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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

Elise Morlet, M.D.,<sup>a,\*</sup>

Jean-François Costemale-Lacoste, M.D.,<sup>a,b</sup>

Emmanuel Poulet, M.D., Ph.D.<sup>c</sup>

Kibby McMahon, M.A.,<sup>d</sup>

Nicolas Hoertel, M.D., M.P.H., Ph.D.,<sup>a,e,f</sup>

Frédéric Limosin<sup>a,c,d</sup>, M.D., Ph.D.,<sup>a,e,f</sup>

CSA Study Group<sup>‡</sup>.

<sup>a</sup> Department of Psychiatry, Corentin Celton Hospital, Issy-les-Moulineaux, France.

<sup>b</sup> INSERM UMRS 1178, CESP, Le Kremlin Bicêtre, France.

<sup>c</sup> INSERM, U1028, CNRS, UMR5292, Lyon Neuroscience Research Center, PSY-R2 Team, Lyon F-69000, France

<sup>d</sup> Department of Psychology & Neuroscience, Duke University, 2213 Elba Street, Durham, NC, 27710.

<sup>e</sup> INSERM UMR 894, Psychiatry and Neurosciences Center, Paris, France.

<sup>f</sup> Paris Descartes University, Sorbonne Paris Cité, Paris, France.

\* Corresponding author:

Elise Morlet,

Department of Psychiatry, Corentin Celton Hospital,

4 Parvis Corentin Celton, 92130 Issy-les-Moulineaux, France,

Phone: 33 (0) 1 58 00 44 21,

Email: [elise.morlet@aphp.fr](mailto:elise.morlet@aphp.fr)

## **Collaborators (174):**

Adès J, Alezrah C, Amado I, Amar G, Andréi O, Arbault D, Archambault G, Aurifeuille G, Barrière S, Béra-Potelle C, Blumenstock Y, Bardou H, Bareil-Guérin M, Barrau P, Barrouillet C, Baup E, Bazin N, Beaufile B, Ben Ayed J, Benoit M, Benyacoub K, Bichet T, Blanadet F, Blanc O, Blanc-Comiti J, Boussiron D, Bouysse AM, Brochard A, Brochart O, Bucheron B, Cabot M, Camus V, Chabannes JM, Charlot V, Charpeaud T, Clad-Mor C, Combes C, Comisu M, Cordier B, Costi F, Courcelles JP, Creixell M, Cuche H, Cuervo-Lombard C, Dammak A, Da Rin D, Denis JB, Denizot H, Deperthuis A, Diers E, Dirami S, Donneau D, Dreano P, Dubertret C, Duprat E, Duthoit D, Fernandez C, Fonfrede P, Freitas N, Gasnier P, Gaillard J, Getten F, Gierski F, Godart F, Gourevitch R, Grassin Delyle A, Gremion J, Gres H, Griner V, Guerin-Langlois C, Guggiari C, Guillin O, Hadaoui H, Haffen E, Hanon C, Haouzir S, Hazif-Thomas C, Heron A, Hubsch B, Jalenques I, Januel D, Kaladjian A, Karnycheff JF, Kebir O, Krebs MO, Lajugie C, Leboyer M, Legrand P, Lejoyeux M, Lemaire V, Leroy E, Levy-Chavagnat D, Leydier A, Liling C, Llorca PM, Loeffel P, Louville P, Lucas Navarro S, Mages N, Mahi M, Maillet O, Manetti A, Martelli C, Martin P, Masson M, Maurs-Ferrer I, Mauvieux J, Mazmanian S, Mechin E, Mekaoui L, Meniai M, Metton A, Mihoubi A, Miron M, Mora G, Niro Adès V, Nubukpo P, Omnes C, Papin S, Paris P, Passerieux C, Pellerin J, Perlberg J, Perron S, Petit A, Petitjean F, Portefaix C, Pringuey D, Radtchenko A, Rahiou H, Raucher-Chéné D, Rauzy A, Reinheimer L, Renard M, René M, Rengade CE, Reynaud P, Robin D, Rodrigues C, Rollet A, Rondepierre F, Rousselot B, Rubingher S, Saba G, Salvarelli JP, Samuelian JC, Scemama-Ammar C, Schurhoff F, Schuster JP, Sechter D, Segalas B, Seguret T, Seigneurie AS, Semmak A, Slama F, Taisne S, Taleb M, Terra JL, Thefenne D, Tran E, Tourtauchaux R, Vacheron MN, Vandell P, Vanhoucke V, Venet E, Verdoux H, Viala A, Vidon G, Vitre M, Vurpas JL, Wagermez C, Walter M, Yon L, Zendjidjian X.

