Twenty-Three Years of Declining Lithium Use: Analysis of a Pharmacoepidemiological Dataset from German-Speaking Countries

Authors

Waldemar Greil[1, 2‡], Mateo de Bardeci[2, 3‡], Nadja Nievergelt[2], Sermin Toto[4], Renate Grohmann[1], Johanna Seifert[4], Georgios Schoretsanitis[3, 5, 6]

Affiliations

1 Department of Psychiatry and Psychotherapy, LMU University Hospital, LMU Munich, Germany
2 Psychiatric Private Hospital, Sanatorium Kilchberg, Zurich, Switzerland
3 Department of Psychiatry, Psychotherapy and Psychosomatics, Hospital of Psychiatry, University of Zurich, Zurich, Switzerland
4 Department of Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School, Hannover, Germany
5 The Zucker Hillside Hospital, Psychiatry Research, Northwell Health, Glen Oaks, New York, USA
6 Department of Psychiatry at the Donald and Barbara Zucker School of Medicine at Northwell/Hofstra, Hempstead, NY, USA

Keywords

lithium, pharmacoepidemiology, bipolar disorders, polypharmacy, psychopharmacology

received 13.03.2024
revised 26.06.2024
accepted 13.07.2024
published online 2024

Bibliography

Pharmacopsychiatry
DOI 10.1055/a-2374-2386
ISSN 0176-3679

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Correspondence

Waldemar Greil, MD
Psychiatric Department, Ludwig Maximilian University Munich
Nussbaumstr. 7
D-80331 Munich
Germany
waldemar.greil@med.uni-muenchen.de
waldemar.greil@gmx.de

Supplementary Material is available at https://doi.org/10.1055/a-2374-2386

ABSTRACT

Introduction Pharmacoepidemiological data suggest that lithium prescriptions for bipolar disorder are gradually decreasing, with less attention having been paid to other indications.

Methods We examined lithium prescriptions between 1994 and 2017 in data provided by the Drug Safety in Psychiatry Program AMSP, including psychiatric hospitals in Germany, Austria and Switzerland. We compared lithium use for different diagnoses before and after 2001 and in three periods (T1: 1994–2001, T2: 2002–2009, and T3: 2010–2017).

Results In a total of 158,384 adult inpatients (54 % female, mean age 47.4 ± 17.0 years), we observed a statistically significant decrease in lithium prescriptions between 1994–2000 and 2001–2017 in patients with schizophrenia spectrum disorder from 7.7 % to 5.1 % and in patients with affective disorders from 16.8 % to 9.6 %. Decreases in use were also observed for diagnostic subgroups: schizoaffective disorder (ICD-10 F25: 27.8 % to 17.4 %), bipolar disorder (F31: 41.3 % to 31 %), depressive episode (F32: 8.1 % to 3.4 %), recurrent depression (F33: 17.9 % to 7.5 %, all: $p < 0.001$) and emotionally unstable (borderline) personality disorder (6.3 % to 3.9 %, $p = 0.01$). The results in T1 vs. T2 vs. T3 were for F25: 26.7 % vs. 18.2 % vs. 16.2 %, F32: 7.7 % vs. 4.2 % vs. 2.7 %, F33: 17.2 % vs. 8.6 % vs. 6.6 % and for F31: 40.8 % vs. 31.7 % vs 30.0 %, i. e. there was no further decrease for lithium use in bipolar disorder after 2002. Lithium's main psychotropic co-medications were quetiapine (21.1 %), lorazepam (20.6 %), and olanzapine (15.2 %).

Discussion In inpatients, the use of lithium has decreased in patients with bipolar disorder and also with various other psychiatric diagnoses.

‡ equal contribution: Waldemar Greil, Mateo de Bardeci

Introduction

Lithium is a first-line mood stabilizer comprising the mainstay of maintenance treatment for bipolar disorders [1]. It is also frequently recommended as an augmentation strategy in patients with unipolar depression who have not responded to previous antidepressant treatments [2]. Although there is some experience in treating other diagnostic groups, such as schizophrenia spectrum disorder, with lithium [3], the evidence quality is low. Lithium is one of the very few drugs with suicide-preventive properties, making it crucial for patients with suicidal ideation [4, 5]. Long-term lithium treatment may benefit illness progression through inflammatory modulation [6] and neuroprotective effects [7].

Despite strong evidence for lithium's efficacy and its recommendation for affective disorders in various international guidelines, pharmacoepidemiological data from several countries indicate a consistent decline in lithium prescriptions [8, 9]. Reasons for this decline include concerns over adverse reactions, intensive blood monitoring requirements [10], a significant challenge especially in an outpatient setting, and the rising dominance of second-generation antipsychotic drugs (SGAs) in the treatment of bipolar and affective disorders during recent years [8] and of off-label prescriptions of antidepressant drugs [9].

