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Psychiatric and physical outcomes of long-term use of lithium in older adults with bipolar disorder and major depressive disorder: a cross-sectional multicenter study.

Running title: Long-term use of lithium in older adults with mood disorder

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INTRODUCTION

Mood disorders are a major public health concern among older adults and constitute a leading cause of premature mortality and morbidity (1,2). In Europe, 13.7% of older people aged 65 to 84 years have presented a mood disorder episode in the past year (3). In the United States, the past-year prevalence of mood disorders is 6.7% among older adults at least 55 years of age (4). Prior work indicates that residual depressive symptomatology (5,6) and cognitive impairment (6,7) are crucial factors that impact psychosocial functioning among older adults with major depressive disorder and bipolar disorder.

Lithium is the gold-standard treatment for bipolar disorder (8,9). It is also recommended as adjunctive strategy for treatment-resistant major depressive episode and as a maintenance therapy in major depressive disorder (10). Prior research has demonstrated the effectiveness of long-term use of lithium in bipolar disorder and in treatment-resistant major depressive disorder among adults (11–20). These studies show that long-term use of lithium is effective in reducing mood disorder relapses and decreasing the risk of psychiatric and general hospitalization admissions. However, its use and efficacy in adults over 55 years old are not well known. Evidence for lithium efficacy in older patients with bipolar or depressive disorders is almost entirely extrapolated from trials conducted among younger adult patients (21,22). Furthermore, the efficacy or tolerability of lithium could differ among older patients compared to younger patients. For example, elderly individuals require lower doses of lithium to achieve similar plasma concentrations as those in younger adults because of age-related pharmacokinetic and pharmacodynamic changes, yet neurotoxicity in older adults more frequently occurs at plasma lithium levels which are considered “therapeutic” in general adult populations (23,24). Although there are no placebo-controlled randomized trials of lithium in the elderly with bipolar disorder and late-life depression to our knowledge, there is agreement that the dosage and plasma lithium concentrations need to be much reduced in the elderly

population (25). In addition, a prior study (26) found no significant association between plasma and brain lithium levels in nine adults over 50 years old, contrary to younger adults. The authors of this study hypothesized that this finding may be due to the age-related decline in the integrity of the blood-brain barrier or changes in sodium–lithium counter-transport. Taken together, these findings suggest that the use and associated risks of lithium in older adults may be substantially different than in younger adults. Despite this discrepancy, data on the efficacy and tolerability of the long-term use of lithium specifically among older adults with bipolar disorder or major depressive disorder are limited (27,28).

However, the existing literature does provide some evidence of lithium's efficacy in older populations. For example, a retrospective study showed that lithium delayed affective relapse in older adults with bipolar disorder (29) and a recent randomized controlled trial concluded that lithium was efficient and well tolerated in treating acute mania among older people (30). In a systematic review on treatments for resistant major depressive episode in older adults, lithium adjunction to antidepressant was associated with a response rate of 42% (31). In addition, lithium may have neuroprotective properties (32), which may be particularly beneficial for the older population with mood disorders. Despite these benefits and relative lack of alternative treatments (e.g. anticonvulsants or atypical antipsychotics), the use of lithium in older adults with mood disorders is decreasing at a significant rate (33,34). This change in prescription pattern may be due to significant concerns in the older population, including the risk of adverse events (35) and particularly renal failure (36).

Therefore, more research on the effects of lithium in older adults would provide a better understanding of its relative advantages and disadvantages within this patient population. To our knowledge, only one pre-post-analysis study (37) has evaluated the clinical course of long-term use of lithium among 60 middle-aged and older adults with bipolar disorder or unipolar depression conducted in one general hospital center. In that study,

a significant reduction of frequency, severity, and duration of depressive or manic relapses, rate and duration of hospitalizations and suicidal behavior was observed during lithium therapy compared to before lithium treatment. These findings provide a preliminary step to investigate the efficacy and tolerability of lithium in larger samples of older adults with mood disorders, and to compare its effects to other mood stabilizers across multiple clinical settings.