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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<sup>2</sup>) 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 ( $\pm$ 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 likely 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 from 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 disorder) 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<sup>2</sup> in this population (66). In our study, the mean GFR of lithium patients was 81.4 (SD=24.0) mL/min/1.73m<sup>2</sup>. Therefore, the patients in our sample may not reach the chronic end stage of renal failure (GFR<15mL/min/1.73m<sup>2</sup>) 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-imaging, 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.

## REFERENCES

1. Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *The Lancet*. 2013 Nov;382(9904):1575–86.
2. Hoertel N, Limosin F, Leleu H. Poor longitudinal continuity of care is associated with an increased mortality rate among patients with mental disorders: results from the French National Health Insurance Reimbursement Database. *Eur Psychiatry*. 2014 Aug;29(6):358–64.
3. Andreas S, Schulz H, Volkert J, Dehoust M, Sehner S, Suling A, et al. Prevalence of mental disorders in elderly people: The European MentDis\_ICF65+ study. *British Journal of Psychiatry*. 2017 Feb;210(2):125–31.
4. Reynolds K, Pietrzak RH, El-Gabalawy R, Mackenzie CS, Sareen J. Prevalence of psychiatric disorders in U.S. older adults: findings from a nationally representative survey. *World Psychiatry*. 2015 Feb;14(1):74–81.
5. Kennedy N, Foy K, Sherazi R, McDonough M, McKeon P. Long-term social functioning after depression treated by psychiatrists: a review. *Bipolar Disord*. 2007 Mar;9(1–2):25–37.
6. Samalin L, Boyer L, Murru A, Pacchiarotti I, Reinares M, Bonnin CM, et al. Residual depressive symptoms, sleep disturbance and perceived cognitive impairment as determinants of functioning in patients with bipolar disorder. *J Affect Disord*. 2017;210:280–6.

7. Terachi S, Yamada T, Pu S, Yokoyama K, Matsumura H, Kaneko K. Comparison of neurocognitive function in major depressive disorder, bipolar disorder, and schizophrenia in later life: A cross-sectional study of euthymic or remitted, non-demented patients using the Japanese version of the Brief Assessment of Cognition in Schizophrenia (BACS-J). *Psychiatry Res.* 2017;254:205–10.
8. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord.* 2018 Mar;20(2):97–170.
9. National Collaborating Centre for Mental Health (UK). *Bipolar Disorder: The NICE Guideline on the Assessment and Management of Bipolar Disorder in Adults, Children and Young People in Primary and Secondary Care* [Internet]. Leicester (UK): British Psychological Society; 2018 [cited 2018 Jun 23]. (National Institute for Health and Care Excellence: Clinical Guidelines).
10. Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. *Can J Psychiatry.* 2016 Sep;61(9):540–60.
11. Miura T, Noma H, Furukawa TA, Mitsuyasu H, Tanaka S, Stockton S, et al. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. *Lancet Psychiatry.* 2014 Oct;1(5):351–9.
12. Severus E, Taylor MJ, Sauer C, Pfennig A, Ritter P, Bauer M, et al. Lithium for prevention of mood episodes in bipolar disorders: systematic review and meta-analysis. *Int J Bipolar Disord.* 2014;2:15.
13. Simhandl C, König B, Amann BL. A prospective 4-year naturalistic follow-up of treatment and outcome of 300 bipolar I and II patients. *J Clin Psychiatry.* 2014 Mar;75(3):254–262; quiz 263.
14. Hayes JF, Marston L, Walters K, Geddes JR, King M, Osborn DPJ. Lithium vs. valproate vs. olanzapine vs. quetiapine as maintenance monotherapy for bipolar disorder: a population-based UK cohort study using electronic health records. *World Psychiatry.* 2016 Feb;15(1):53–8.
15. Joas E, Karanti A, Song J, Goodwin GM, Lichtenstein P, Landén M. Pharmacological treatment and risk of psychiatric hospital admission in bipolar disorder. *Br J Psychiatry.* 2017;210(3):197–202.
16. Lähteenvuo M, Tanskanen A, Taipale H, Hoti F, Vattulainen P, Vieta E, et al. Real-world Effectiveness of Pharmacologic Treatments for the Prevention of Rehospitalization in a

Finnish Nationwide Cohort of Patients With Bipolar Disorder. *JAMA Psychiatry*. 2018 Apr 1;75(4):347–55.

