Incidence of Delirium in Older Adults Newly Prescribed Lithium or Valproate: A Population-Based Cohort Study

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Background: The use of lithium carbonate for the treatment of mood disorders in old age has decreased at a dramatic rate in favor of valproate. Because of lithium's narrow therapeutic range, neurotoxicity can be an important complication in lithium therapy and potentially influence prescription patterns. Therefore, we compared the incidence of delirium in older adults with mood disorders who were newly dispensed either lithium or valproate.

Method: Using 4 population-based administrative databases from the province of Ontario, Canada (the Ontario Drug Benefit program, the Canadian Institute for Health Information, the Ontario Health Insurance Plan, and the Registered Persons Data Base), we were able to identify a cohort of mood disorder patients 66 years and older who were newly dispensed lithium or valproate over an 8-year period (1993–2001). Measures were taken to ensure that the sample was composed of mood disorder patients. As a comparator, we included a known deliriogenic drug, benztropine. The main outcome measure was a new diagnosis of delirium on a hospitalization record during 1 year of follow-up.

Results: Our study cohort consisted of 2422 new users of lithium and 2918 new users of valproate over an 8-year period. There was no statistically significant difference in the incidence of delirium between lithium (2.8 per 100 person-years) and valproate (4.1 per 100 person-years). Compared with patients who received lithium, patients who received benztropine had a significantly higher risk of delirium ($p < .001$).

Conclusion: The incidence of hospitalizations with delirium was similar in patients treated with lithium and valproate. These findings add to the evidence suggesting that the shift away from the use of lithium carbonate to manage mood disorders in older adults is not justified on the basis of concerns of neurotoxicity.

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There has been a dramatic change in prescription patterns for new use of lithium and valproate in old age.[1,2] The new use of lithium carbonate has decreased in favor of valproate for the management of mood disorders in the elderly despite a lack of data to support this shift in clinical practice. In Ontario, Canada, the number of new lithium users per year fell from 653 older adults in 1993 to 281 in 2001, whereas the number of new valproate users rose from 183 in 1993 to 1090 in 2001.[1] Yet, a recent study showed that the effectiveness of lithium in preventing suicide attempts and death by suicide was greater than that of valproate.[2]

Since the adverse event profile of a drug may influence prescribing habits, this study addresses a common concern in old age, namely the potential for neurotoxicity associated with lithium therapy, which has a narrow therapeutic range.[3] One clear manifestation of neurotoxicity in old age is delirium, a common multidetermined syndrome in older patients.[4] This study used administrative health databases from Ontario, Canada, to examine the incidence of hospitalizations with delirium, an issue relevant to the safety and effectiveness of valproate compared with lithium. In light of the lack of clinical data, we adopted the null hypothesis that there would not be a significant difference in the incidence of delirium between lithium and valproate. We hope that these findings will help to inform the use of mood stabilizers in older adults.

METHOD

Study Design

We conducted a population-based observational cohort study using administrative databases that contain information on over 1.3 million older adults in Ontario who receive universal health care coverage in terms of physician services, drugs, and hospitalizations.

Sources of Data

We used 4 administrative databases linked by an encrypted and electronically verified health card number.

***Ontario Drug Benefit (ODB) program*.** The ODB program provides drug benefits for all adults 65 years and older in Ontario. Information in the database includes drug identification number, dispensing date, quantity of pills dispensed, number of days supplied, and encrypted patient identifiers. We used this data set to identify our cohorts and to obtain drug-based diagnostic information and comorbidity history.

***Canadian Institute for Health Information (CIHI)*.** All hospitals in Ontario are required to submit demographic and clinical information about all hospital admissions and discharges (including transfers and deaths) to CIHI, which collates these data. Information in this database includes diagnoses coded using the *International Classification of Diseases*, Ninth Revision. We used this data set to obtain outcome information, as well as to obtain the patients' medical diagnoses.

***Ontario Health Insurance Plan (OHIP*).** The OHIP database contains records for all physician services billed in Ontario. We used this database to obtain additional clinical history information.

***Registered Persons Data Base*.** This database was used to obtain demographic information on the patients.

Drugs of Interest

Since the incidence of delirium is the focus of the study, in addition to lithium and valproate, we also chose to study an anticholinergic agent, as this class of drugs has been associated with an increased risk of delirium in old age.[5] Therefore, as a comparator and method of validating the methodology, we used benztropine mesylate, a potent anticholinergic medication known to precipitate delirium.[6,7] Our cohort consisted of all Ontarians 66 years and older who were newly dispensed 1 of the 3 drugs under study (i.e., lithium, valproate, or benztropine) between April 1, 1993, and March 31, 2001 (N = 27,049). We defined a new user as an older adult with no use of the specific study medication in the previous year. We restricted our study to patients 66 years or older to enable us to examine their drug use for the prior year, since we have information on drug use for all Ontarians 65 years or older.