To address this gap in the literature, the present study recruited a sample of patients with major depressive disorder and bipolar disorder from multiple centers to evaluate: (i) the efficacy of long-term use of lithium on depressive symptoms severity, perceived clinical severity of the disorder, lifetime number of psychiatric admissions, past-year history of psychiatric admission, and overall cognitive functioning; and (ii) its tolerability, assessed with the past year history of medical comorbidities and general hospital admissions. To answer these questions, we used data from a multicenter cross-sectional study of older adults aged 55 years or more with an ICD-10 diagnosis of bipolar disorder (n=139) and major depressive disorder (n=142). We hypothesized that lithium use is effective and is relatively well tolerated among older adults with major depressive disorder and bipolar disorder.

METHODS

Design, Settings, and Participants

Data were drawn from the CSA study (Cohort of individuals with Schizophrenia and mood disorders Aged 55 years or more) (38–42), a cohort of individuals aged 55 years or more with an ICD-10 diagnosis of schizophrenia spectrum disorder (n=353), bipolar disorder (n=139) or major depressive disorder (n=142), recruited between February 2010 and June 2013 from French psychiatric public-sector departments covering 64 mutually independent catchment areas (43). In France, state hospitalization services are organized into sectors. Each psychiatric sector is in charge of the mental health of a mutually independent catchment area

comprising a mean population of 54,000 inhabitants aged over 20 years (44). Exclusion criteria included having limited French proficiency, being not affiliated to the social security system, meeting ICD-10 criteria for any pervasive developmental disorder or major neurocognitive disorder, and having any neurological disorder affecting the central nervous system or any serious, life threatening medical or surgical condition that requires immediate treatment. Each participant was interviewed face-to-face by his/her treating psychiatrist, who collected all clinical data.

The present analyses focused on participants with bipolar disorder (n=139) or major depressive disorder (n=142), as these disorders constitute the main indications of lithium therapy in current practice. Patients with a diagnosis of schizophrenia were excluded from our analyses. Two groups of participants were compared: (i) those currently treated by lithium and (ii) those receiving any other psychotropic medication.

The research protocol, including collection of consents, was the subject of a comprehensive ethics review by the local research ethics committee, the advisory committee on information processing in the field of health and the National Council on Information and Computerized Freedom. The study was conducted in accordance with the Helsinki Declaration. Written informed consent forms were obtained from all participants.

Measures

Lithium use

All the patients currently taking lithium were included in the lithium group. Indication of the treatment (i.e., main therapy or adjunctive therapy), the duration since which the treatment was prescribed and the dose were recorded.

Sociodemographic and clinical characteristics

Sociodemographic characteristics included sex, age, education (categorized as less than high school, high school, and college and higher), urbanicity (defined as living in an area comprising more than 1000 inhabitants per km^2) and long-term institutionalization, which was defined as living in a dwelling that offers some form of formal supervision, including nursing homes, homes for the aged, hospital stays longer than 3 months, chronic care beds, and psychiatric institutions (45).

Clinical characteristics included the diagnosis (i.e., major depressive disorder or bipolar disorder), the age at onset and duration of disorder, the lifetime number of psychiatric admissions, the lifetime history of suicide attempts and their number. The current consumption of alcohol and tobacco was also recorded. For each patient, all psychotropic medications prescribed at the time of the interview were collected and aggregated according to their pharmacological class: antipsychotics, antiepileptics, antidepressants and benzodiazepines.

Psychiatric outcomes

Depressive symptoms were evaluated with the Center for Epidemiology Studies Depression Scale (CES-D) (46,47). The psychometric validity of this 20-item questionnaire has been well established (48). The CES-D was validated in older adults with a threshold score of 16 to characterize a significant depressive symptomatology (49). The perceived clinical severity was evaluated by the investigator using the Clinical Global Impression – Severity (CGI-S) scale (50). The number of psychiatric admissions in the past year was also recorded.

Geriatric outcomes

The Mini-Mental State Examination (MMSE) (51) was used to investigate global cognitive impairment. The Instrumental Activities of Daily Living scale (IADL) (52) was used to assess independent living skills.

Physical outcomes

Physical outcomes included hypothyroidism, renal impairment (Glomerular Filtration Rate_GFR), cancers, cardiovascular disorders, cardiovascular risk factors (overweight, high blood pressure, hyperglycemia, dyslipidemia (hyper Low Density Lipoprotein (LDL) cholesterolemia and hypertriglyceridemia), and the number of general hospital admissions in the past year. Investigators were asked to provide results of laboratory tests for patients who had a blood test in the past year. **Table S1** summarizes the metabolic and biological variables of interest and their standards.