17. Bauer M, Adli M, Ricken R, Severus E, Pilhatsch M. Role of lithium augmentation in the management of major depressive disorder. *CNS Drugs*. 2014 Apr;28(4):331–42.

18. Tundo A, de Filippis R, Proietti L. Pharmacologic approaches to treatment resistant depression: Evidences and personal experience. *World J Psychiatry*. 2015 Sep 22;5(3):330–41.

19. Tiihonen J, Tanskanen A, Hoti F, Vattulainen P, Taipale H, Mehtälä J, et al. Pharmacological treatments and risk of readmission to hospital for unipolar depression in Finland: a nationwide cohort study. *Lancet Psychiatry*. 2017 Jul;4(7):547–53.

20. Abou-Saleh MT, Müller-Oerlinghausen B, Coppen AJ. Lithium in the episode and suicide prophylaxis and in augmenting strategies in patients with unipolar depression. *Int J Bipolar Disord*. 2017 Dec;5(1):11.

21. MacQueen GM, Frey BN, Ismail Z, Jaworska N, Steiner M, Lieshout RJV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 6. Special Populations: Youth, Women, and the Elderly. *Can J Psychiatry*. 2016 Sep;61(9):588–603.

22. D'Souza R, Rajji TK, Mulsant BH, Pollock BG. Use of Lithium in the Treatment of Bipolar Disorder in Late-Life. *Current Psychiatry Reports*. 2011 Dec;13(6):488–92.

23. Gitlin M. Lithium side effects and toxicity: prevalence and management strategies. *Int J Bipolar Disord*. 2016 Dec;4(1):27.

24. Sproule BA, Hardy BG, Shulman KI. Differential pharmacokinetics of lithium in elderly patients. *Drugs Aging*. 2000 Mar;16(3):165–77.

25. Rej S, Beaulieu S, Segal M, Low NCP, Mucsi I, Holcroft C, et al. Lithium dosing and serum concentrations across the age spectrum: from early adulthood to the tenth decade of life. *Drugs Aging*. 2014 Dec;31(12):911–6.

26. Forester BP, Streeter CC, Berlow YA, Tian H, Wardrop M, Finn CT, et al. Brain lithium levels and effects on cognition and mood in geriatric bipolar disorder: a lithium-7 magnetic resonance spectroscopy study. *Am J Geriatr Psychiatry*. 2009 Jan;17(1):13–23.

27. Dols A, Kessing LV, Strejilevich SA, Rej S, Tsai S-Y, Gildengers AG, et al. Do current national and international guidelines have specific recommendations for older adults with bipolar disorder? A brief report. *Int J Geriatr Psychiatry*. 2016;31(12):1295–300.

28. Arandjelovic K, Eyre HA, Lavretsky H. Clinicians' Views on Treatment-Resistant Depression: 2016 Survey Reports. *Am J Geriatr Psychiatry*. 2016 Oct;24(10):913–7.