Understanding the reasons behind the reduced lithium prescriptions is challenging, especially given the variation in decline rates across different treatment settings and patient subgroups. For instance, a population-based study showed an early decline in lithium prescriptions until 2006, followed by an increase in 2010 [11]. Similarly, in a large outpatient cohort over a 20-year period, Rhee and associates reported a drastic reduction in lithium prescriptions until 2012, with a subsequent increase by 3.4 % between 2013–2016 [8]. In other studies, lithium prescription remained stable after the first episode of bipolar disorder [12] and even showed a gradual increase over a 10-year period in Canada [13]. Most available data focus on bipolar disorder, with less attention on other diagnostic groups.

Our study aims to provide additional data on lithium use across various psychiatric disorders over a long period using a large pharmacoepidemiological dataset from three German-speaking countries. Unlike outpatient studies, where it is uncertain if the patients take their prescribed medication, our inpatient study reflects actual use, and the data represent the "real world".

Methods

We analyzed prescription data provided by the AMSP (German: Arzneimittelsicherheit in der Psychiatrie) program [14–16], an ongoing international multicenter drug safety project. AMSP collects data on psychotropic drug use as well as reports of adverse drug-induced reactions (ADRs) from psychiatric hospitals in Germany, Switzerland, and Austria, between 1994–2017. The number of participating hospitals steadily increased over time. After 2005, between 50 and 60 hospitals participated annually, including 30–40 from Germany. Data were collected cross-sectionally on two reference days per year, providing information on drug use, age, sex, and diagnoses of psychiatric inpatients, independent of treatment duration and prescription purpose. Detailed methods are described in previous publications (13, 14, 15). In this study, we used the primary diagnoses determined by hospital staff according to the ICD. Patients may have had additional diagnoses.

Statistical methods

To capture temporal trends for the use of lithium, we compared lithium use for different diagnoses and within different diagnostic groups based on the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) before versus after 2001 (1994–2000 versus 2001–2017) using a chi-squared test (χ^2). The year 2001 was chosen as a cutoff due to changes in ADR definitions in the AMSP project, although this is not relevant to our evaluations. An average of around 20 hospitals took part in the first period and around 50 hospitals in the second. We further divided the years 1994–2017 into three periods (T1: 1994–2001, T2: 2002–2009, T3: 2010–2017) and performed pairwise comparisons of lithium prescription percentages using $\chi 2$ tests. Additionally, we analyzed yearly prescriptions of antidepressants, antipsychotics, tranquilizers, hypnotics, lithium, and anticonvulsants, as well as yearly prescription patterns in patients with various psychiatric disorders (ICD-10: F0-F9). For time-trend analysis, we used linear regression to estimate the statistical significance of trends. All analyses were performed using R 4.2.2 with a significance level of at least 0.01.

Results

We investigated prescription patterns in 158,384 adult inpatients (54 % female, mean age 47.4 ± 17.0 years) treated with an average of 2.5 ± 1.3 drugs.

Lithium use in different psychiatric diagnostic groups

The results of the comparisons of lithium prescriptions in different psychiatric diagnostic groups are provided in ▶ **Table 1**.

Between 1994–2000 and 2001–2017, lithium prescriptions decreased significantly across various psychiatric disorders. For schizophrenia spectrum disorders (ICD-10 F2: F20–29), prescriptions fell from 7.7 % to 5.1 % ($p < 0.001$); for affective disorders (F3: F30–F39), from 16.8 % to 9.6 % ($p < 0.001$). In the other diagnostic groups, the differences were not significant or were based on very small numbers.

In three periods (T1: 1994–2001, T2: 2002–2009, T3: 2010–2017), we observed significant changes in F2 and F3 diagnoses. For F2, rates were 7.4 %, 5.3 %, and 4.7 %, respectively; for F3, they were 16.3 %, 10.6 %, and 8.6 % ($p < 0.01$ for all comparisons, see **Table S1a, supplementary material**).

Lithium use in different diagnostic subgroups of schizophrenia spectrum disorders (F2)

For schizoaffective disorders (ICD10 F25), lithium prescription rates dropped from 27.8 % to 17.4 % ($p < 0.001$, ▶ **Table 2**). The rates for F25 during T1, T2, and T3 were 26.7 %, 18.2 %, and 16.2 %, respectively. The decline for schizophrenia was also significant, from 3.5 % to 2.0 %, with rates of 3.8 %, 2.4 %, and 1.6 % over the three periods (see **Table S1b, supplementary material**).

▶ **Table 1** Lithium prescriptions in different psychiatric diagnostic groups compared between 1994–2000 vs. 2001–2017.