Statistical analysis

Descriptive information was provided as percentages or means (±standard deviations (SD)). Bivariate associations were tested using $\chi 2$ tests or Fisher exact tests for categorical variables, and parametric (t-tests) or nonparametric tests (U Mann-Whitney tests) for continuous variables, as appropriate. The Shapiro-Wilk normality test was performed to examine the normality of each continuous variable. Multivariable logistic or linear regression analyses were conducted to examine differences in each psychiatric and physical outcome (i.e., dependent variables) between patients currently treated with lithium and those not treated with lithium. Covariates were selected *a priori* for their usual effect on disease course or tolerability to treatments, and included age (53), sex (54), duration of disorder, diagnosis, smoking status (55), alcohol use (56) and antipsychotics, antiepileptics and antidepressants. The total percentage of missing data was low (<2%). Missing data were imputed using mean

imputation for each multivariate analysis. To examine the robustness of our findings, we planned to perform sensitivity analyses excluding respondents with missing data to examine whether significant results remained unchanged. Furthermore, to examine whether the relationships observed differ between participants with major depressive disorder and bipolar disorder, we also tested the interactions between lithium and the diagnosis for each model. Statistical significance was evaluated using a two-sided design with alpha risk set *a priori* at 0.05. Statistical analyses were performed using SPSS 20 software (IBM SPSS Statistic 20).

RESULTS

Lithium use

Among the 281 older adults with either major depressive disorder or bipolar disorder included in our study, 44 (15.7%) were treated with lithium and were included in the lithium group. Among those 44 patients, 33 (75%) received lithium as the main treatment for an average of 12.5 (SD=11.6) years, 26 (59.1%) at an average dose of 723.8 (SD=299.8) mg for the sustained-release form and 7 (15.9%) at an average dose of 546.4 (SD=149.6) mg for the immediate-release form, while 11 patients (25%) received it as adjunctive treatment to their main treatment for an average of 3.0 (SD=2.8) years, at an average dose of 487.5 (SD=180.7) mg of the sustained-release form.

Sociodemographic characteristics

The two groups did not significantly differ in age, gender, education, urbanicity and institutionalization (**Table 1**).

Clinical characteristics

Participants from the lithium group were more to have a bipolar disorder than a major depressive disorder (75% vs. 25%) and participants from the non-lithium group were more likely to have a major depressive disorder (44.7% vs. 55.3%, p<0.005) (**Table 2**). Older participants with either major depressive disorder or bipolar disorder from the lithium group (n=44) showed an earlier age at onset of the disorder (36.8 (SD=12.3) years vs. 43.2 (SD=15.2) years, p=0.009) and a higher disorder duration (30.5 (SD=13.8) years vs. 26.5 (SD=16.0) years, p=0.080) than those form the non-lithium group. There were no significant differences in lifetime suicide attempt rate (43.2% vs. 33.8%, p=0.229) or their number (0.7 (SD=1.3) vs. 0.7 (SD=1.6), p=0.486), or in the number of psychiatric admissions (5.7 (SD=6.1) vs. 3.7 (SD=3.7), p=0.076). There were also no significant differences in alcohol use and tobacco consumption, and in prescription rates of other mood stabilizing treatments (antiepileptics: 38.6% vs. 37.6%, p=0.200; antipsychotics: 20.5% vs. 30.0%, p=0.892). On the other hand, patients from the lithium group were significantly less likely to receive antidepressants (45.5% vs. 62.4%, p=0.035) and benzodiazepines (31.8% vs 48.9%, p=0.036) than those from the non-lithium group. Clinical characteristics by diagnosis (i.e., major depressive disorder or bipolar bipolar) are presented in **Supplementary Table 2**.

Psychiatric outcomes

Bivariate analysis

The patients receiving lithium were significantly less likely to present significant depressive symptomatology than their counterparts (36.4% vs. 57.4%, *p*=0.01). The patients receiving lithium also reported significantly lower perceived clinical severity as measured by the CGI-S (2.9 (SD=1.4) vs. 3.5 (SD=1.3), p<0.001) and a lower number of psychiatric admissions in the past year (0.4 (SD=1.4) vs. 0.8 (SD=1.1), p=0.001) compared to patients not currently treated with lithium. (**Table 2**).