29. Sajatovic M, Gyulai L, Calabrese JR, Thompson TR, Wilson BG, White R, et al. Maintenance Treatment Outcomes in Older Patients with Bipolar I Disorder. *The American Journal of Geriatric Psychiatry*. 2005 Apr;13(4):305–11.
30. Young RC, Mulsant BH, Sajatovic M, Gildengers AG, Gyulai L, Al Jurdi RK, et al. GERI-BD: A Randomized Double-Blind Controlled Trial of Lithium and Divalproex in the Treatment of Mania in Older Patients With Bipolar Disorder. *Am J Psychiatry*. 2017;174(11):1086–93.
31. Cooper C, Katona C, Lyketsos K, Blazer D, Brodaty H, Rabins P, et al. A systematic review of treatments for refractory depression in older people. *Am J Psychiatry*. 2011 Jul;168(7):681–8.
32. Morlet É, Hozer F, Costemale-Lacoste J-F. Neuroprotective effects of lithium: what are the implications in humans with neurodegenerative disorders? *Gériatrie et Psychologie Neuropsychiatrie du Vieillessement*. 2018 Mar;(1):78–86.
33. Paton C, Barnes TR, Shingleton-Smith A, Hamish McAllister-Williams R, Kirkbride J, Jones PB, et al. Lithium in bipolar and other affective disorders: prescribing practice in the UK. *Journal of Psychopharmacology*. 2010 Dec;24(12):1739–46.
34. Shulman KI. Lithium for older adults with bipolar disorder: Should it still be considered a first-line agent? *Drugs Aging*. 2010 Aug 1;27(8):607–15.
35. Öhlund L, Ott M, Oja S, Bergqvist M, Lundqvist R, Sandlund M, et al. Reasons for lithium discontinuation in men and women with bipolar disorder: a retrospective cohort study. *BMC Psychiatry*. 2018 07;18(1):37.
36. Rej S, Li BW, Looper K, Segal M. Renal function in geriatric psychiatry patients compared to non-psychiatric older adults: effects of lithium use and other factors. *Aging & Mental Health*. 2014 Oct 3;18(7):847–53.
37. Lepkifker E, Iancu I, Horesh N, Strous RD, Kotler M. Lithium therapy for unipolar and bipolar depression among the middle-aged and older adult patient subpopulation. *Depression and Anxiety*. 2007;24(8):571–6.
38. Abou Kassm S, Hoertel N, Naja W, McMahon K, Barrière S, Blumenstock Y, et al. Metabolic syndrome among older adults with schizophrenia spectrum disorder: Prevalence and associated factors in a multicenter study. *Psychiatry Res*. 2019 May;275:238–46.
39. Hoertel N, Rotenberg L, Blanco C, Pascal de Raykeer R, Hanon C, Kaladjian A, et al. Psychiatric symptoms and quality of life in older adults with schizophrenia spectrum disorder: results from a multicenter study. *Eur Arch Psychiatry Clin Neurosci*. 2019 May 27;
40. Pascal de Raykeer R, Hoertel N, Blanco C, Lavaud P, Kaladjian A, Blumenstock Y, et al. Effects of depression and cognitive impairment on quality of life in older adults with schizophrenia spectrum disorder: Results from a multicenter study. *J Affect Disord*. 2019 May 28;256:164–75.

41. Schuster J-P, Hoertel N, von Gunten A, Seigneurie A-S, Limosin F, CSA Study group. Benzodiazepine use among older adults with schizophrenia spectrum disorder: prevalence and associated factors in a multicenter study. *Int Psychogeriatr*. 2019 May 7;1–11.
42. Hoertel N, Jaffré C, Pascal de Raykeer R, McMahon K, Barrière S, Blumenstock Y, et al. Subsyndromal and syndromal depressive symptoms among older adults with schizophrenia spectrum disorder: Prevalence and associated factors in a multicenter study. *J Affect Disord*. 2019 15;251:60–70.
43. Raucher-Chéné D, Hoertel N, Béra-Potelle C, Terrien S, Barrière S, Da Rin D, et al. Mental healthcare in older adults with schizophrenia: results from 118 French public psychiatric departments. *Int Psychogeriatr*. 2015 Oct;27(10):1749–50.
44. Verdoux H, Tignol J. Focus on psychiatry in France. *Br J Psychiatry*. 2003 Nov;183:466–71.
45. Hébert R, Dubois MF, Wolfson C, Chambers L, Cohen C. Factors associated with long-term institutionalization of older people with dementia: data from the Canadian Study of Health and Aging. *J Gerontol A Biol Sci Med Sci*. 2001 Nov;56(11):M693-699.
46. Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. *Applied Psychological Measurement*. 1977;1(3):385–401.
47. Morin AJS, Moullec G, Maïano C, Layet L, Just J-L, Ninot G. Psychometric properties of the Center for Epidemiologic Studies Depression Scale (CES-D) in French clinical and nonclinical adults. *Rev Epidemiol Sante Publique*. 2011 Oct;59(5):327–40.
48. Shafer AB. Meta-analysis of the factor structures of four depression questionnaires: Beck, CES-D, Hamilton, and Zung. *J Clin Psychol*. 2006 Jan;62(1):123–46.
49. Lewinsohn PM, Seeley JR, Roberts RE, Allen NB. Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. *Psychol Aging*. 1997 Jun;12(2):277–87.
50. Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: US Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration.; 1976.
51. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975 Nov;12(3):189–98.
52. Graf C. The Lawton instrumental activities of daily living scale. *Am J Nurs*. 2008 Apr;108(4):52-62-63.
53. Faravelli C, Alessandra Scarpato M, Castellini G, Lo Sauro C. Gender differences in depression and anxiety: the role of age. *Psychiatry Res*. 2013 Dec 30;210(3):1301–3.

