess the best model fit. The level, trend, damping, and seasonality smoothing weights were determined to optimize the fit of the model. The statistical significance of the smoothing weights was tested using t tests. Stationarity was determined with the use of the autocorrelation function and the augmented Dickey-Fuller test.[33] The autocorrelation, partial autocorrelation, and inverse autocorrelation functions were further calculated for model parameter appropriateness and seasonality. The presence of white noise was assessed by examining the autocorrelations at various lag points using the Ljung-Box χ^2 statistic.[34] Additionally, on a post hoc basis, we

FIGURE 1. Illustration of development of one sub-cohort, Quarter 1 2004.



used exponential smoothing models to forecast the prescription rate of select psychotropic classes that exhibited impactful changes in dispensing during the 10-year study period (2004 to 2013); rates were forecasted to 2017. For assessment of differences in baseline characteristics across the selected time points, we conducted the χ^2 test to examine the changes in proportion of categorical variables and Kruskal-Wallis test to examine the changes in medians of continuous variables. SAS software package for Windows, Version 9.3 (SAS Institute, Inc., Cary, NC,) was used for all statistical analyses.

RESULTS

Dementia Patients in Ontario Long-Term Care Homes

The number of patients included in the study increased by 21% from 49,251 in Q1 2004 to 59,785 in Q1 2013. The proportion of women reduced from 74% in Q1 2004 (36,204 of 49,251) to 71% (42,739 of 59,785, $\chi^2 = 55.74$, df = 2, $p < 0.001$). The median age increased from 85 years to 86 years (Kruskal-Wallis Test, $\chi^2 = 556.24$, df = 2, $p < 0.0001$) over the study period. Alzheimer dementia was the most commonly diagnosed form of dementia, (98%: 47,903 of 49,251 in Q1 2004 and 58,237 of 59,785 in Q1 2013, $\chi^2 = 13.33$, df = 2, $p = 0.0013$). The baseline characteristics of these patients did not appear to change considerably over time (Table 1).

Dispensing Changes

The proportion of patients dispensed each psychotropic drug class from January 1, 2004, to March 31, 2013, is presented in Figure 2. Further statistical details of all model results presented herein are available in Table 2. Among the classes of psychotropics included in the analyses, the proportion of patients on anti-epileptics (2 percentage point