Multivariate analysis

Adjusting for age, sex, duration of disorder, diagnosis, smoking status, alcohol use and use of antipsychotics, antiepileptics and antidepressants, patients treated with lithium had significantly lower intensity of depressive symptoms, as measured by the CES-D score (p=0.005), and lower perceived clinical severity, as measured by the CGI score (p=0.003). We only observed a trend towards significance (p=0.051) between lithium treatment and a lower number of psychiatric admissions in the past year, possibly because of insufficient statistical power. (**Table 3**). For all outcomes, there were no significant interactions between lithium and the diagnosis (all p>0.05). All significant results remained unchanged in sensitivity analyses excluding respondents with missing data.

Geriatric outcomes

Bivariate analysis

There were no significant between-group differences in IADL and MMSE scores (both p>0.42) (**Table 2**).

Multivariate analysis

There were no significant associations between lithium use and IADL and MMSE scores (both p>0.35) (**Table 3**). For these outcomes, there were no significant interactions between lithium and the diagnosis (all p>0.05).

Physical outcomes

Bivariate analysis

Hypothyroidism was more prevalent in the lithium group (14.8% vs. 1.0%, p=0.003). There were no significant between-group differences in the prevalence of renal impairment, cardiovascular disorders, cancers, cardiovascular risk factors and number of general hospital admissions in the past year (**Table 2**).

Multivariate analysis

There were no significant associations between lithium use and each physical outcome (all p>0.064) (**Table 4**). For all these outcomes, there were no significant interactions between lithium and the diagnosis (all p>0.05).

DISCUSSION

In a multicenter study of 281 older adults with bipolar disorder or major depressive disorder, we found that patients currently treated with long-term lithium therapy (i.e., with a mean duration of more than 10 years) may have better clinical outcomes, characterized by lower depressive symptomatology and lower perceived clinical severity, compared to those not currently treated with lithium, while taking into account potential confounding factors such as age, sex, duration of disorder, smoking status, alcohol use and use of antipsychotics, antiepileptics and antidepressants. However, there were no significant differences in rates of psychiatric admissions in the past year or in overall and cognitive functioning between patients currently treated with lithium compared to those who were not. Long-term use of lithium was not associated with greater rates of general hospital admissions in the past year or medical comorbidities, except for hypothyroidism. Furthermore, older patients with long-term lithium therapy were less likely to use benzodiazepines than patients not treated with lithium.

In line with our hypotheses, we found that long-term lithium use may be associated with improved clinical outcomes in older adults. Compared to patients who were not currently

treated with lithium, patients treated with lithium reported lower depressive symptoms and were perceived as less severely mentally ill by their clinicians. These findings extend previous research (24-26) by demonstrating lithium's efficacy using a multicenter, naturalistic design and a relatively large sample size (N=281) of older adults (mean age =68.9 years). Our study included older adults aged from 55 years to 92 years, which is an understudied population in the literature (57). Because our sample included patients with both bipolar and major depressive disorder, our findings also support the argument that lithium can be beneficial for older adults with bipolar or unipolar depression (37,58).

The tolerability of long-term use of lithium appeared to be relatively good as we found that long-term use of lithium was not associated with greater rates of medical comorbidities, except for hypothyroidism. Hypothyroidism is a common side effect of lithium use in older adults (59,60), which is not associated with lithium therapy duration (61). Our study showed that lithium treatment was not associated with increased risk of renal impairment, although the mean duration of treatment in our study was only 12.5 years. However, numerous studies have reported a deterioration of renal function in older adults with longer use of lithium therapy (36,62–65). The annual decrease of GFR is estimated at 2.3 ml/min/1.73m^2 in this population (66). In our study, the mean GFR of lithium patients was 81.4 (SD=24.0) mL/min/1.73m^2. Therefore, the patients in our sample may not reach the chronic end stage of renal failure (GFR<15mL/min/1.73m^2) attributable to lithium in their lifetime. These findings are possibly due to the use of lower serum lithium concentrations in this population (25) in response to the implementation of specific guidelines (8). Although some studies had suggested an increase in the incidence of solid renal tumors associated to lithium (67,68), we did not find an association between cancers and lithium treatment in line with recent studies (69,70).

