Title

Demographic and clinical characteristics of lithium-treated older adults with bipolar disorder.

Journal

Acta Psychiatrica Scandinavica, 146(5)

Authors

Forlenza, Orestes
Hajek, Tomas
Almeida, Osvaldo
et al.

Publication Date

2022-11-01

DOI

10.1111/acps.13474

Peer reviewed

HHS Public Access

Author manuscript

Acta Psychiatr Scand. Author manuscript; available in PMC 2023 November 01.

Published in final edited form as:

Acta Psychiatr Scand. 2022 November ; 146(5): 442–455. doi:10.1111/acps.13474.

Demographic and clinical characteristics of lithium-treated older adults with bipolar disorder

Orestes V. Forlenza[1], **Tomas Hajek**[2], **Osvaldo P. Almeida**[3], **Alexandra J.M. Beunders**[4], **Hilary P. Blumberg**[5], **Farren B.S. Briggs**[6], **Vanessa J. R. De-Paula**[7], **Annemiek Dols**[4], **Lisa T. Eyler**[8], **Brent P. Forester**[9], **Ariel Gildengers**[10], **Esther Jimenez**[11], **Nicole C.M. Korten**[4], **Beny Lafer**[1], **Sean R. McWhinney**[2], **Benoit Mulsant**[12], **Soham Rej**[13], **Kaylee Sarna**[14], **Sigfried Schouws**[4], **Ashley Sutherland**[15], **Shangying Tsai**[16], **Eduard Vieta**[11], **Joy Yala**[14], **Martha Sajatovic**[14,17] **on behalf of GAGE-BD initiative**

[1]Department & Institute of Psychiatry, Hospital das Clínicas Faculdade de Medicina da Universidade de São Paulo HCFMUSP, São Paulo, Brazil

[2]Department of Psychiatry, Dalhousie University, Halifax, Canada

[3]Medical School, University of Western Australia, Perth, Australia.

[4]GGZ inGeest, Amsterdam UMC, VU Medical Center, Amsterdam Neuroscience, Amsterdam Public Health Research Institute, the Netherlands.

[5]Department of Psychiatry, Yale School of Medicine, New Haven, USA

[6]Department of Population and Quantitative Health Sciences, Case Western Reserve University School of Medicine, Cleveland, USA

[7]Vanessa J. R. De-Paula, Laboratory of Neuroscience (LIM-27), Institute of Psychiatry, Faculdade de Medicina da Universidade de São Paulo HCFMUSP, São Paulo, Brazil

[8]Department of Psychiatry, University of California San Diego, San Diego, CA, USA and Desert-Pacific Mental Illness Research Education and Clinical Center, VA San Diego Healthcare System, San Diego, USA

[9]Division of Geriatric Psychiatry, McLean Hospital, Belmont; Harvard Medical School, Boston, USA

[10]Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, USA

[11]Bipolar and Depressive Disorders Unit, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Spain

Correspondence Orestes V. Forlenza. Laboratório de Neurociências (LIM-27), Departamento e Instituto de Psiquiatria, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo. Rua Doutor Ovídio Pires de Campos 785, CEP 05403-010, São Paulo, SP, Brazil. forlenza@usp.br.

Author Contribution:

OVF and TH conceived the project, conducted the analyses, and drafted the initial version of the paper. LTE, AS and MS provided the harmonised dataset and coordinate the GAGE-BD project. VJRP and SRMW contributed to statistical analyses. MS, LTE, BL, SR, AD, AG, FB and OPA critically reviewed the manuscript drafts. All GAGE-BD members involved in this study contributed to data collection, definition of study aims, manuscript review and approval of its final version for publication.

Conflict of interest

The authors declare no conflicts of interest with the published work. The results of this study have not been published elsewhere.

[12]Benoit Mulsant, Department of Psychiatry, University of Toronto, Center for Addiction & Mental Health, Toronto, Canada

[13]Soham Rej, Lady Davis Institute, Jewish General Hospital, McGill University, Montreal, Canada

[14]Kaylee Sarna, Case Western Reserve University School of Medicine, Cleveland, USA

[15]Ashley Sutherland, Department of Psychiatry, University of California at San Diego, San Diego, USA

[16]Shangying Tsai, Department of Psychiatry, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

[17]Global Aging & Geriatric Experiments in Bipolar Disorder (GAGE-BD): please see Supplemental Material for members of the GAGE-BD initiative.

Abstract

Objectives: There is limited information on the characteristics of older adults with bipolar disorder (OABD) treated with lithium, along with safety concerns about its use by older adults.

Experimental proecdures: Cross-sectional analysis of the GAGE-BD dataset to determine differences and similarities between lithium users and non-users. We analysed data from 986 participants aged 50 years or older (mean age 63.5 years; 57.5% females) from 12 study sites. Two subgroups (‘Lithium’; ‘Non-lithium’) were defined according to the current prescription of lithium. We compared several outcomes between these groups, controlling for age, gender, and study site.

Results: OABD treated with lithium had lower scores on depression rating scales and were less likely to be categorised as with moderate or severe depression. There was a lower proportion of lithium users than non-users among those with evidence of rapid cycling and non-bipolar psychiatric diagnoses. Assessment of global cognitive state and functionality indicated better performance among lithium users. The current use of antipsychotics was less frequent among lithium users, who also reported fewer cardiovascular comorbidities than non-users.

Conclusion: We found several potentially relevant differences in the clinical profile of OABD treated with lithium compared to those treated with other mood stabilisers. However, the interpretation of the present results must take into account the methodological limitations inherent to the cross-sectional approach and data harmonisation.

Keywords

bipolar disorder; older adults; pharmacotherapy; lithium

The aim of the present study is to describe the demographic and clinical characteristics of OABD receiving lithium therapy, using data from the Global Aging & Geriatric Experiments in Bipolar Disorder (GAGE-BD).

1. INTRODUCTION

Lithium salts have been widely used for the treatment of mood disorders over the past decades, and still represent a first-line therapeutic option for the management of bipolar disorder (BD).[1] There is limited information on the characteristics of older adults with BD (OABD) prescribed lithium.[2] Most of the evidence supporting lithium use in this population has been extrapolated from studies conducted in younger cohorts or has been based on post-hoc analyses of trials with mixed-age samples, open-label trials or observational studies.[3] Single-site studies dedicated to OABD often draw conclusions from small patient samples addressing specific clinical questions – e.g., treatment response, risk factors, comorbidities, or cognitive symptoms – and are often underpowered to test differences in efficacy outcomes.[2] An exception is the GERI-BD study, a randomised clinical trial of lithium carbonate vs. divalproex sodium for the treatment of OABD,[4] in which 224 type-I BD patients aged 60 years or older presenting with manic, hypomanic or mixed episodes were randomly assigned to receive either treatment for nine weeks. Overall efficacy and tolerability was similar in both groups, but lithium-treated patients showed more marked improvement in manic symptoms.[4] In a cross-sectional study in 76 OABD, lithium users reported a more positive attitude towards pharmacotherapy than non-users, including better self-reported contentedness, subjective somatic health, and social functioning, in spite of reporting more side-effects.[5] Finally, according to a Delphi survey of 25 experts from nine countries, lithium was the preferred choice for maintenance monotherapy in OABD, and emphasised the view that tolerability can be improved by maintaining lithium treatment at lower serum levels of lithium (0.4–0.8mmol/L).[6]