We used 2 methods to ensure that we were studying the specific effect of the study drugs on the incidence of delirium in patients who were prescribed this therapy for the management of a mood disorder. Because valproate can also be prescribed for the management of epilepsy or behavioral disturbances associated with dementia, we first restricted our cohort by excluding anyone with a past diagnosis of dementia (N = 10,012) or epilepsy (N = 2824) as identified by the diagnostic information from the OHIP and CIHI databases in the 5 years prior to index date. We further restricted our cohort to exclude anyone with a past history of a condition that might predispose to delirium, thus excluding those with a prior history of delirium (N = 2024), brain tumor (N = 190), or schizophrenia (N = 1758) and 11 patients with inconsistent data. Second, as a further step to ensure that drug cohorts were composed of patients with mood disorders and therefore comparable, we identified those patients who met all of the previously identified criteria who also had a documented diagnosis of mood disorder occurring in the 5 years prior to the index date in either the CIHI or OHIP database. The relevant codes included any CIHI code 2962 or 2963 (depression), any CIHI code 2964–2967 (bipolar disorder), any CIHI code 2957 (schizoaffective disorder), OHIP code 296 (manic-depressive psychosis–involutional melancholia), and OHIP code 311 (depressive or other nonpsychotic disorders).

Because hearing and visual impairment are also risk factors for delirium,[4] we determined the prevalence of these conditions within each drug cohort. We also controlled for comorbidity, defined as the number of different drugs that the patient was taking in the year prior to index.[8] The index date was the date of first treatment for the drug of interest, and patients were followed for a minimum of 1 year. The outcome of interest was the appearance of a new diagnosis of delirium on a hospitalization record during 1-year follow-up. A patient was censored if a record with delirium also contained evidence of a brain tumor, if the patient died, or if the patient discontinued the drug (i.e., no claim for 120 days).

Analysis

Standard descriptive statistics for each cohort were produced and Kaplan-Meier curves were constructed. The outcome was analyzed using the Cox proportional hazards model, controlling for age, sex, comorbidity, visual impairment, and hearing impairment. We used the lithium cohort as a reference group, producing hazard ratios with confidence intervals for the other 2 cohorts. We also performed a sensitivity analysis, applying the same Cox regression model to the 4062 patients with no history of dementia or epilepsy and a documented diagnosis of mood disorder.

RESULTS

Our study cohort consisted of 2442 new users of lithium, 2918 new users of valproate, and 4870 new users of

Table 1. Characteristics of Older Adults (aged 66+ years) Without Epilepsy, Dementia, or Schizophrenia Newly Dispensed Lithium, Valproate, or Benztropine, April 1993 to March 2001

Characteristic	Total (N = 10,230)	Lithium (N = 2442)	Valproate (N = 2918)	Benztropine (N = 4870)
Age at index, y				
Mean ± SD	74.66 ± 6.82	72.79 ± 5.70	73.81 ± 6.18	76.10 ± 7.36
N (%)				
66–69	2840 (27.8)	853 (34.9)	883 (30.3)	1104 (22.7)
70–74	2932 (28.7)	816 (33.4)	883 (30.3)	1233 (25.3)
75–79	2047 (20.0)	446 (18.3)	613 (21.0)	988 (20.3)
80–84	1370 (13.4)	216 (8.8)	338 (11.6)	816 (16.8)
85+	1041 (10.2)	111 (4.5)	201 (6.9)	729 (15.0)
Sex, N (%)				
Female	6255 (61.1)	1484 (60.8)	1774 (60.8)	2997 (61.5)
Male	3975 (38.9)	958 (39.2)	1144 (39.2)	1873 (38.5)
Comorbidity (no. of drugs taken in year prior to index), mean ± SD	13.66 ± 8.04	12.85 ± 7.37	14.29 ± 8.06	13.68 ± 8.32
Hearing impairment, N (%)	1084 (10.6)	307 (12.6)	337 (11.5)	440 (9.0)
Visual impairment, N (%)	166 (1.6)	27 (1.1)	49 (1.7)	90 (1.8)

Table 2. Cox Proportional Hazards Models Comparing Lithium, Valproate, and Benztropine on Time to Delirium in All Older Adults (N = 10,230) and in Those With a Documented History of Mood Disorder (N = 4062)

	Crude Results					Cox Regression Results		
Drug	N	Mean Completed Follow-Up (mo)	Total Person-Years	No. of Patients With Delirium	Rate of Delirium per 100 Person-Years	Hazard Ratio	95% CI	p Value
All older adults								
Lithium	2442	8.2	1671	46	2.8	1.00	…	…
Valproate	2918	7.5	1811	75	4.1	1.36	0.94 to 1.97	.1
Benztropine	4870	6.5	2631	161	6.1	1.88	1.35 to 2.62	< .001
Older adults with documented mood disorder history								
Lithium	1509	8.5	1070	37	3.5	1.00	…	…
Valproate	1328	8.3	915	35	3.8	1.07	0.67 to 1.70	.8
Benztropine	1225	6.6	668	56	8.4	2.12	1.39 to 3.22	< .001

benztropine from April 1993 to March 2001 (Table 1). The groups were similar in age (mean ages of 73, 74, and 76 years for lithium, valproate, and benztropine, respectively), although the benztropine group had a higher proportion of people aged 85+ years (15%) relative to the valproate (7%) and lithium (5%) groups. The groups had similar distributions of sex (61%, 61%, and 62% women, respectively) and similar rates of factors known to predispose to delirium—visual impairment (1%, 2%, 2%) and hearing impairment (13%, 12%, 9%). Coding practices within administrative databases may underestimate rates of such sensory impairments, but such undercoding would be balanced across the different cohorts in this study. With the use of a drug comorbidity index, patients in the lithium group were dispensed a mean of 13 drugs in the previous year, while patients in the valproate and benztropine groups were dispensed a mean of 14 drugs.