54. Forlani C, Morri M, Ferrari B, Dalmonte E, Menchetti M, De Ronchi D, et al. Prevalence and gender differences in late-life depression: a population-based study. *Am J Geriatr Psychiatry*. 2014 Apr;22(4):370–80.
55. Zvolensky MJ, Bakhshaie J, Sheffer C, Perez A, Goodwin RD. Major depressive disorder and smoking relapse among adults in the United States: a 10-year, prospective investigation. *Psychiatry Res*. 2015 Mar 30;226(1):73–7.
56. Boden JM, Fergusson DM. Alcohol and depression. *Addiction*. 2011 May;106(5):906–14.
57. Mody L, Miller DK, McGloin JM, Div M, Freeman M, Marcantonio ER, et al. Recruitment and Retention of Older Adults in Aging Research. *J Am Geriatr Soc*. 2008 Dec;56(12):2340–8.
58. Souza FG, Goodwin GM. Lithium treatment and prophylaxis in unipolar depression: a meta-analysis. *Br J Psychiatry*. 1991 May;158:666–75.
59. Shine B, McKnight RF, Leaver L, Geddes JR. Long-term effects of lithium on renal, thyroid, and parathyroid function: a retrospective analysis of laboratory data. *The Lancet*. 2015;386(9992):461–8.
60. van Melick EJM, Wilting I, Meinders AE, Egberts TCG. Prevalence and determinants of thyroid disorders in elderly patients with affective disorders: lithium and nonlithium patients. *Am J Geriatr Psychiatry*. 2010;18(5):395–403.
61. Kraszewska A, Chlopocka-Wozniak M, Abramowicz M, Sowinski J, Rybakowski JK. A cross-sectional study of thyroid function in 66 patients with bipolar disorder receiving lithium for 10-44 years. *Bipolar Disorders*. 2015;17(4):375–80.
62. Kessing LV, Gerds TA, Feldt-Rasmussen B, Andersen PK, Licht RW. Use of Lithium and Anticonvulsants and the Rate of Chronic Kidney Disease: A Nationwide Population-Based Study. *JAMA Psychiatry*. 2015;72(12):1182–91.
63. Rodrigo C, de Silva NL, Gunaratne R, Rajapakse S, De Silva VA, Hanwella R. Lower estimated glomerular filtration rates in patients on long term lithium: a comparative study and a meta-analysis of literature. *BMC Psychiatry*. 2014;14:4.
64. Rej S, Looper K, Segal M. The Effect of Serum Lithium Levels on Renal Function in Geriatric Outpatients: A Retrospective Longitudinal Study. *Drugs & Aging*. 2013 Jun;30(6):409–15.
65. Rej S, Shulman K, Herrmann N, Harel Z, Fischer HD, Fung K, et al. Prevalence and Correlates of Renal Disease in Older Lithium Users: A Population-Based Study. *The American Journal of Geriatric Psychiatry*. 2014;22(11):1075–82.
66. Bocchetta A, Cabras F, Pinna M, Poddighe A, Sardu C, Ardu R, et al. An observational study of 110 elderly lithium-treated patients followed up for 6 years with

particular reference to renal function. *International Journal of Bipolar Disorders* [Internet]. 2017 Dec [cited 2018 Jan 27];5(1).