Taken together, currently available evidence supports the hypothesis that lithium is an efficacious treatment of OABD; yet, safety and tolerability issues cannot be ignored.[1,7,8] Lithium-related side-effects can be both unpleasant (e.g., tremor) and clinically relevant in the long term (e.g., renal insufficiency or hypothyroidism), jeopardising the patient's adherence to treatment and discouraging clinicians to prescribe it.[9] According to register studies conducted in Denmark and Sweden, the pattern of prescription of mood-stabilising drugs for the treatment of BD has changed over the past years, with a decline in the use of lithium and valproate,[10] alongside an increase in the use of lamotrigine and quetiapine.[11] Also, underutilisation of lithium has been reported in Scotland[12] and in North America,[13] which may have been driven by safety concerns and marketing investments by pharma favouring the prescription of newer drugs. Nonetheless, in a recent retrospective cohort study addressing predictors of discontinuation of lithium therapy in OABD, the main reason for discontinuation was lack of efficacy, and only a minority of cases discontinued lithium because of side-effects.[14] Nonetheless, other mood-stabilisers, such as anticonvulsants and antipsychotics, are also associated with potentially serious adverse effects, including increased risk of metabolic syndrome and cardiovascular events.[1]

1.1. Aims of the study:

The Global Aging & Geriatric Experiments in Bipolar Disorder (GAGE-BD) project is a consortium of investigators dedicated to research in OABD, assembling studies conducted by different groups from around the globe, including sites in North and South America,

Europe, Asia and Oceania.[3] Measures have been integrated and harmonised to enable hypothesis-driven analyses in the largest to date dataset in this field. The present study used GAGE-BD data to investigate the clinical profile of lithium-treated OABD compared to those treated with other mood-stabilising drugs. Therefore, the objective of the present study is to describe the demographic and clinical characteristics of OABD undergoing lithium therapy in this large, collaborative dataset.

2. MATERIAL AND METHODS

2.1. Study design and participants:

We conducted a cross-sectional analysis of the GAGE-BD dataset (as of August 2021) to describe the demographic and clinical characteristics of OABD treated with lithium compared with those treated with other drugs by the time of assessment. This integrated database derives from archival datasets from 12 study sites (with a total number of 1,761 subjects) distributed across North and South America, Europe, Asia and Oceania, namely: *Case Western Reserve University* (CWRU), Cleveland, Ohio, USA (4 studies, n=283); *University of California at San Diego* (UCSD), California, USA (n=173); *McLean Hospital*, Massachusetts, USA (n=73); *University of Pittsburgh* (UPMC), Pittsburgh, Pennsylvania, USA (n=143); *Yale School of Medicine* (YSM), New Haven, Connecticut, USA (n=88); *Lady Davis Institute* (LDI), Montreal, Canada (2 studies, n=114); *Center for Addiction & Mental Health* (CAMH), Toronto, Canada (n=48); *University of Sao Paulo* (USP), Sao Paulo, Brazil (n=144); *GGZ inGeest*, Amsterdam, the Netherlands (2 studies, n=367); *University of Barcelona*, Catalonia, Spain (n=161); *Taipei Medical University* (TMU), Taipei, Taiwan (2 studies, n=99); *University of Western Australia*, Perth, Australia (n=68). Approval to contribute data was obtained by each site's institutional review boards or ethics committees and by the GAGE-BD coordinating board. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

The inclusion criteria for the present analysis were: age of 50 years or more (n=1,103);[2] diagnosis of BD type-I (64.7%), BD type-II (22.6%) or 'BD subtype unknown' (12.7%); and availability of information about lithium use (n=986). The mean age of the study sample was 63.5 years (maximum age 95 years), and 57.5% were women. Two experimental groups were constituted, i.e., 'Lithium' (n=406) and 'Non-lithium' (n=580). Allocation in the former was defined by current prescription of lithium salts for the treatment of BD, not accounting for previous history of lithium use. Of note, only four sites (Barcelona, GGZ, LDI and USP) had a higher proportion of lithium users than non-users (60.2%, 59.4%, 70.0% and 52.8% respectively). The proportion of lithium users was lowest in North-American sites (CWRU, 9.7%; UCSD, 9.7%; YSM, 23.9%; UPMC, 24.0%; and CAMH, 33.3%) and Taipei (TMU, 42.1%).

2.2. Study measures:

The following assessment scales were used to quantify current symptoms of depression, mania and psychosis: Hamilton Depression Rating Scale (HAMD),[15] Montgomery-Asberg

Depression Rating Scale (MADRS)[16] Center for Epidemiologic Studies-Depression Scale, (CES-D),[17] Young Mania Rating Scale (YMRS)[18] and Brief Psychiatric Rating Scale (BPRS).[19] The Mini-Mental State Examination (MMSE),[20] the Global Assessment of Functionality (GAF)[21] and the Clinical Global Impression (CGI)[22] were used for the assessment of global cognitive, functional and clinical state, respectively. Data harmonisation followed the same principles reported in previous publications of the GAGE-BD consortium.[3,7] The characterisation of current mood state was done by the assessment of total scores on related assessment scales (HAMD, MADRS and CES-D). Severity of depression symptoms was also estimated by transforming raw scores on 17-, 21- and 24-item HAMD scales (HAMD-17, HAMD-21 and HAMD-24) into an aggregated continuous variable, where the latter two were rescaled to fit the same scoring amplitude of the 17-item version. This was achieved by dividing HAMD-21 and HAMD-24 total scores by the maximum possible score that can be obtained on each of these scales, and then multiplying the result by 63, which is the maximum possible score that can be achieved on HAMD-17. A similar procedure was undertaken to harmonise the 24-item BPRS scores into a single continuous variable with the same amplitude of BPRS-18. The presence of suicidal thoughts was evaluated by assessing the sub-scores of items 3 and 10 of HAMD and MADRS, respectively. Because only a small subset of contributing studies used each of the depression measures, to increase power, we also harmonised depression scores across HAMD, MADRS and CES-D scales to yield the new categorial variable (‘depression band’) based of cut-off scores of the various scales, i.e., no depression (HAMD ≤7; MADRS ≤6; CES-D ≤15); mild-or-moderate depression (HAMD 8–23; MADRS 7–34; CES-D 16–27); or severe depression (HAMD ≥24; MADRS ≥35; CES-D ≥28).