TABLE 1. Clinical and Demographic Characteristics of the Study Sample

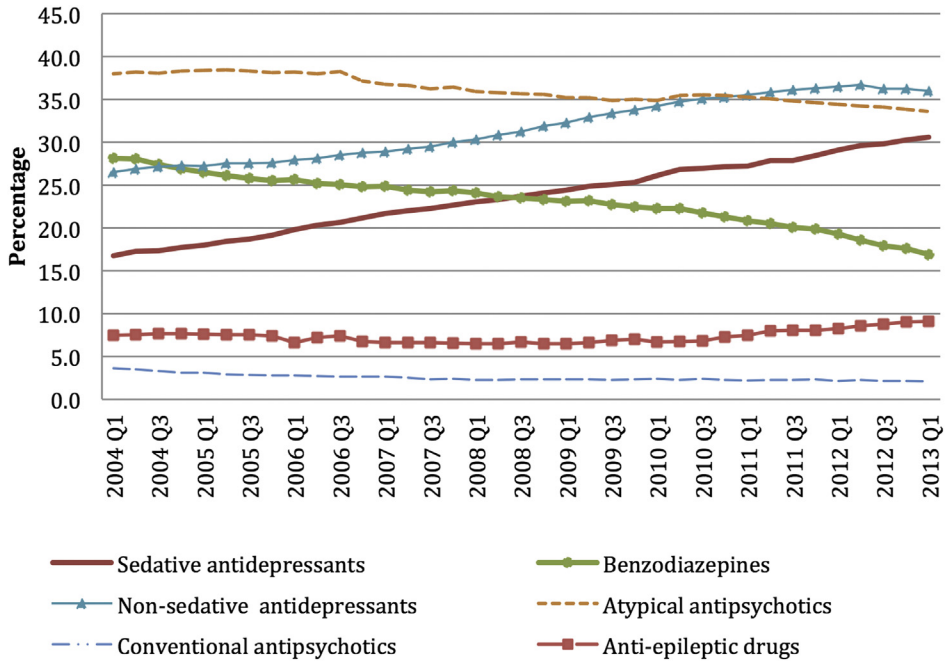
	January 1, 2004		January 1, 2009		January 1, 2013	
	Total N = 49,251	%	Total N = 56,723	%	Total N = 59,785	%
Demographics						
Age (years)						
Mean (SD)	84.41 (7.35)		84.92 (7.24)		85.36 (7.39)	
Median (IQR)	85 (80–90)		85 (80–90)		86 (81–91)	
66–75.9	6,127	12.44	6,154	10.85	6,463	10.81
76–85.9	20,433	41.49	22,525	39.71	21,456	35.89
86–95.9	19,850	40.30	24,567	43.31	27,751	46.42
96+	2,841	5.77	3,477	6.13	4,115	6.88
Sex – Female, N	36,204	73.51	41,157	72.56	42,739	71.49
Diagnosis of type of dementia, N						
Alzheimer dementia	47,903	97.26	55,350	97.58	58,327	97.56
Vascular dementia	1,621	3.29	1,454	2.56	1,366	2.28
Other dementias	8,020	16.28	4,151	7.32	3,890	6.51
Unspecified dementias	5,627	11.43	11,829	20.85	14,580	24.39
Organic brain syndrome	305	0.62	257	0.45	154	0.26
Delirium superimposed on dementia	1,435	2.91	1,949	3.44	3,201	5.35
Comorbidities (Charlson Comorbidity Index Categorizations), N						
AMI	3,003	6.10	2,831	4.99	2,776	4.64
CHF	5,326	10.81	5,061	8.92	5,151	8.62
PVD	1,750	3.55	1,479	2.61	1,406	2.35
CVD	5,506	11.18	4,402	7.76	3,996	6.68
COPD / Other respiratory disease	4,780	9.71	3,963	6.99	4,119	6.89
Rheumatologic disease	668	1.36	491	0.87	528	0.88
Digestive ulcer	682	1.38	641	1.13	693	1.16
Mild liver disease	366	0.74	242	0.43	272	0.45
Diabetes	5,459	11.08	3,994	7.04	3,777	6.32
Diabetes with chronic complications	1,018	2.07	5,406	9.53	8,061	13.48
Hemi or paraplegia	2,106	4.28	1,775	3.13	1,680	2.81
Renal disease	2,069	4.20	3,348	5.90	3,273	5.47
Primary cancer	991	2.01	1,278	2.25	1,406	2.35
Moderate / Severe liver disease	83	0.17	111	0.20	119	0.20
Metastatic cancer	334	0.68	337	0.59	407	0.68
HIV infection	≤5	<0.01	≤5	<0.01	≤5	<0.01
Charlson Index (Weighted Sum)						
Mean (SD)	1.69 (1.09)		1.62 (1.02)		1.61 (0.99)	
Median (IQR)	1 (1–2)		1 (1–2)		1 (1–2)	
1	30,074	61.06	35,940	63.36	37,018	61.92
2	10,188	20.69	11,756	20.73	13,369	22.36
3	5,124	10.40	5,421	9.56	5,721	9.57
4+	3,865	7.85	3,606	6.36	3,677	6.15

Notes: AMI: acute myocardial infarction; CHF: congestive heart failure; CVD: cerebrovascular disease; COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus; IQR: interquartile range; PVD: peripheral vascular disease; SD: standard deviation.