67. Rookmaaker MB, van Gerven HAJM, Goldschmeding R, Boer WH. Solid renal tumours of collecting duct origin in patients on chronic lithium therapy. *Clin Kidney J.* 2012 Oct;5(5):412–5.
68. Zaidan M, Stucker F, Stengel B, Vasiliu V, Hummel A, Landais P, et al. Increased risk of solid renal tumors in lithium-treated patients. *Kidney Int.* 2014 Jul;86(1):184–90.
69. Kessing LV, Gerds TA, Feldt-Rasmussen B, Andersen PK, Licht RW. Lithium and renal and upper urinary tract tumors - results from a nationwide population-based study. *Bipolar Disord.* 2015;17(8):805–13.
70. Pottegård A, Hallas J, Jensen BL, Madsen K, Friis S. Long-Term Lithium Use and Risk of Renal and Upper Urinary Tract Cancers. *J Am Soc Nephrol.* 2016 Jan;27(1):249–55.
71. Terao T, Nakano H, Inoue Y, Okamoto T, Nakamura J, Iwata N. Lithium and dementia: A preliminary study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry.* 2006;30(6):1125–8.
72. Nunes PV, Forlenza OV, Gattaz WF. Lithium and risk for Alzheimer's disease in elderly patients with bipolar disorder. *The British Journal of Psychiatry.* 2007;190(4):359–60.
73. Kessing LV, Søndergård L, Forman JL, Andersen PK. Lithium Treatment and Risk of Dementia. *Archives of General Psychiatry.* 2008;65(11):1331.
74. Kessing LV, Forman JL, Andersen PK. Does lithium protect against dementia? *Bipolar Disorders.* 2010;12(1):87–94.
75. Gerhard T, Devanand DP, Huang C, Crystal S, Olfson M. Lithium treatment and risk for dementia in adults with bipolar disorder: population-based cohort study. *The British Journal of Psychiatry.* 2015;207(1):46–51.
76. Tu K, Mamdani MM, Hux JE, Tu JB. Progressive trends in the prevalence of benzodiazepine prescribing in older people in Ontario, Canada. *J Am Geriatr Soc.* 2001 Oct;49(10):1341–5.
77. Airagnes G, Pelissolo A, Lavallée M, Flament M, Limosin F. Benzodiazepine Misuse in the Elderly: Risk Factors, Consequences, and Management. *Curr Psychiatry Rep.* 2016 Oct;18(10):89.
78. Billioti de Gage S, Moride Y, Ducruet T, Kurth T, Verdoux H, Tournier M, et al. Benzodiazepine use and risk of Alzheimer's disease: case-control study. *BMJ.* 2014 Sep 9;349:g5205.
79. Penninkilampi R, Eslick GD. A Systematic Review and Meta-Analysis of the Risk of Dementia Associated with Benzodiazepine Use, After Controlling for Protopathic Bias. *CNS Drugs.* 2018 Jun 20;



80. Balloková A, Peel NM, Fialova D, Scott IA, Gray LC, Hubbard RE. Use of benzodiazepines and association with falls in older people admitted to hospital: a prospective cohort study. *Drugs Aging*. 2014 Apr;31(4):299–310.
81. Machado-Duque ME, Castaño-Montoya JP, Medina-Morales DA, Castro-Rodríguez A, González-Montoya A, Machado-Alba JE. Association between the use of benzodiazepines and opioids with the risk of falls and hip fractures in older adults. *Int Psychogeriatr*. 2018 Jul;30(7):941–6.
82. Le Strat Y, Hoertel N. Correlation is no causation: gymnasium proliferation and the risk of obesity. *Addiction*. 2011 Oct;106(10):1871–2.
83. Haddad P, Wieck A, Yarrow M, Denham P. The Lithium Side Effects Rating Scale (LISERS); development of a self-rating instrument. *European Neuropsychopharmacology*. 1999 Sep;9:231–2.
84. Hoertel N, de Maricourt P, Gorwood P. Novel routes to bipolar disorder drug discovery. *Expert Opin Drug Discov*. 2013 Aug;8(8):907–18.