Although several studies have shown neuroprotective effects of lithium in older adults with psychiatric disorders (32,71–75), we did not find any significant association of long-term lithium use with cognitive functioning. Our result might be explained by the limited statistical power. We also found that older patients with bipolar disorder or major depressive disorder under lithium therapy were less likely to take benzodiazepines. Previous work has shown that benzodiazepine use disorder is highly prevalent among older adults (76) and associated with multiple deleterious effects, including greater risk for confusion (77), cognitive impairment (78,79), falls and hip fractures (80,81). One may hypothesize that the lower severity of depressive symptoms observed among participants receiving lithium may partly explain this finding.

Our study has several limitations. First, our study may have suffered from limited statistical power as the sample size of the lithium group was relatively small. Particularly, our relatively limited sample of patients currently receiving lithium (n=44) has prevented us to reproduce analyses separately for older adults with bipolar disorder (n=33) or major depressive disorder (n=11) to identify potential differences in psychiatric and physical outcomes associated with lithium use. However, this sample size was adequate to test our main hypotheses. Second, patients in the lithium group were more likely to have a bipolar disorder and those in the non-lithium group a major depressive disorder. Although this imbalance may have impacted on clinical outcomes such as depressive symptoms, there was no significant interaction between lithium and the diagnosis for any outcomes. Third, the lifetime history of psychotropic treatments was not available, and some patients who had benefited from lithium treatment during their lifetime might have discontinued it for inefficiency or poor tolerability, resulting in a possible selection bias. However, this bias would have led to underestimate between-group differences, further supporting our findings. In addition, long-term lithium users could be patients for whom the treatment was both

effective and well tolerated, and patients who could tolerate lithium in the long term might be generally healthier than those who cannot. Older patients with impaired kidney function and who take medication that could interact with lithium may be less likely to be prescribed lithium. Therefore, it is possible that the findings reported in this study might not be applicable to the broader population of older patients with mood disorders, but may be more applicable to those who would not have contraindications to lithium treatment. However, it is also possible that older patients in the non-lithium group taking other medications are likely to respond and tolerate these medications as well. Fourth, owing to the cross-sectional design of this study, measures of association do not imply any causal association (82). Fifth, there was no information on lapses in treatment, compliance, and blood levels of lithium. Finally, although a wide range of indicators for tolerability were included in the present study, several specific lithium side effects, such as hyperparathyroidism, tremors and gastrointestinal symptoms, were not assessed (83).

Our findings suggest that lithium therapy may be efficient and relatively well tolerated in older adults with bipolar disorder and major depressive disorder, supporting the argument that this medication might be recommended as a first-line treatment for bipolar disorder or as adjunctive therapy in antidepressant-refractory major depressive disorder. Our results call for continued research on lithium among older adults with mood disorders, and the potential value of conducting a large controlled prospective study examining efficacy and tolerability to lithium. Studies that also investigate the role of serum lithium concentrations, inflammatory markers and neuro-imagin, such as volumetric Magnetic Resonance Imaging and Magnetic Resonance Spectroscopy, could confirm our findings, advance our knowledge on the mechanisms underpinning its effects in this population, and help determine older adults with mood disorders who may benefit from this treatment (84).

CONCLUSION

To our knowledge, this is the first study to date to show that long-term use of lithium may be effective and relatively well-tolerated in older adults with bipolar disorder or treatment-resistant major depressive disorder across multiple centers. Particularly, our results suggest that long-term use of lithium among older adults with major depressive disorder or bipolar disorder is associated with lower depressive symptomatology, lower perceived clinical severity and less benzodiazepine use. We did not find greater rates of general hospital admissions or medical comorbidities in patients treated with lithium, except for hypothyroidism. Future prospective studies are needed to extend our knowledge about long-term lithium therapy efficacy and tolerability in this vulnerable population.

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Table 1. Sociodemographic characteristics of patients of at least 55 years of age with major depressive disorder or bipolar disorder.