Other measures of interest included: age, gender, education, relationship and employment status, family history of mental illness, BD subtype, age of onset, illness duration, number of major affective episodes, number of hospitalisations, history of rapid cycling, current mood symptoms, use of antipsychotics, having medical or psychiatric comorbidities, body weight, smoking status, global cognitive state and functionality. Psychiatric comorbidities were estimated by the evidence of current or lifetime diagnoses of anxiety disorders and/or substance/alcohol use disorders. The occurrence of physical comorbidities was ascertained according to reported impairments in 8 distinct systems (cardiovascular, respiratory, gastrointestinal, hepatic/pancreatic, renal, genitourinary, musculoskeletal and endocrine), in addition to the number of affected systems reported for each participant (cummulative somatic burden).

2.3. Statistical analysis:

Data were analysed with SPSS (version 25.0) and R (version 4.1.2). We first described the data, providing raw means and standard deviations (SD) for continuous variables and counts and proportions for categorical variables in ‘Lithium’ and ‘Non-lithium’ groups, and compared these raw estimates between the groups using Pearson’s Chi-squared tests (X2), t-tests for independent samples and Mann-Whitney tests as appropriate for categorical, continuous and ordinal measures, respectively. Next, we used generalised linear mixed model (GLMM) for binomial family and logit link function to compare the ‘Lithium’ and ‘Non-lithium’ groups while controlling for age, gender and the random effect (intercept) of

clustering according to study site. In situations, where lithium was used as a predictor, we used linear regression, linear mixed (LMM), and GLMM models for binomial, cumulative binomial and multinomial families with their respective canonical link functions. No automated method for variable selection was used. Linear regressions models were fit with least squares estimator, whereas LMM used restricted maximum likelihood, and GLMM used maximum likelihood estimation using Laplace approximation. We ruled out collinearity by determining the variance inflation factor (maximum VIF was 1.04). These model tested the association between lithium use and a set of continuous variables indicative of current mood state (including scores in HAMD, CES-D, YMRS, BPRS), global cognitive/functional state (MMSE, GAF), clinical impression (CGI), number of affective episodes, cumulative somatic burden (as defined by the total number of somatic comorbidities) and body weight. In these models, we treated lithium as the fixed effect, assuming that the distribution of the response variable should be the same for lithium users and non-users, while controlling for age and gender. We also included a random effect of study site for all measures, except MADRS, CES-D and CGI, which were only fully measured (i.e., all variables in model without missing values) in one site. We used F-values in linear regression, and likelihood ratios (LR) in LMM and GLMM. Alpha was set at 5% and all probability estimates were two-tailed. Although these analyses were exploratory (i.e., hypotheses generating), we used Benjamini-Hochberg adjusted p-values to ascertain the statistical significance of the associations after controlling for multiple comparisons and therefore reduce false discovery rate.

3. RESULTS

Table 1 presents a descriptive summary of demographic and clinical variables in ‘Lithium’ and ‘Non-lithium’ groups. The univariate analyses showed statistically significant differences between the two groups for the following measures: age, age of onset, history of rapid cycling, smoking status, body weight, antipsychotic drug use, severity of current depression, scores on psychometric scales and somatic comorbidities.

Tables 2A and 3A display the distribution of study measures by treatment groups and the corresponding statistics in the first regression model (GLMM), using age and gender as fixed predictors, study site as random intercept and ‘Lithium’ as response. There was no evidence that either age or gender modified the probability of using lithium. A set of predictor variables was added to the model one at a time. The variables education (p=0.05), family history of mental illness (p=0.03) and lifetime non-BD psychiatric diagnoses (p=0.03) showed statistically significant associations with lithium use. Each additional year in education increased the odds of using lithium by 5% (OR=1.05; SE=0.03; 95%CI=[1.00, 1.10]; z=1.97; p=0.049). A lower proportion of lithium users reported a positive family history of mental illness (32.7% vs. 45.8%), and the analysis of the model’s parameters showed that OABD patients with a positive family history of mental illness had 47% lower odds of using lithium than those without (OR=0.53; SE=0.16; 95%CI=[0.30, 0.95]; z=−2.15; p=0.032). Finally, patients with previous history of anxiety disorder, or comorbid anxiety plus substance use disorders, had respectively 50% (OR=0.50; SE=0.14; 95%CI=[0.29, 0.86]; z=−2.49; p=0.013) and 56% (OR=0.44; SE=0.16; 95%CI=[0.22, 0.90]; z=−2.26;

p=0.024) lower odds of using lithium then those without another psychiatric diagnosis. The remaining variables did not show statistically significant associations with the use of lithium.

In a second model using 'Lithium' as a predictor of multiple outcomes, controlling for age and gender plus a random intercept for study site (Table 2B), we found that lithium users had lower harmonised HAMD (p=0.004) and CES-D (p<0.001) scores, and higher MMSE (p=0.02) and GAF (p=0.007) scores than non-users. We found no statistically significant associations between lithium use and number of affective episodes, MADRS or YMRS scores, BPRS, CGI, body weight, or cumulative somatic burden. Pearson's correlation coefficients for the total sample indicated that GAF scores were inversely associated with HAMD (r=−0.623, p=0.001) and MADRS scores (r=−0.765, p=0.001), but not with MMSE scores (r=−0.022, p=0.68).

Using a similar approach to evaluate fixed effect of 'Lithium' on a set of categorical variables, controlling for age and gender plus a random intercept for study site (Table 3B), we found that lithium users were less represented among BD patients with rapid cycling (p=0.04) and those with moderate/severe depression (p<0.001). Also, lithium users were less frequently prescribed antipsychotic drugs (p<0.001) and had less comorbid cardiovascular conditions (p=0.008). No statistically significant associations with lithium use were found for the variables occupation, relationship status, smoking, and other somatic comorbidities. Finally, there was no obvious association between lithium use and higher scores on items related to suicidality on HAMD and MDRS scales. After correction for multiple comparisons, six variables retained statistically significant associations with lithium use, namely CES-D (adjusted p=0.03); HAMD (0.01); GAF (0.04); moderate/severe depression (0.005); antipsychotic use (0.01) and cardiovascular morbidity (0.04).

4. DISCUSSION

With nearly a thousand individuals from multiple sites around the world, this is currently the largest sample dedicated to the study of OABD, including their use of lithium. We found some salient differences between the two groups. Lithium-treated patients had higher levels of education, were less likely to have family history of psychiatric disorders or personal history of psychiatric comorbidities. They had significantly lower mean scores in depression rating scales and lower frequency of severe forms of depression, in addition to better global cognitive and functional state. Also, participants in the lithium-treated group were less likely to be prescribed antipsychotic drugs and to have comorbid cardiovascular conditions. Two lines of explanation could be considered to interpret these findings: first, lithium use is indeed associated with better outcomes in depression, functionality and cognition; alternatively, complex and difficult-to-treat patients could have been less likely to be treated with lithium in the first place or more likely to be switched from lithium to other medications.