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

	All patients (n=281)	Patients receiving lithium	
		Yes (n=44)	No (n=237)
<b>Sociodemographic characteristics</b>			
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 <sup>2</sup>	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		p*
	Yes (n=44)	No (n=237)	
<b>Clinical characteristics</b>			
Diagnosis, n(%)			<b>&lt;0.0005</b>
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)	<b>0.009</b>
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
<b>Psychotropic medications</b>			
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)	<b>0.035</b>
Antipsychotics + antidepressants, n(%)	8 (18.2)	41 (17.3)	0.887
Antipsychotics + antiepileptics, n(%)	4 (9.1)	29 (12.2)	0.552
Antiepileptics + 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)	<b>0.036</b>
<b>Psychiatric outcomes</b>			
CES-D <sup>a</sup> score >16, n=279, n(%)	16 (36.4)	135 (57.4)	<b>0.01</b>
CGI-severity <sup>b</sup> score, n=279, m(SD)	2.9 (1.4)	3.5 (1.3)	<b>0.005</b>
Past-year psychiatric admissions, number, n=280, m(SD)	0.4 (1.4)	0.8 (1.1)	<b>0.001</b>
<b>Geriatric outcomes</b>			
MMSE <sup>c</sup> score, n=276, m(SD)	26.4 (3.6)	25.9 (3.8)	0.426
IADL <sup>d</sup> score, n=221, m(SD)	7.2 (1.4)	7.2 (1.4)	0.726
<b>Physical outcomes</b>			
Hypothyroidism, n=126, n(%)	4 (14.8)	1 (1.0)	<b>0.001</b>
Renal impairment <sup>e</sup> , n=166, n(%)	5 (15.6)	29 (21.6)	0.449
GFR <sup>f</sup> , mL/min/1.73m <sup>2</sup> , 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 <sup>g</sup> , n=278, n(%)	9(20.9)	44(18.7)	0.735

HBP <sup>h</sup> , n=272, n(%)	11 (25.6)	45 (19.7)	0.377
Diabetes <sup>i</sup> , n=157, n(%)	3 (10.3)	12 (9.4)	0.873
HyperLDL <sup>j</sup> , n=117, n(%)	3 (15)	13 (13.4)	0.850
HyperTG <sup>k</sup> , 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<sup>2</sup>. f: Glomerular filtration rate. g: obesity defined as body mass index >30 kg/m<sup>2</sup>. 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 <sup>a</sup> score > 16	0.33	[0.15-0.71]	<b>0.005</b>	0.33	[0.15-0.70]	<b>0.004</b>
	B	SD	p**	B	SD	p**
CGI <sup>b</sup> -severity score	-0.681	0.229	<b>0.003</b>	-0.683	0.226	<b>0.003</b>
Psychiatric admission in the past year	-0.395	0.202	0.051	-0.391	0.201	0.051
MMSE score <sup>c</sup>	0.538	0.625	0.390	0.571	0.620	0.358
IADL score <sup>d</sup>	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 <sup>a</sup>	NA			NA		
Renal impairment <sup>b</sup>	NA			NA		
Cancers <sup>‡</sup>	1.48	[0.48-4.56]	0.499	1.48	[0.48-4.56]	0.499
Neurologic disorders <sup>‡</sup>	0.28	[0.06-1.35]	0.114	0.28	[0.06-1.35]	0.114
Cardiovascular disorders <sup>‡</sup>	0.49	[0.23-1.04]	0.064	0.49	[0.23-1.04]	0.064
Cardiovascular risk factors						
Obesity <sup>c</sup>	0.86	[0.35-2.08]	0.737	0.84	[0.35-2.03]	0.840
HBP <sup>d</sup>	1.52	[0.66-3.52]	0.324	1.49	[0.65-3.45]	0.345
Diabetes <sup>e</sup>	NA			NA		
HyperLDL <sup>f</sup>	NA			NA		
HyperTG <sup>g, ‡</sup>	1.41	[0.48-4.12]	0.525	1.41	[0.48-4.12]	0.525
	<b>B</b>	<b>SD</b>	<b>p**</b>	<b>B</b>	<b>SD</b>	<b>p**</b>
General hospital admissions in the past year <sup>‡</sup>	-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<sup>2</sup>. c: obesity defined as body mass index>30 kg/m<sup>2</sup>. 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.