Medical comorbidity, acute medical care use in late-life bipolar disorder: a comparison of lithium, valproate, and other pharmacotherapies

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ABSTRACT

Objective: Bipolar disorder is associated with high rates of medical comorbidity, particularly in late life. Little is known about medical health service utilization and potential effects of bipolar pharmacotherapy. We hypothesized that lithium use would not be associated with higher rates of medical hospitalization.

Methods: Population-based retrospective cohort study of 1388 bipolar disorder patients aged ≥66 years discharged from a psychiatric hospitalization in Ontario, Canada, between 2006 and 2012. Patients were divided into lithium users, valproate users, and non-lithium/non-valproate users. The main outcome was acute non-psychiatric, medical/surgical hospitalization during 1-year follow-up.

Results: The rate of medical hospitalizations was 0.22 per patient-year. Time-to-medical hospitalization did not differ among lithium, valproate, and non-lithium/non-valproate users after adjusting for age, sex, past medical hospitalization, and antipsychotic use. Lithium, valproate, and non-lithium/non-valproate users did not differ markedly in terms of reason for medical hospitalization, 1-year acute medical health utilization outcomes, and medical comorbidity rates.

Conclusion: There were high rates of health service use for medical conditions among older adults with bipolar disorder, but this did not appear to be associated with lithium use, compared to valproate and other medication use (e.g., antipsychotics). A proactive collaborative care approach may prevent medical service utilization in severe late-life bipolar disorder.

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1. Introduction

Patients with bipolar disorder have much higher rates of physical illness burden compared to people with unipolar depression or no psychiatric disorder [1–3]. Older adults with bipolar disorder are particularly susceptible to medical comorbidity: patients have an average of 3–4 medical conditions, particularly metabolic syndrome (up to 50%), hypertension (45–69%), diabetes mellitus (18–31%), and cardiovascular disease (9–49%) [2–4]. However, there has been only one previous study that included older adults with bipolar disorder examining acute medical health utilization. Hendrie et al. found that older adults with severe mental illness have longer medical hospitalizations and more frequent emergency room visits [3].

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There is some speculation that one of the first-line therapies for bipolar disorder, lithium, may contribute to these medical comorbidities [5,6]. Lithium, despite its superior efficacy [7], has been prescribed dramatically less in favor of valproate [8] and atypical antipsychotics [9], largely due to fears of renal toxicity [10]. In addition to kidney disease, lithium has been associated with hypothyroidism, psoriasis, and hypercalcemia [5].

Alternative bipolar pharmacotherapies are also associated with medical comorbidity. Valproate has been linked to thrombocytopenia and hepatic dysfunction [5]. Atypical antipsychotics have significant effects on parkinsonism [11], weight gain, diabetes [12], and cardiac effects [13]. Valproate, atypical antipsychotics, and lithium have all been implicated in metabolic syndrome, cardiovascular illness [14], movement disorders, and delirium [15]. Moreover, compared to other bipolar pharmacotherapies, lithium may be protective against diabetes mellitus [16] and cancer [17] and may have antioxidant [18], antiinflammatory [19], and neuroprotective properties against cerebral ischemia [20] and dementia [21]. Taken together, even though clinicians remain concerned about lithium's medical effects in older adults [7,10],

it is not evident whether lithium *in particular* contributes to the increased rates of acute medical health service use in late-life bipolar disorder [3].

The effects of geriatric bipolar pharmacotherapy on acute medical health utilization have not yet been examined, even though the implications for service delivery, clinical decision-making, and health system costs are considerable. In this study of older adults with bipolar disorder, we hypothesized that, compared to non-users, lithium users will not differ significantly with regard to acute non-psychiatric, medical health service utilization.

2. Material and Methods

2.1. Design, setting, and participants

This was a population-based retrospective cohort study in Ontario, Canada. We identified all adults ≥66 years of age that had an inpatient psychiatric hospitalization for bipolar disorder between April 2006 and March 2012. Using patients' first hospitalization in that period, we then looked for the first date of an outpatient prescription claim within 30 days of that discharge. This date of the prescription claim was designated as the "index date". Patients were then followed for 1 year following the index date to assess acute medical health service utilization outcomes.

Patients were excluded from the analyses if they met the following criteria: (1) if they had concurrent lithium and valproate use ($n=55$) or (2) if they were transferred directly to an acute non-psychiatric, medical inpatient facility immediately following their index psychiatric admission.