The lower burden of depression among individuals treated with lithium is important, given that older age patients are more likely to have depressive-predominant polarity than their younger counterparts.[23] This finding can have several explanations. Episodic course is one of the key predictors of lithium response, and individuals with episodic illness will be

less likely to show depressive symptoms at any given time relative to people with chronic presentations. Consequently, prescribing lithium primarily to people with episodic illness could explain the lower rates of depressive symptoms in this group, but this prescriber bias would not necessarily explain the observation that lithium-treated individuals had less severe depressive episodes. We could also think of indication bias: if lithium is indicated for the management of mania and maintenance, those with depression or with frequent depressive episodes would be less likely to be prescribed lithium. Alternatively, it is possible that patients treated with lithium are better protected against depressive symptoms/episodes, or that lithium alleviates the severity of depression. This is in accordance with studies documenting antidepressant properties of lithium and its efficacy in preventing depressive episodes.[1] In contrast to previous studies,[24] we found no evidence of association between lithium use and suicide symptoms.

The association between lithium use and better functionality and cognition merits discussion. The possibility of lithium causing cognitive toxicity is a matter of concern in the clinical practice.[8,25] On the other hand, growing evidence from pre-clinical and clinical research suggests that lithium use may also deliver neurotrophic and protective effects in the long term,[26] improving neurocognitive performance,[27] modifying pathogenic mechanisms commonly associated with neurodegeneration,[28] and eventually attenuating the risk of dementia.[29–31] The fact that lithium treatment was associated with higher MMSE scores in the present analysis does not support the hypothesis that lithium has detrimental effects on the cognitive performance of older adults. At the same time, we cannot clearly interpret this as a beneficial effect of lithium on cognition, because of the cross-sectional design of the study. It is possible that better cognitive and general functioning increased the chance of lithium prescription, as this treatment requires closer monitoring and compliance, which may be compromised in people with impaired cognition and functionality. Lithium use was also associated with a better overall functional status, with mean GAF scores 10% higher than among non-users. It is also possible that the better functional status observed among lithium users may be related to being less depressed, as suggested by the finding of a strong negative correlation between functionality and depression ratings.

We also found that lithium users were less likely to have psychiatric comorbidities than non-users, although our analyses were restricted to anxiety and substance use disorders. These differences may also reflect prescription biases, where comorbidity with other psychiatric disorders may be a reason not to prescribe lithium, which would be reserved for individuals with more classical phenotype and fewer comorbidities. Our findings are in contrast with those reported by Burton and colleagues,[32] suggesting that older adults treated with lithium were similar to those treated with second generation antipsychotics with respect to the occurrence of psychiatric comorbidities, namely anxiety, PTSD and substance abuse. Differences in sample size might explain the discrepancy between studies, given that the latter study was based on a smaller number of subjects (n=24) in each treatment group.[32]

In the present analysis, both groups had similar rates of respiratory, gastrointestinal, hepatic/pancreatic, renal, genitourinary, musculoskeletal and endocrine disorders, consistent with the findings by Pfennig and colleagues,[25] although the characterization of comorbidities in this dataset was not supported by subsidiary laboratory data. The lack of association between

lithium use and endocrine or renal dysfunctions in the present sample is intriguing. Lithium use accelerates loss of renal function in the elderly, which can be additionally impacted by polypharmacy.[33] The study of older adults aged 70 years or over found that progressive renal dysfunction leading to discontinuation of lithium treatment was recorded for 30% of users.[32] However, in a population-based cohort study, the risk of renal decline in older adults treated with lithium (compared to valproate treatment) was minimal when serum concentrations of lithium were kept below 0.7mmol/L.[34] These findings are also in keeping with a controlled study in older adults with mild cognitive impairment,[30,35] in which long-term use of lithium carbonate at sub-therapeutic concentrations was not associated with a decline in renal function after four years of follow-up. We concede that the absence of association between lithium treatment and renal impairment can also be an artefact arising from data harmonisation or participant selection. Patients with more severe comorbid conditions (e.g., renal failure) may have been excluded from the studies that contributed to the GAGE-BD dataset. Alternatively, discontinuation of lithium treatment due to incident adverse events could selectively and artefactually increase the rate of these conditions in the non-lithium group. However, the study by Burton and colleagues[32] does not support this hypothesis, given that they found no statistically significant differences in adverse effects or changes in laboratory parameters when comparing patients treated with lithium vs. second-generation antipsychotics in a long-term retrospective cohort.

Interestingly, cardiovascular comorbidities were less frequent among lithium users. This is in keeping with the preponderance of hypertension and metabolic syndrome among OABD, with uneven distribution across therapeutic groups.[36] In a nationwide study using Danish healthcare registries including all BD patients and community cases of cardiac arrest, lithium was not shown to be associated with increased rates of cardiac arrest, as compared to subjects receiving no mood-stabilising drugs or monotherapy with atypical antipsychotics or anticonvulsants.[37] The lower rates of cardiovascular disorders could also reflect lower rates of antipsychotic exposure in the lithium group. Yet, this finding could also reflect prescription bias, where better functioning and healthier individuals with BD may be considered better candidates for treatment with lithium in routine clinical practice. Our descriptive data suggest a trend that favours lithium users in this regard, although cumulative somatic burden was not statistically associated with lithium use. The present data do not allow dismissing residual confounding and confounding due to unmeasured factors; still, the lack of association between lithium use and somatic burden suggests that the observed associations were not driven by a selection bias favouring the prescription of lithium for healthier patients. The same applies to body weight. Lithium users had lower body weight and this may be explained by lower use of antipsychotics in that group and also the fact that weight gain is relatively limited in patients treated with lithium.[38] Some antipsychotics carry much higher weight-gain liability[39] and are also more likely to be prescribed in more severe patients, with more comorbidities.

The present study has several strengths. Most of the clinical findings in OABD come from single-site studies, which are limited by small sample sizes and local composition of patient groups. These methodological constraints invariably weaken the statistical power of analyses and the generalisability of findings. The combination and integration of data from multiple study sites is potentially circumventing the challenge of interpreting findings from smaller

studies, taking advantage of the fact that many research groups utilise similar assessment methods in their protocols, along with the possibility of harmonising data where different, but equivalent, measurement tools are used to evaluate overlapping construct domains.[3] Nonetheless, the interpretation of our results requires caution, given the methodological limitations inherent to this approach. First, the cross-sectional design precludes the establishment of cause-effect relationships.[40] Also, clustering and harmonisation of archival data obtained from different protocols, and using different assessment scales and instruments to collect data for depression, mania and cognition, may undermine the reliability of the information collected, preventing stratification and a more detailed assessment of associations. It is noteworthy that the present sample had low manic symptom severity. Therefore, findings might have been different in the presence of more significant manic symptoms or episodes, as there is likely differential in who is prescribed lithium (as opposed to antipsychotic drugs) based on manic symptoms, as well as in manic vs. depressive symptom response. Besides, the dataset we used in this analysis did not contain information about current use of other common medications used in BD, such as antidepressants and anticonvulsants. Another shortcoming is the lack of information about lifetime exposure to lithium, meaning that the present analysis was restricted to the availability of information about *current* lithium use, overlooking any potential effects of past treatments — either beneficial or deleterious. Also, detailed information about lithium treatment (e.g. serum levels or dosing; duration of exposure; compliance, etc.) was only available in a few subsets of data. Aiming for such specific questions would create unbalanced and underpowered subgroups, so these variables were not included in the analyses. At the same time, we aimed for generalizability. Clinicians would often see people where these additional variables are unknown and yet it is still relevant to ask what are the general characteristics of people who are currently on lithium, and if these characteristics differ from people who are not currently on lithium. This was our main question, which capitalized on the large and generalizable sample and which closely resembled clinical practice.