increase: 3,669 of 49,251 = 7% in Q1 2004 and 5,450 of 59,785 = 9% in Q1 2013) and conventional antipsychotics (1 percentage point decrease: 1,784 of 49,251 = 3% in Q1 2004 and 1,247 of 59,785 = 2% in Q1 2013) demonstrated modest changes over the study period. We found a larger reduction in the proportion of the patients dispensed benzodiazepines (11 percentage point decrease: 13,835 of 49,251 = 28% in Q1 2004 to 10,103 of 59,785 = 17% in Q1 2013) and atypical antipsychotics (4 percentage point decrease: 18,700 of 49,251 = 38% in Q1 2004 to 20,082 of 59,785 = 34% in Q1 2013). There was a concurrent large change in proportion of patients dispensed a sedative antidepressant (15 percentage point increase: 8,245 of 49,251 = 16% in Q1 2004 and 18,277 of 59,785 = 31% in Q1 2013), as well as non-sedative antidepressants (9 percentage point increase: 13,053 of 49,251 = 27% in Q1 2004 and 21,512 of 59,785 = 36% in Q1 2013).

Overall, the proportion of patients dispensed any psychotropic drug increased from 75% in Q1 2004 (36,825 of 49,251) to 79% in Q1 2013 (47,330 of

FIGURE 2. Proportion of patients (percentage) dispensed six classes of psychotropics from January 1, 2004 to March 31, 2013 among patients with dementia in long-term care facilities in Ontario, Canada.



59,785). Over the same period, the proportion of study patients on two or more different classes of psychotropics increased from 42% (21,019 of 49,251) to 50% (29,928 of 59,785) (Fig. 3).

Projection of Dispensing Proportions

Based on the three psychotropic classes that exhibited the largest changes during the past decade (2004–2013), over the next four years (2014–2017) the following projections were made: The proportion of patients dispensed atypical antipsychotics may decrease from 34% to 31% and benzodiazepine use may decrease from 17% to 8% of patients while the proportion dispensed sedative antidepressant is expected to continue increasing from 32% to 36% of patients (Fig. 4).

DISCUSSION

This study provides an analysis of trends over time (2004–2013) in the dispensing of six classes of psychotropics for the treatment of NPS among frail, older patients with dementia residing in long-term care facilities in Ontario, Canada. Over the past decade the overall psychotropic use has remained stable, with nearly three-quarters of all patients dispensed at least one medication. We observed a marginal but statistically significant decline in the proportion of patients dispensed antipsychotics (atypical and conventional) and anti-epileptics, and a more dramatic decline in proportion of patients on benzodiazepines was observed. Conversely, use of sedative and non-sedative antidepressants increased markedly. We also observed an overall increase in psychotropic combination therapy.

Interpretation

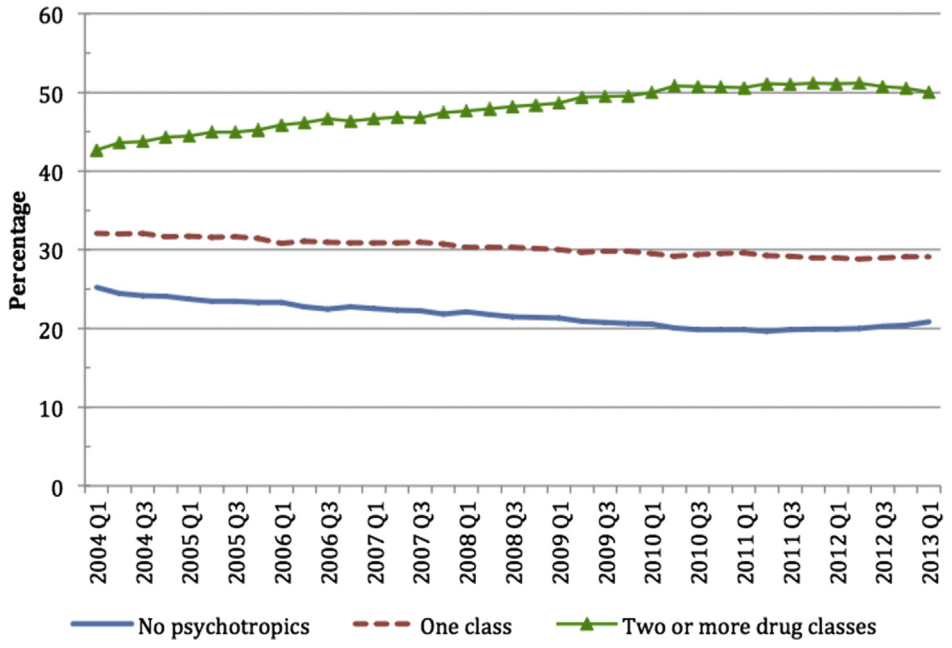
Among other findings, we saw a relatively high and steady usage of antipsychotics contrasting with a declining use of benzodiazepines; this pattern has been shown in previous studies. Those studies, however, did not examine psychotropic drug use in patients living in long-term care homes.[6,19,35,36] The ongoing and projected high dispensing of atypical antipsychotics is of concern in the context of multiple warnings around cerebrovascular events and death associated with these