	All patients	Patients receiving lithium	
		Yes	No
	(n=281)	(n=44)	(n=237)
Sociodemographic characteristics			
Age, years, m(SD)	68.9 (7.8)	67.3 (6.4)	69.2 (8.1)
Sex, n(%) (women)	178 (63.3)	26 (59.1)	152 (64.1)
Education, n(%)			
Less than high school	152 (54.1)	23 (52.3)	129 (54.4)
High school	46 (16.4)	6 (13.6)	40 (16.9)
College	83 (29.5)	15 (34.1)	68 (28.7)
Urbanicity n=278, n(%)			
<1000 inhabitants/km^2	34 (12.1)	6 (13.6)	28 (12.0)
1000 to 10000t	111 (39.5)	16 (36.4)	95 (40.6)
>10000	133 (47.3)	22 (50.0)	111 (47.4)
Institutionalization, n(%)	28 (10.0)	3 (6.8)	25 (10.5)

Table 2. Associations of clinical characteristics, psychotropic medications, psychiatric, geriatric and physical outcomes of long-term use of lithium among patients of at least 55 years of age with major depressive disorder or bipolar disorder.

	Patients receiving lithium		
	Yes (n=44)	No (n=237)	p*
Clinical characteristics			
Diagnosis, n(%)			**<0.0005**
Bipolar disorder	33 (75)	106 (44.7)	
Major depressive disorder	11 (25)	131 (55.3)	
Age at onset, years, n=278, m(SD)	36.8 (12.3)	43.2 (15.2)	**0.009**
Disorder duration, years, m(SD)	30.5 (13.8)	26.5 (16.0)	0.08
Lifetime psychiatric admissions, number, n=233, m(SD)	5.7 (6.1)	3.7 (3.7)	0.076
Lifetime history of suicide attempt, n(%)	19 (43.2)	80 (33.8)	0.229
Lifetime suicide attempts, number, m(SD)	0.7 (1.3)	0.7 (1.6)	0.486
Smoker, n(%)	6 (13.6)	56 (23.6)	0.142
Alcohol use, n(%)	7 (15.9)	44 (18.6)	0.675
Psychotropic medications			
Antipsychotics, n(%)	17 (38.6)	89 (37.6)	0.892
Antiepileptics, n(%)	9 (20.5)	71 (30)	0.200
Antidepressants, n(%)	20 (45.5)	148 (62.4)	**0.035**
Antipsychotics + antidepressants, n(%)	8 (18.2)	41 (17.3)	0.887
Antipsychotics + antiepileptics, n(%)	4 (9.1)	29 (12.2)	0.552
Antiepilectics + antidepressants, n(%)	4 (9.1)	30 (12.7)	0.505
Antipsychotics + antidepressants + antiepileptics, n(%)	3 (6.8)	11 (4.6)	0.542
Benzodiazepines, n(%)	14 (31.8)	116 (48.9)	**0.036**
Psychiatric outcomes			
CES-D[a] score>16, n=279, n(%)	16 (36.4)	135 (57.4)	**0.01**
CGI-severity[b] score, n=279, m(SD)	2.9 (1.4)	3.5 (1.3)	**0.005**
Past-year psychiatric admissions, number, n=280, m(SD)	0.4 (1.4)	0.8 (1.1)	**0.001**
Geriatric outcomes			
MMSE[c] score, n=276, m(SD)	26.4 (3.6)	25.9 (3.8)	0.426
IADL[d] score, n=221, m(SD)	7.2 (1.4)	7.2 (1.4)	0.726
Physical outcomes			
Hypothyroidism, n=126, n(%)	4 (14.8)	1 (1.0)	**0.001**
Renal impairment[e], n=166, n(%)	5 (15.6)	29 (21.6)	0.449
GFR[f], mL/min/1.73m2, n=166, m(SD)	79.1 (19.7)	77.1 (23.1)	0.589
Cancers, n(%)	5 (11.4)	23 (9.7)	0.736
Cardiovascular disorder, n(%)	17 (38.6)	117 (49.4)	0.191
Obesity[g], n=278, n(%)	9(20.9)	44(18.7)	0.735

HBP[h], n=272, n(%)	11 (25.6)	45 (19.7)	0.377
Diabetes[i], n=157, n(%)	3 (10.3)	12 (9.4)	0.873
HyperLDL[j], n=117, n(%)	3 (15)	13 (13.4)	0.850
HyperTG[k], n(%)	6 (13.6)	24 (10.1)	0.489
Past-year general hospital admissions, number, n=280, m(SD)	0.4 (1.8)	0.5 (1.2)	0.185

a: Center of Epidemiologic Studies Depression scale. b: Clinical global Impression-Severity. c: Mini Mental State Examination. d: Instrumental Activities of Daily Living. e: renal impairment defined as having a Glomerular Filtration Rate (MDRD)<60mL/min/1.73m^2. f: Glomerular filtration rate. g: obesity defined as body mass index >30 kg/m^2. h: high blood pressure defined as systolic blood pressure>140mmHg or diastolic blood pressure >90mmHg. i: diabetes defined as glycemia>1.26g/L. j: low density lipoprotein hypercholesterolemia defined as LDL>1.6g/L. k: hypertriglyceridemia defined as TG >1.7g/L.