It is also possible that some non-lithium users could be lithium failures (i.e., lithium was tried but discontinued), while others could have been lithium-naïve. In addition, the relatively low proportion (56%) of cases with information about lithium use in relation to the total number of participants in the original dataset indicates that the prescription of lithium was not balanced with other drugs equally recommended for the treatment of BD. Therefore, prescriber bias – including site-related prescription preferences – may have influenced the observed associations. Thus, lithium may have been prescribed to patients who were more compliant with treatment, more adherent to clinical recommendations, generally healthier, or those with a specific subtype of BD. These suppositions are reinforced by some of our findings, such as the association between lithium use and education (i.e., additional years of schooling increasing the odds of lithium use), and the lower frequency of psychiatric comorbidities or family history of BD among lithium users.

In conclusion, we found salient differences between OABD individuals treated with lithium compared to those treated with other mood stabilisers. The lithium-treated group generally had a more favourable clinical profile, with better global cognitive state and functionality, lower levels of depressive symptoms and fewer comorbid psychiatric and cardiovascular disorders. Future prospective studies should clarify whether these clinical characteristics are

drivers or consequences of lithium prescription. Regardless, the notion that clinical benefits of lithium use by older adults are overshadowed by unacceptable risks and adverse outcomes is not warranted by the present results, therefore supporting the prescription and careful monitoring of lithium treatment for BD in geriatric patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

The authors are deeply grateful to Dr. Charles L. Bowden, who passed away in March of 2022, and his wife Virginia Massey Bowden, for establishing the Bowden Massey Research Initiative, which has supported the GAGE-BD project. Dr. Bowden's deep commitment to advancing care for individuals living with BD is a continuously inspiring presence to our GAGE-BD study team and the broader community of scientists focused on research in BD.

Funding Information

Research reported in this publication was supported by the ISBD Bowden Massey Strategic Research Initiative in Bipolar Disorder Award and made possible by logistical support from the ISBD. Support was also received from the Clinical and Translational Science Collaborative (CTSC) of Cleveland which is funded by the National Institutes of Health (NIH), National Center for Advancing Translational Science (NCATS), Clinical and Translational Science Award (CTSA) grant (UL1TR002548). Hilary Blumberg is supported by (NIH grant R01 MH113230). The corresponding author's work is supported by research grants from FAPESP (2019/08507–3, 2014/50873–3), CNPq (465412/2014–9) and Associação Beneficente Alzira Denise Hertzog da Silva (ABADHS).

Data availability statement

The data that support the findings of this study are available on reasonable request from the GAGE-BD Core Group (Martha.Sajatovic@UHhospitals.org), subject to approval by the Steering Committee.

REFERENCES

1. Yatham LN, Kennedy SH, Parikh SV, 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;20(2):97–170. [PubMed: 29536616]
2. Sajatovic M, Strejilevich SA, Gildengers AG, et al. A report on older age bipolar disorder from the International Society for Bipolar Disorders Task Force. Bipolar Disord. 2015;17:689–704. [PubMed: 26384588]
3. Sajatovic M, Eyler LT, Rej S, et al. The Global Aging & Geriatric Experiments in Bipolar Disorder Database (GAGE-BD) project: Understanding older-age bipolar disorder by combining multiple datasets. Bipolar Disord. 2019;21:642–649. [PubMed: 31081573]
4. Young RC, Mulsant BH, Sajatovic M, 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;174:1086–1093. [PubMed: 29088928]
5. Rej S, Schuurmans J, Elie D, et al. Attitudes towards pharmacotherapy in late-life bipolar disorder. Int Psychogeriatr. 2016;28(6):945–950. [PubMed: 26778416]
6. Shulman KI, Almeida OP, Herrmann N, et al. Delphi survey of maintenance lithium treatment in older adults with bipolar disorder: an ISBD task force report. Bipolar Disord. 2019; 21(2):117–123. [PubMed: 30375703]

7. Sajatovic M, Dols A, Rej S, et al. Bipolar symptoms, somatic burden, and functioning in older-age bipolar disorder: Analyses from the Global Aging & Geriatric Experiments in Bipolar Disorder Database project. Bipolar Disord. 2021;Jul 27. Epub ahead of print.
8. Gitlin M Lithium side effects and toxicity: prevalence and management strategies. Int J Bipolar Disord. 2016 Dec 4;(1):27. [PubMed: 27900734]
9. Barbuti M, Colombini P, Ricciardulli S, et al. Treatment adherence and tolerability of immediate- and prolonged-release lithium formulations in a sample of bipolar patients: a prospective naturalistic study. Int Clin Psychopharmacol. 2021;36(5):230–237. [PubMed: 34310434]
10. Kessing LV, Vradi E, Andersen PK. Nationwide and population-based prescription patterns in bipolar disorder. Bipolar Disord. 2016;18(2):174–182. [PubMed: 26890465]
11. Karanti A, Kardell M, Lundberg U, Landén M. Changes in mood stabilizer prescription patterns in bipolar disorder. J Affect Disord. 2016;195:50–56. [PubMed: 26859073]
12. Lyall LM, Penades N, Smith DJ. Changes in prescribing for bipolar disorder between 2009 and 2016: national-level data linkage study in Scotland. Br J Psychiatry. 2019;215(1):415–421. [PubMed: 30816839]
13. Rhee TG, Olfson M, Nierenberg AA, Wilkinson ST. 20-year trends in the pharmacologic treatment of bipolar disorder by psychiatrists in outpatient care settings. Am J Psychiatry. 2020;177(8):706–715. [PubMed: 32312111]
14. Flapper M, van Melick E, van Campen J, et al. Tolerability of lithium: A naturalistic discontinuation study in older inpatients (≥60 years). Int J Geriatr Psychiatry. 2021;36(8):1231–1240. [PubMed: 33644915]
15. Hamilton M A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62. [PubMed: 14399272]
16. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382–389. [PubMed: 444788]
17. Radlof LS. The CES-D Scale: a self-report depressive scale for research in the general population. Appl Psychol Meas. 1977;1:385–401.
18. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry. 1978;133:429–435. [PubMed: 728692]
19. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychological Reports. 1962; 10:799–812.
20. 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;12(3):189–198. [PubMed: 1202204]
21. Spitzer RL, Gibbon M, Williams JBW, Endicott J. Global assessment of functioning (GAF) scale. In: Sederer LJ, Dickey B, eds. Outcome assessment in clinical practice. 1st ed. Williams & Wilkins, 1996.
22. Guy W 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.
23. Nivoli AM, Murru A, Pacchiarotti I, et al. Bipolar disorder in the elderly: a cohort study comparing older and younger patients. Acta Psychiatr Scand. 2014;130(5):364–373. [PubMed: 24702648]
24. Ahearn EP, Chen P, Hertzberg M, et al. Suicide attempts in veterans with bipolar disorder during treatment with lithium, divalproex, and atypical antipsychotics. J Affect Disord. 2013;145(1):77–82. [PubMed: 22871534]
25. Pfennig A, Alda M, Young T, et al. Prophylactic lithium treatment and cognitive performance in patients with a long history of bipolar illness: no simple answers in complex disease-treatment interplay. Int J Bipolar Disord. 2014 Dec 24; 2:1.
26. Puglisi-Allegra S, Ruggieri S, Fornai F. Translational evidence for lithium-induced brain plasticity and neuroprotection in the treatment of neuropsychiatric disorders. Transl Psychiatry. 2021 Jul 5;11(1):366. [PubMed: 34226487]
27. Burdick KE, Millett CE, Russo M, et al. The association between lithium use and neurocognitive performance in patients with bipolar disorder. Neuropsychopharmacology. 2020;45(10):1743–1749. [PubMed: 32349118]