TABLE 2. Statistical Details of Best-Fitting Smoothing Models

Drug Class	Best Fitting Model	t Test Statistic	Degrees of Freedom	Mean Square Error	R^2 Value	Schwarz Bayesian Information Criterion (BIC)	p Value
Sedative antidepressants	Winter Additive	7.9802	34	0.03259	0.998	−115.84848	<0.001
Cognitive enhancers	Winter Additive	9.1833	34	0.02068	0.999	−132.67327	<0.001
Non-sedative antidepressants	Linear (Holt) Exponential Smoothing	5.4507	35	0.02886	0.998	−123.95571	<0.001
Benzodiazepines	Linear (Holt) Exponential Smoothing	6.3588	35	0.04548	0.995	−107.12739	<0.001
Atypical antipsychotics	Log Double (Brown) Exponential Smoothing	10.3349	35	0.07874	0.966	−90.42799	<0.001
Conventional antipsychotics	Log Linear (Holt) Exponential Smoothing	5.6427	35	0.0054253	0.964	−185.79540	<0.001
Anti-epileptic drugs	Log Double (Brown) Exponential Smoothing	8.2677	35	0.06551	0.881	−97.23334	<0.001
Any one class of psychotropic	Winter Additive	4.3938	34	0.03247	0.987	−115.98170	0.001
Two or more different classes of psychotropics	Winter Additive	7.0046	34	0.07041	0.989	−87.34621	<0.001

Note: p values test the null hypothesis that the level (intercept) smoothing weight equals 0.