2.2. Data sources

Data from multiple linked health care databases in Ontario, Canada, were used, where hospital care, physician services, and outpatient prescription drugs are provincially subsidized for individuals aged ≥65 years. The Ontario Mental Health Reporting System (OMHRS) is a centralized database containing extensive clinical information on inpatients admitted to psychiatric units in Ontario: psychiatric diagnosis, years of education, substance use, and other psychosocial variables [22]. Drug use data were obtained from the Ontario Drug Benefit Database (ODB) that records all outpatient prescription drugs dispensed to all residents aged ≥65 years. The Ontario Health Insurance Plan (OHIP) Database contains information from all outpatient and inpatient physician billing claims, including primary diagnoses given during health appointments. The Canadian Institute for Health Information Discharge Abstract Database contains discharge information on all acute care hospitalizations, including diagnoses and length of stay. The National Ambulatory Care Reporting System records data from all emergency department visits in Ontario. The Ontario Registered Persons Database includes information on age, sex, and date of death. These datasets were linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES).

Ethics approval was obtained from Sunnybrook Health Sciences Centre's Research Ethics Board for this study.

2.3. Main exposures

Patients were divided into three mutually exclusive groups: (1) *lithium users* (lithium prescription on the index date and no valproate use in the 30-day post-OMHRS psychiatric discharge), (2) *valproate users* (valproate prescription on index date, but not lithium in the 30-day post-discharge), and (3) *non-lithium/non-valproate users* (those who received neither lithium nor valproate in their first ODB prescription within 30-day post-discharge).

2.4. Other clinical and demographic characteristics

Additional demographic and clinical data potentially relevant to medical health utilization in late-life bipolar disorder were described. These included age, gender, currently residing in long-term care, level of education (>12 years vs. <12 years) [23], substance use, cigarette smoking, lithium/valproate doses at index date, lithium/valproate duration during 1-year follow-up, concurrent psychotropic medication use on the index date (antidepressants, antipsychotics, non-lithium/non-valproate mood stabilizers, sedatives, anxiolytics, and cholinesterase inhibitors), psychiatric hospitalization in the year prior to index psychiatric hospitalization, and length of index psychiatric hospitalization.

Using data from 5 years prior to index psychiatric hospitalization, we examined the presence of major medical conditions at baseline [14]: heart disease (congestive heart failure, coronary artery disease), diabetes mellitus, dyslipidemia (based on dyslipidemia medication prescriptions), hypertension, cancer, cerebrovascular disease, congestive–obstructive pulmonary disease (COPD), dementia, delirium, and chronic kidney disease.

2.5. Outcomes

The main outcome was acute (non-elective), non-psychiatric, medical, or surgical inpatient hospitalization in the year following the index date. The term "medical hospitalization" was used for the remainder of the manuscript for brevity.

Secondary outcomes included (1) time-to-medical hospitalization, (2) number of days hospitalized, (3) emergency room visits, and (4) number of emergency room visits for non-psychiatric and non-elective medical reasons during 1-year follow-up.

2.6. Statistical analysis

Baseline clinical characteristics, including the presence of major medical conditions, were first compared among lithium, valproate, and non-lithium/non-valproate groups using Chi-squared tests. The groups were then compared for other medical health service utilization outcomes using Chi-squared tests, Kaplan–Meier survival analyses, and Bonferroni post-hoc tests, as appropriate. We also described and compared reasons for acute medical hospitalization in 1-year follow-up between groups using Chi-squared tests. In order to comply with ICES' privacy requirements, if cell sizes <6 were encountered, information allowing the back-calculation of those actual cell sizes was omitted from this manuscript.

Cox regression survival analyses were used to examine the effects of lithium and valproate exposure on time-to-first non-psychiatric medical hospitalization, after controlling for age, male sex, non-psychiatric hospitalization in year prior to index date, and antipsychotic use [3]. Cases of death during 1-year follow-up were censored.

3. Results

A total of 1388 patients with bipolar disorder met inclusion and exclusion criteria. Two hundred and seventy-nine were lithium users, 452 were valproate users, and 657 were non-lithium/non-valproate users. Their baseline demographic and clinical characteristics are described (Table 1).

Aside from hypertension being more common in valproate users (74.6% vs. 69.3% in non-lithium/non-valproate and 57.3% in lithium users, $P<.001$), prior medical hospitalization rates and baseline medical comorbidities did not differ between groups, including chronic kidney disease, dementia, and cardiovascular risk factors.

Lithium, valproate, and non-lithium/non-valproate groups did not differ with regard to 1-year non-psychiatric, medical hospitalization rates (20.8% vs. 21.2% vs. 23.0%, $P=.68$) or unadjusted mean time-to-medical hospitalization (310.8 vs. 317.9 vs. 312.7 days, log-rank