28. Forlenza OV, Aprahamian I, de Paula VJ, Hajek T. Lithium, a Therapy for AD: Current Evidence from Clinical Trials of Neurodegenerative Disorders. Curr Alzheimer Res. 2016;13(8):879–886. [PubMed: 26892289]
29. Nunes PV, Forlenza OV, Gattaz WF. Lithium and risk for Alzheimer's disease in elderly patients with bipolar disorder. Br J Psychiatry. 2007;190:359–360. [PubMed: 17401045]
30. Forlenza OV, Radanovic M, Talib LL, Gattaz WF. Clinical and biological effects of long-term lithium treatment in older adults with amnestic mild cognitive impairment: randomised clinical trial. Br J Psychiatry. 2019;215(5):668–674. [PubMed: 30947755]
31. Chen S, Underwood BR, Jones PB, et al. Association between lithium use and the incidence of dementia and its subtypes: A retrospective cohort study. PLoS Med. 2022;19(3):e1003941. [PubMed: 35298477]
32. Burton C, Mathys M, Gutierrez E. Comparison of lithium to second generation antipsychotics for the treatment of bipolar disorder in older veterans. Psychiatry Research. 2021;303:114063. [PubMed: 34171570]
33. Bocchetta A, Cabras F, Pinna M, et al. An observational study of 110 elderly lithium-treated patients followed up for 6 years with particular reference to renal function. Int J Bipolar Disord. 2017 Dec;5(1):19. [PubMed: 28393327]
34. Rej S, Herrmann N, Gruneir A, et al. Association of lithium use and a higher serum concentration of lithium with the risk of declining renal function in older adults: a population-based cohort study. J Clin Psychiatry. 2020;81(5):19m13045.
35. Aprahamian I, Santos FS, dos Santos B, et al. Long-term, low-dose lithium treatment does not impair renal function in the elderly: a 2-year randomized, placebo-controlled trial followed by single-blind extension. J Clin Psychiatry. 2014;75(7):e672–8. [PubMed: 25093483]
36. Kemp DE, Sylvia LG, Calabrese JR, et al. General medical burden in bipolar disorder: findings from the LiTMUS comparative effectiveness trial. Acta Psychiatr Scand. 2014;129(1):24–34. [PubMed: 23465084]
37. Christensen DM, Mohr GH, Kessing LV, et al. Association of lithium use with rate of out-of-hospital cardiac arrest in patients with bipolar disorder. J Affect Disord Rep. 2021;5:100164.
38. Gomes-da-Costa S, Marx W, Corponi F, et al. Lithium therapy and weight change in people with bipolar disorder: A systematic review and meta-analysis. Neurosci Biobehav Rev. 2022;134:104266. [PubMed: 34265322]
39. Nestsiarovich A, Gaudiot CES, Baldessarini RJ, et al. Preventing new episodes of bipolar disorder in adults: Systematic review and meta-analysis of randomized controlled trials. Eur Neuropsychopharmacol. 2022;54:75–89. [PubMed: 34489127]
40. Vieta E, Angst J. Bipolar disorder cohort studies: Crucial, but underfunded. Eur Neuropsychopharmacol. 2021;47:31–33. [PubMed: 33895615]

Significant Outcomes:

- In a sample of 986 older adults with bipolar disorder (OABD), lithium use was associated with a more favourable clinical profile, compared to those treated with other drugs.
- Lithium users had lower levels of depressive symptoms, better global cognitive/functional state, fewer comorbid psychiatric and cardiovascular disorders, and less antipsychotic use.
- The present data do not support the notion that lithium use by OABD is necessarily associated with unacceptable risks and adverse outcomes.

Limitations:

- The interpretation of findings must take into account the methodological limitations related to the cross-sectional design and data harmonisation.
- The dataset we used had limited information about lifetime exposure to lithium; the present analysis was restricted to the availability of information about *current* lithium use.
- Non-inclusion of patients with more severe comorbid conditions in the lithium group, as well as the discontinuation of lithium treatment due to incident adverse events, could selectively and artefactually increase the rate of these conditions in the comparison group.

Table 1.

Descriptive summary of demographic and clinical variables in ‘Lithium’ and ‘Non-lithium’ groups.