*: $\chi 2$ tests or Fisher exact tests for qualitative variables, and parametric (t-tests) or nonparametric tests (U Mann-Whitney test) for continuous variables, as appropriate.

Table 3. Multivariable analyses of the effect of long-term use of lithium on efficacy indicators among older patients with major depressive disorder or bipolar disorder.

	Model excluding participants with missing data			Model with imputed data		
	OR	**95%[CI]**	**p***	**OR**	**95%[CI]**	**p***
CES-D[a] score > 16	0.33	[0.15-0.71]	**0.005**	0.33	[0.15-0.70]	**0.004**
	B	**SD**	**p****	**B**	**SD**	**p****
CGI[b]-severity score	-0.681	0.229	**0.003**	-0.683	0.226	**0.003**
Psychiatric admission in the past year	-0.395	0.202	0.051	-0.391	0.201	0.051
MMSE score[c]	0.538	0.625	0.390	0.571	0.620	0.358
IADL score[d]	0.115	0.265	0.665	0.092	0.216	0.670

a: Center of Epidemiologic Studies Depression scale. b: Clinical global Impression. c: Mini-Mental State Examination. d: Instrumental Activities of Daily Living.

*: binary logistic regression analyses were used and adjusted for age, sex, duration of disorder, diagnosis, alcohol use, smoking, antipsychotics, antiepileptics, and antidepressants.

**: linear regression analyses were used and adjusted for age, sex, duration of disorder, diagnosis, alcohol use, smoking, antipsychotics, antiepileptics, and antidepressants.

Table 4. Multivariable analyses of the effect of long-term use of lithium on tolerability indicators among older patients with major depressive disorder or bipolar disorder.

	Model excluding participants with missing data			Model with imputed data		
	OR	**95%[CI]**	**p***	**OR**	**95%[CI]**	**p***
Hypothyroidism[a]		NA			NA	
Renal impairment[b]		NA			NA	
Cancers[¥]	1.48	[0.48-4.56]	0.499	1.48	[0.48-4.56]	0.499
Neurologic disorders[¥]	0.28	[0.06-1.35]	0.114	0.28	[0.06-1.35]	0.114
Cardiovascular disorders[¥]	0.49	[0.23-1.04]	0.064	0.49	[0.23-1.04]	0.064
Cardiovascular risk factors						
Obesity[c]	0.86	[0.35-2.08]	0.737	0.84	[0.35-2.03]	0.840
HBP[d]	1.52	[0.66-3.52]	0.324	1.49	[0.65-3.45]	0.345
Diabetes[e]		NA			NA	
HyperLDL[f]		NA			NA	
HyperTG[g, ¥]	1.41	[0.48-4.12]	0.525	1.41	[0.48-4.12]	0.525
	B	**SD**	**p****	**B**	**SD**	**p****
General hospital admissions in the past year[¥]	-0.131	0.076	0.087	-0.131	0.076	0.087

a: hypothyroidism defined as TSH>4mUI/L. b: renal impairment defined as Glomerular Filtration Rate GFR<60mL/min/1.73m^2. c: obesity defined as body mass index>30 kg/m^2. d: high blood pressure defined as systolic blood pressure>140mmHg or diastolic blood pressure >90mmHg. e: diabetes defined as glycemia>1.26g/L. f: low density lipoprotein hypercholesterolemia defined as LDL>1.6g/L. g: hypertriglyceridemia defined as TG>1.7g/L.

NA: not applicable.

¥: no missing data.

*: binary logistic regression analyses were used and adjusted for age, sex, duration of disorder, diagnosis, alcohol use, smoking, antipsychotics, antiepileptics, and antidepressants.

**: linear regression analyses were used and adjusted for age, sex, duration of disorder, diagnosis, alcohol use, smoking, antipsychotics, antiepileptics, and antidepressants.