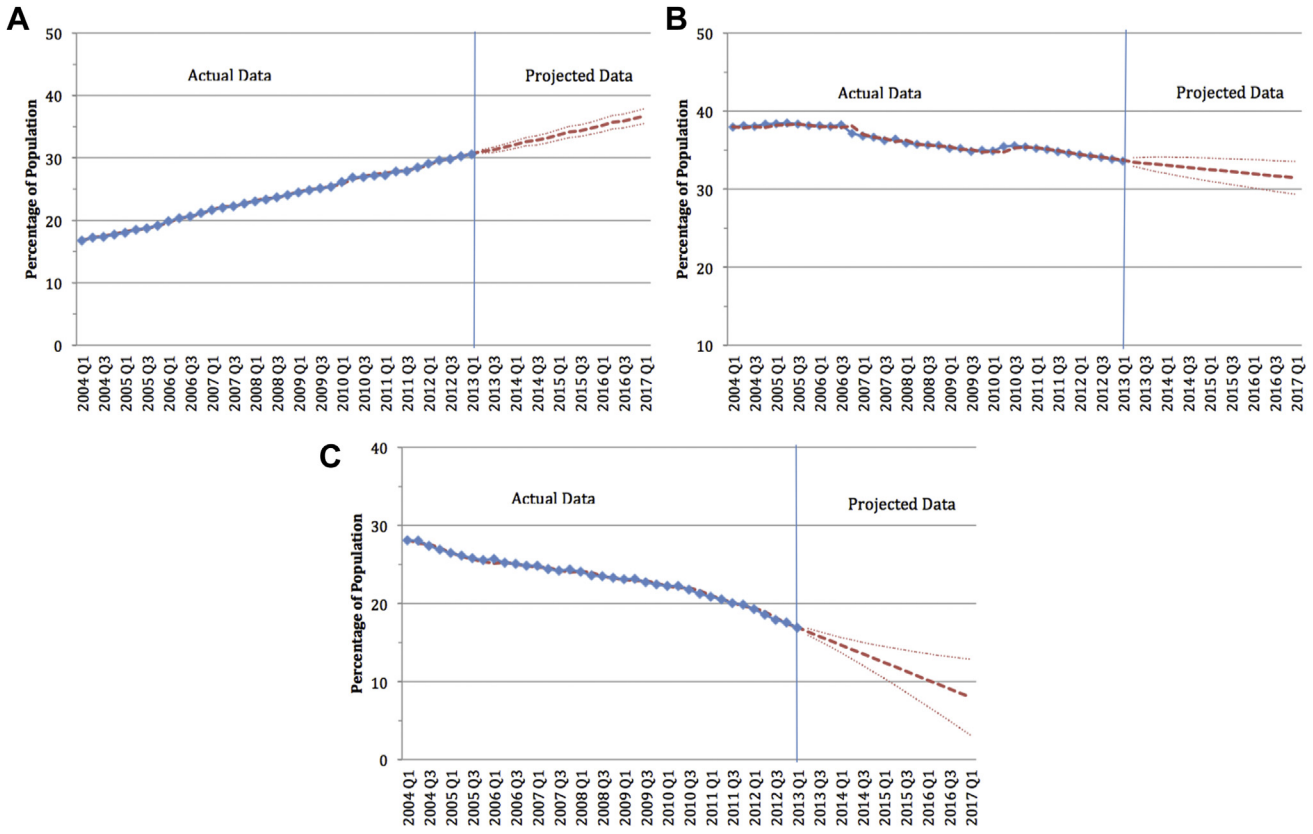
FIGURE 3. Proportion of patients on one or more classes of psychotropics among patients with dementia living in long-term care facilities in Ontario, Canada, from 2004 to 2013.



agents.[6–12] On the other hand, the declining use of benzodiazepines is reassuring, as this would have likely resulted in fewer incidents of falls, fractures, and subsequent hospital admissions over the past decade.[37]

This study highlights an increased use of non-sedative antidepressants. This trend needs to be viewed in the context of the Canadian Consensus Conference on the Diagnosis and Treatment of

FIGURE 4. Actual and projected use of [A] sedative antidepressants, [B] atypical antipsychotics, and [C] benzodiazepines among patients with dementia living in long-term care facilities in Ontario, Canada. from 2004 to 2013.



Notes: The number of actual prescriptions from Q1 2004 to Q1 2013 are depicted by solid blue squares; the predicted prescriptions are depicted by dotted red lines; 95% confidence intervals around the projected prescriptions beyond Q1 2013 are presented as red dashed lines/error bars. The vertical blue line denotes the beginning of the period of projected data.

Dementia (CCCDTD),[12] which acknowledges that the use of antidepressants for managing affective disturbances associated with dementia are an option, but not a firm recommendation. These recommendations were partly based on a recent non−industry-sponsored large sample study, which failed to find any difference in the effects of sertraline, mirtazapine, or placebo in a randomized controlled setting.[38] Nevertheless, a more recent study focusing on the management of agitation in the context of dementia found some benefits with citalopram, a non-sedative antidepressant,[39] although there were adverse effects on cognition and the cardiovascular system.

We also found that long-term care residents with dementia are increasingly being dispensed sedative antidepressants, which include medications such as trazodone, mirtazapine, and tricyclic antidepressants. We suspect that the increased use of sedative antidepressants is for the promotion of sedation, the treatment of comorbid depression, or to manage the agitation or aggression associated with dementia. Because of the large sample-based nature of this study we are unable to confirm any of the above reasons for this usage. Although not specifically tested, however, the converse increase in antidepressant dispensing with declines in benzodiazepine dispensing suggests that prescribers may be substituting benzodiazepines with antidepressants in an attempt to manage NPS. The ongoing and projected increase in the usage of sedative antidepressants is of possible concern as the safety and effectiveness of these agents is based only on small-scale studies.[40−42] For instance, the administration

of mirtazapine for the treatment of depressive symptoms in outpatients with dementia led to reports of excessive drowsiness and sedation in 44% of patients.[24] Such symptoms could increase the risk of falls, injuries, fractures, and mortality. Therefore, the use of sedative antidepressants for the NPS of dementia needs to be further investigated.