	Lithium (N=406)		Non-lithium (N=580)	
	n	**Mean (SD) / %**	**n**	**Mean (SD) / %**
Age * (years)	406	64.7 (9.2)	580	62.3 (8.8)
Gender (% female)	406	57.6%	580	58.1%
Education (years)	315	12.7 (4.1)	445	12.9 (3.5)
Relationship status (% currently married)	321	47.8%	446	34.7%
Employment status (% currently working)	218	28.0%	365	22.5%
BD subtype[a] (% BD-I/BD-II)	367	73.0% / 27.0%	542	75.1% / 24.9%
Age of onset * (years)	330	33.1 (14.6)	430	30.1 (15.1)
Duration of BD (years)	355	31.5 (13.6)	511	32.5 (13.8)
Family history of mental illness * (% yes)	115	61.7%	198	73.7%
Ever hospitalised due to BD[a] (% yes)	300	76.3%	347	71.8%
Number of psychiatric hospitalisations[b]	269	3.0 (4.6)	319	3.7 (5.3)
Number of major affective episodes	312	13.6 (16.2)	374	15.3 (18.6)
History of rapid cycling * (% yes/probable)	236	10.6%	226	22.6%
YMRS score *	347	3.0 (5.1)	527	4.4 (5.5)
HAMD-17 score *	143	4.2 (4.2)	262	7.3 (5.6)
MADRS score	14	19.6 (9.4)	142	19.6 (9.2)
CES-D score *	158	11.1 (8.2)	98	15.3 (9.7)
HAMD harmonised * (score %)[c]	181	4.6 (5.0)	338	8.4 (7.3)
Currently depressed * (% yes)[d]	313	21.7%	490	52.0%
Suicidal thoughts[e]:				
HAMD-3	59	0.1 (0.3)	219	0.2 (0.6)
MADRS-10	42	0.5 (0.7)	245	0.6 (1.0)
BPRS-18 score	10	33.2 (10.2)	85	33.8 (7.3)
BPRS-24 score	3	36.7 (5.5)	25	42.3 (9.4)
BPRS harmonised (score %)[c]	16	26.2 (14.9)	111	33.4 (7.3)
Antipsychotic use * (% yes)	404	39.1%	576	51.9%
Psychiatric comorbidity:				
Anxiety disorder	17	9.6%	70	26.5%
Substance/alcohol use	15	8.5%	17	6.4%
Both	2	1.1%	9	3.4%
None	143	80.8%	168	63.6%
Somatic comorbidity:				
Cardiovascular *	383	38.9%	530	50.2%
Respiratory *	323	26.9%	497	41.2%

	Lithium (N=406)		Non-lithium (N=580)	
	n	**Mean (SD) / %**	**n**	**Mean (SD) / %**
Gastrointestinal *	244	20.5%	458	28.4%
Hepatic/pancreatic	244	6.1%	456	8.3%
Renal	200	4.5%	415	8.7%
Genitourinary *	191	12.6%	335	24.8%
Musculoskeletal	261	30.3%	475	47.4%
Endocrine	382	34.6%	533	36.8%
Cumulative somatic burden[f]	384	1.42 (1.48)	533	2.21 (1.84)
Body weight * (kg)	182	78.54 (17.9)	401	84.8 (21.7)
Smoking status * (% current or ever)	218	67.4%	322	78.0%
MMSE (total score)	213	27.8 (2.7)	225	27.5 (2.9)
GAF * (score)	136	66.3 (13.2)	301	60.1 (12.3)
CGI (score)	16	3.7 (1.4)	149	3.8 (1.1)

N: number of occurrences in the total sample and in Lithium/Non-lithium groups; Descriptive data presented as means and standard deviations (SD) or percentages of the number of occurrences for each variable of interest (n). BD: bipolar disorder; YMRS, Young Mania Rating Scale; HAMD: Hamilton Depression Rating Scale; MADRS: Montgomery-Asberg Depression Rating Scale; CES-D: Center for Epidemiologic Studies Depression scale; BPRS: Brief Psychiatric Rating Scale; MMSE: Mini-Mental State Examination; GAF: Global Assessment of Functioning; CGI: Clinical Global Impression.

[a] BD subtype not specified in 12.7% of the total sample

[b] Hospitalisations due to BD excluding substance use-related disorders

[c] Harmonised scores of depression (according to HAMD-17, HAMD-21 or HAMD-24) or psychiatric symptoms (BPRS-18 or BPRS-24) based on HAMD-17 or BPRS-18 scoring range, respectively

[d] Patients categorised as having ‘mild or moderate depression’ (n=310) or ‘severe depression’ (n=36) according to HAMD, MADRS or CES-D cut-off scores

[e] Mean scores relative to item 3 of HAMD (range 0–4) or item 10 of MADRS (range 0–6)

[f] Mean total number of domains (or systems) with reported somatic comorbidities.

* Statistically significant differences ($p<0.05$) comparing ‘Lithium’ vs. ‘Non-lithium’ groups (Pearson’s Chi-squared or Student’s t-tests).

Table 2.

Association between Li treatment and continuous variables, controlling for age and gender as fixed predictors and site as random intercept. (A) 'Lithium' regarded as an outcome variable; (B) 'Lithium' regarded as a predictor.

A	*Lithium*	*N*	*Missing*	*Mean*	*SD*	*95%CI*	*Model*	*LR*	*df*	*p-value*
Age (years)	No	580	0	62.3	8.8	61.6–63.0	GLMM	0.188	1	0.665
	Yes	406	0	64.7	9.2	63.8–65.6				
Education (years)	No	445	135	12.9	3.5	12.6–13.3	GLMM	3.870	1	**0.049**
	Yes	315	91	12.7	4.1	12.2–13.1				
Age of onset (years)	No	430	150	30.1	15.1	28.7–31.6	GLMM	0.03	1	0.854
	Yes	330	76	33.1	14.6	31.6–34.7				
Number of psychiatric hospitalisations[a]	No	319	261	3.7	5.3	3.1–4.3	GLMM	0.077	1	0.781
	Yes	269	137	3.0	4.6	2.5–3.7				
Illness duration (years)	No	511	69	32.5	13.8	31.3–33.7	GLMM	0.14	1	0.071
	Yes	355	51	31.5	13.6	30.0–32.9				
B	*Lithium*	*N*	*Missing*	*Mean*	*SD*	*95%CI*	*Model*	*LR/F* *	*df*	*p-value*
Number of affective episodes	No	374	206	15.3	18.6	13.6–17.4	LMM	0.579	1	0.447
	Yes	312	94	13.6	16.2	12.0–15.7				
MADRS [T]	No	142	438	19.6	9.2	18.1–21.1	LRG	0.006	1, 15	0.941
	Yes	14	392	19.6	9.4	14.8–24.3				
HAMD [H]	No	338	242	8.4	7.3	7.7–9.2	LMM	8.111	1	**0.004**
	Yes	181	225	4.6	5.0	3.9–5.4				
CES-D [T]	No	98	482	15.3	9.7	13.5–17.3	LRG	13.024	1, 25	**<0.001**
	Yes	158	248	11.1	8.2	10.0–12.5				
YMRS [T]	No	527	53	4.4	5.5	4.0–4.9	LMM	0.009	1	0.927
	Yes	347	59	3.0	5.1	2.5–3.6				
BPRS [H]	No	111	469	33.4	7.3	32.1–34.8	LMM	0.629	1	0.428
	Yes	16	390	26.2	14.9	18.6–32.8				
MMSE [T]	No	225	355	27.5	2.9	27.1–27.9	LMM	5.711	1	**0.017**
	Yes	213	193	27.8	2.7	27.4–28.1				
GAF [T]	No	301	279	60.1	12.0	58.7–61.4	LMM	7.284	1	**0.007**