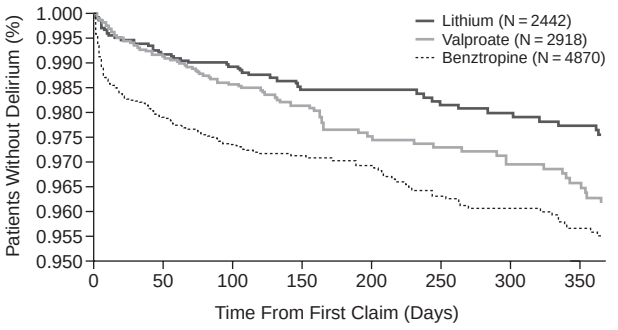
The mean follow-up times for the 3 groups were comparable: 8.2 months for lithium, 7.5 months for valproate, and 6.5 months for benztropine. The rate of delirium per 100 person-years was 2.8 for lithium, 4.1 for valproate, and 6.1 for benztropine.

The results of the Cox proportional hazards model are presented in Table 2. We found no difference in delirium risk between lithium and valproate (valproate hazard ratio = 1.36, 95% CI = 0.94 to 1.97). Compared with those taking lithium, people taking benztropine had a significantly higher risk of delirium (hazard ratio = 1.88, CI = 1.35 to 2.62, $p < .001$). The Kaplan-Meier survival curves (Figure 1) illustrate these results. Despite some differences in age distribution noted above, the differences in delirium frequencies by drug were consistent across all age groups. In particular, among patients aged 85+ years, the rates of delirium per 100 person-years among lithium, valproate, and benztropine patients were 4.2, 5.4, and 8.2, respectively. In addition to the results for all patients, Table 2 also shows the virtually identical results found when we analyzed the data using only 4062 patients with no history of dementia or epilepsy and a documented diagnosis of mood disorder in the previous 5 years.

DISCUSSION

Lithium carbonate and valproate both produced a small but clinically significant rate of delirium within the first year of use in a cohort of older adults with probable mood disorders. There was no difference found between

Figure 1. Kaplan-Meier Survival Curves for Incidence of Delirium in New Users of Lithium, Valproate, or Benztropine Among Older Adults



the incidence of delirium among older adults newly dispensed lithium therapy relative to those dispensed valproate. In fact, we found a nonsignificant trend toward a lower incidence of delirium with lithium compared with valproate, which is of particular interest in light of recent evidence highlighting lithium's potential neuroprotective properties.[9]

Our findings may underestimate the true incidence of delirium, which is underrecognized in this population.[10] One potential limitation of our study is the accuracy of coding for delirium among hospitalized older adults. However, CIHI discharge abstracts are completed by trained data abstractors; thus, we may be seeing just a "tip of the iceberg" in the rates of delirium documented here. Previous studies suggest that while delirium is underrecognized, its identification is usually accurate (i.e., it is a highly specific diagnosis).[11] Further, the higher rate of delirium seen among new users of benztropine—a potent anticholinergic drug known to be associated with this condition—lends credence to the relative rates of delirium seen among our other drug cohorts. This higher rate of delirium in benztropine-treated patients is further supported by the consistency of the results when the analysis was restricted to patients with a documented diagnosis of mood disorder in the previous 5 years. Despite assiduous attempts to eliminate patients with dementia, there may be more patients treated with valproate suffering from dementia than patients treated with lithium. Although comorbidity as measured by number of drugs was distributed equally, the large number of drugs prescribed (mean of 13–14) may have increased the overall risk of delirium.

The findings from this study provide one more piece of evidence to suggest that the shift away from lithium carbonate in favor of valproate may not be justified and requires further careful evaluation. Efficacy and effectiveness data comparing these agents in late-life mood disorders are essential. We echo Goodwin and colleagues'[2] suggestion that for the foreseeable future lithium should remain a mainstay treatment for bipolar disorders and recurrent mood disorders. The incidence of hospitalizations with delirium is not significantly different among older adults with mood disorders who are receiving either lithium or valproate. Nonetheless, there is a small but clinically significant incidence of delirium with both lithium and valproate, and careful monitoring of cognition and drug levels is necessary. Other potential side effects of lithium such as gastrointestinal upset and thyroid and renal dysfunction also need to be taken into account in its use in older adults. Moreover, evidence-based therapeutic serum levels still need to be established for lithium in older adults.

These findings from a population-based cohort study suggest that the increasing use of valproate instead of lithium may not be supported by an advantage in terms of prevention of delirium.

Drug names: benztropine (Cogentin and others), lithium (Lithobid, Eskalith, and others).

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