One of the other recommendations of the CCCDTD was to reduce reliance on the usage of anti-epileptics, particularly valproate, as it has been associated with significant toxicity, accelerated brain volume loss, greater cognitive impairment, and a similar risk of mortality as that previously found with antipsychotics.[10] The ongoing use of such agents is therefore of some concern.

We also examined the extent of the dispensing of combination psychotropic medications; such usage may further increase the risk of cognitive impairment, orthostatic hypotension, falls, and skeletal fractures.[43] In order to compare psychotropic prescription rates we divided the patients into two groups: those on one, and those on two or more classes of agents. We did not attempt to categorize whether certain psychotropic combination prescriptions were pharmacologically appropriate or not, as there is an inadequate evidence base for taking this approach.[44] We do, however, recognize that physicians caring for patients with dementia in long-term care settings are often faced with the dilemma of balancing the use of psychotropic combination therapy with its associated risks. These physicians must also take into account the need to reduce the anxiety in staff and other residents caused by patients' calling out, agitation, hallucinations, and other NPS associated with dementia.[45] Fortunately, it is possible to reduce potentially inappropriate combination therapy through concerted multidisciplinary and frequent medication reviews.[46]

In light of the limitations posed by pharmacological treatments, nonpharmacological interventions using music or environmental manipulation may provide alternatives for the management of NPS. There is some evidence that such interventions can be of benefit if tailored to the individual patient, and if healthcare providers are given adequate support to offer such treatments.[47] High-quality large-scale studies for assessing the efficacy of such therapies have yet to be performed.[48]

Study Limitations

There are several limitations to the present study. First, this study was retrospective in nature and hence suffers from inherent biases associated with such a design. Second, healthcare databases do not code dementias using the more stringent standardized diagnostic criteria for characterizing the type or severity of dementia as suggested by the National Institute on Aging/Alzheimer's Association Diagnostic Guidelines for Alzheimer's Disease; such diagnoses are typically used for characterizing patients in prospective randomized controlled trials. Our approach of using either an outpatient, or an inpatient physician coding, however, would offer increased sensitivity, without compromising on specificity of diagnosis.[27–29] Third, we were unable to accurately capture the dispensing of cognitive enhancers as they were not universally covered under the drug compensation plan in Ontario (ODB) during the study period. Fourth, we did not characterize the usage of individual psychotropic within each drug class, as this would have led to an inordinately large amount of data, making it difficult to interpret the results. Fifth, additional clinical information is required to better characterize patients; this better understanding of a patient's needs will help to identify appropriate drug use, and to develop a structured approach for dealing with polymedicated patients. Finally, the extrapolated prediction-model–projected psychotropic usages are based on assumptions inherent to the model used, and as such do not account for outside variables that may influence future trends such as changes in formulary coverage, introduction of new medications, or changes in practice guidelines.

Conclusions and Implications

This study outlines current trends in the dispensing of various classes of psychotropics for the treatment of NPS in patients with dementia residing in long-term care facilities in Ontario, Canada. The results suggest a high prevalence of sedative antidepressant usage with a concomitant decline in the usage of antipsychotics and benzodiazepines, suggesting that the former have supplanted the latter in their role as sedative agents. The increase in psychotropic polypharmacy suggests an ongoing

reliance on psychotropic usage in the management of patients with dementia in long-term care where provisions of nonpharmacological therapies are likely inadequate. In the absence of firm evidence from large-scale randomized controlled trials regarding the efficacy and safety of various psychotropics (including sedative antidepressants) for the treatment of NPS in the context of frail elderly with dementia in long-term care, this report represents an important contribution to research on a major public health concern.

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