CGI *[T]*	Yes	136	270	66.3	13.2	64.1–68.5	LRG	0.222	1, 16	0.638
	No	149	431	3.8	1.1	3.6–4.0				
	Yes	16	390	3.7	1.4	3.0–4.3				
Suicidal thoughts (HAMD)*[b]*	No	219	706	0.2	0.6	0.2–0.3	LMM	1.868	1	0.172
	Yes	59	414	0.1	0.3	0.0–0.2				
Suicidal thoughts (MADRS)*[c]*	No	245	680	0.6	1.0	0.5–0.7	LMM	0.105	1	0.746
	Yes	42	431	0.5	0.7	0.3–0.7				
Cumulative somatic burden*[d]*	No	533	47	2.2	1.8	2.1–2.4	LMM	3.019	1	0.082
	Yes	384	22	1.4	1.5	1.3–1.6				
Weight (kg)	No	401	179	84.8	21.7	82.8–87.0	LMM	0.014	1	0.906
	Yes	182	224	78.5	17.9	76.0–81.2				

GLMM, generalised linear mixed model for binomial family and logit link function; LMM, linear mixed model; LRG, linear regression; LR, likelihood ratio

*F-values relative to LRG (LR otherwise); df, degree of freedom

*[a]*Psychiatric hospitalisations excluding those due to substance use disorders

*[b]*Mean score relative to item 3 of HAMD (range 0–4)

*[c]*Mean score relative to item 10 of MADRS (range 0–6)

*[d]*Number of somatic domains with reported comorbidities

*[T]*Total score

*[H]*Harmonised score.

Acta Psychiatr Scand. Author manuscript; available in PMC 2023 November 01.

Table 3.

Association between Li treatment and categorical variables, controlling for age and gender as fixed predictors and site as random intercept. (A) 'Lithium' regarded as an outcome variable; (B) 'Lithium' regarded as a predictor.

A	*Level*	*Lithium N (%)*	*Non-lithium N (%)*	*Model*	*LR*	*df*	*p-value*
Gender	Female	331 (58.6)	234 (41.4)	GLMM [a]	0.346	1	0.556
	Male	249 (59.1)	172 (40.9)				
Diagnosis (BD subtype)	Bipolar 1	407 (60.3)	268 (39.7)	GLMM [a]	2.147	1	0.143
	Bipolar 2	135 (57.7)	99 (42.3)				
Family history of mental illness	No	52 (54.2)	44 (45.8)	GLMM [a]	4.622	1	**0.032**
	Yes	146 (67.3)	71 (32.7)				
Non-BD psychiatric diagnosis (current)	None	168 (54.0)	143 (46.0)	GLMM [a]	1.681	3	0.641
	Anxiety disorder	71 (80.7)	17 (19.3)				
	Substance/alcohol use disorder	17 (50.0)	17 (50.0)				
	Both	9 (81.8)	2 (18.2)				
Non-BD psychiatric diagnosis (lifetime)	None	146 (53.3)	128 (46.7)	GLMM [a]	8.890	3	**0.031**
	Anxiety disorder	103 (78.0)	29 (22.0)				
	Substance/alcohol use disorder	79 (64.8)	43 (35.3)				
	Both	85 (85.0)	15 (15.0)				
Psychiatric hospitalisations (ever) (excluding due to substance use disorders)	No	98 (58.0)	71 (42.0)	GLMM [a]	1.166	1	0.280
	Yes	249 (52.1)	229 (47.9)				
Hospitalisations due to substance use related disorders (ever)	No	78 (76.5)	24 (23.5)	GLMM [a]	0.588	1	0.443
	Yes	40 (87.0)	6 (13.0)				
B	*Level*	*Lithium N (%)*	*Non-lithium N (%)*	*Model*	*LR*	*df*	*p-value*
Occupation	Not working	283 (77.5)	157 (72.0)	GLMM [b]	1.594	1	0.207
	Working	82 (22.5)	61 (28.0)				
Relationship status	Single	292 (65.5)	169 (52.7)	GLMM [b]	2.542	1	0.214
	Married/common law	154 (34.5)	152 (47.4)				
Rapid cycling	No	175 (77.4)	211 (89.4)	GLMM [b]	4.303	1	**0.038**

	Yes	51 (22.6)	25 (10.6)			
	Equivalently asymptomatic	14 (3.6)	20 (12.9)			
Mixed symptoms	Equivalently symptomatic	159 (40.7)	61 (39.4)	GLMM [c]	4.851	3	0.183
	Mania > depression	113 (28.9)	28 (18.1)				
	Depression > mania	105 (26.9)	46 (29.7)				
	No depression	235 (48.0)	245 (78.3)				
Depression severity	Mild to moderate	232 (47.4)	59 (18.9)	GLMM [d]	17.590	1	**<0.001**
	Severe	23 (4.7)	9 (2.9)				
	Never	71 (22.1)	71 (32.6)				
Smoking	Lifetime	125 (38.8)	87 (39.9)	GLMM [d]	1.695	1	0.193
	Current	126 (39.1)	60 (27.5)				
Antipsychotic medication use	No	277 (48.1)	246 (60.9)	GLMM [b]	13.049	1	**<0.001**
	Yes	299 (51.9)	158 (39.1)				
Cardiovascular comorbidity	No	264 (49.8)	234 (61.1)	GLMM [b]	6.935	1	**0.008**
	Yes	266 (50.2)	149 (38.9)				
Respiratory comorbidity	No	292 (58.8)	236 (73.1)	GLMM [b]	0.706	1	0.401
	Yes	205 (41.3)	87 (26.9)				
Gastrointestinal comorbidity	No	328 (71.6)	194 (79.5)	GLMM [b]	0.321	1	0.571
	Yes	130 (28.4)	50 (20.5)				
Hepatic/pancreatic comorbidity	No	418 (91.7)	229 (93.9)	GLMM [b]	0.005	1	0.947
	Yes	38 (8.3)	15 (6.2)				
Renal comorbidity	No	379 (91.3)	191 (95.5)	GLMM [b]	2.652	1	0.103
	Yes	36 (8.7)	9 (4.5)				
Genitourinary comorbidity	No	252 (75.2)	167 (87.4)	GLMM [b]	1.058	1	0.304
	Yes	83 (24.8)	24 (12.6)				
Musculoskeletal comorbidity	No	250 (52.6)	182 (69.7)	GLMM [b]	0.194	1	0.660
	Yes	225 (47.4)	79 (30.3)				
Endocrine comorbidity	No	337 (63.2)	250 (65.5)	GLMM [b]	0.445	1	0.505
	Yes	196 (36.8)	132 (34.6)				

BD, bipolar disorder. GLMM, generalised linear mixed model with

[a] binomial family and logit link function

[b] binomial logit link

[c] multinomial logit link, or

[d] binomial cumulative logit; LR, likelihood ratio; df, degree of freedom.