ICD-10	Prescriptions filled during 1994–2000			Prescriptions filled during 2001–2017			p-value
	Lithium-treated	Total	%	Lithium-treated	Total	%	
F0	24	1'650	1.45	79	8'501	0.93	0.07
F1	30	1'755	1.71	162	12'661	1.28	0.18
F2**	748	9'736	7.68	2'228	43'910	5.07	**<0.001**
F3**	1'209	7'211	16.77	4'976	52'009	9.57	**<0.001**
F4	28	1'586	1.77	130	9'197	1.41	0.34
F5**	5	44	11.36	9	537	1.68	**<0.001**
F6	53	1'113	4.76	244	6'672	3.66	0.10
F7	7	209	3.35	33	1'051	3.14	1.00
F8	1	27	3.70	3	181	1.66	1.00
F9*	4	33	12.12	8	296	2.70	**0.04**
Total**	2'109	23'364	9.03	7'872	135'015	5.83	**<0.001**

*statistical significance $p < 0.05$; **statistical significance $p < 0.001$. Comparing the two time periods, there was a decrease in F2 diagnoses from 41.7 % to 32.5 % and an increase in F3 diagnoses from 30.8 % to 38.4 % (F2: 9´736/23´364 vs 43´910/135´015; F3: 7211/23364 vs 52009/135´015). ICD-10: International Classification of Diseases. The ICD-10 diagnosis was missing for 5 patients ICD-10; F0: Organic, including symptomatic, mental disorders; F1: Mental and behavioural disorders due to psychoactive substance use; F2: Schizophrenia, schizotypal and delusional disorders; F3: Mood [affective] disorders; F4: Neurotic, stress-related and somatoform disorders; F5: Behavioral syndromes associated with physiological disturbances and physical factors; F6: Disorders of adult personality and behaviour; F7: Mental retardation F8: Disorders of psychological development; F9: Behavioural and emotional disorders with onset usually occurring in childhood and adolescence.

Lithium use in different diagnostic subgroups of affective disorders (F3)

For affective disorders, lithium prescriptions decreased in bipolar disorder (ICD-10 F31) from 41.3 % to 31.1 %, depressive episodes (ICD-10 F32) from 8.1 % to 3.4 %, and recurrent depressive disorder (ICD-10 F33) from 17.9 % to 7.5 % (all $p < 0.001$, ▶ **Table 3**). Over the three periods, rates for bipolar disorder were 40.8 %, 31.7 %, and 30.0 %; for depressive episodes, 7.7 %, 4.2 %, and 2.7 %; and for recurrent depression, 17.2 %, 8.6 %, and 6.6 %. That means, there was no essential change for bipolar disorder from 2002 onwards (see **Table S1c, supplementary material**).

Lithium use in different diagnostic subgroups of adult personality and behavior disorders

In personality disorders (ICD-10 F60), lithium prescriptions dropped statistically, not significantly, from 5.0 % to 3.6 % ($p = 0.04$, in ▶ **Table 4**). For borderline personality disorder (F60.3), rates decreased from 6.3 % to 3.9 % ($p = 0.01$). No significant differences were found across the three periods for F60 diagnoses (**table S1d**).

Yearly prescriptions of various drug groups: antidepressant and antipsychotic drugs, tranquilizers, hypnotics, lithium and anticonvulsants

From 1994 to 2017, lithium prescriptions decreased from 10.9 % to 5.4 %. Antidepressant prescriptions rose from 38.2 % to 57.6 %. Anticonvulsant prescriptions increased from 14.5 % to 25.7 % in 2007, then fell to 20.7 % in 2017 (▶ **Fig. 1**, **Table S2**).

To study the evolution of psychotropic prescriptions in our study population, we grouped the prescribed drugs into antidepressant drugs (ADD), antipsychotic drugs (APD), tranquilizing drugs (TRD), hypnotic drugs (HYPD), lithium (LI), and antiepileptic drugs (AEP). For each of these groups, we calculated the number of patients who received a prescription. The exact values for the figure can be found in the supplement material.

Combination of lithium with other drugs

The most common psychotropic drugs combined with lithium were quetiapine (21.1 %), lorazepam (20.6 %), and olanzapine (15.2 %, ▶ **Table 5**). Quetiapine, olanzapine, venlafaxine, and clozapine were more frequently prescribed with lithium than in the overall study population ($p < 0.01$).

Lithium prescriptions by most relevant diagnoses

Lithium prescriptions significantly decreased from 1994/1995 to 2016/2017 for schizoaffective disorders (F25) from 25.4 % to 15 %, bipolar disorder (F31) from 45.1 % to 29.9 %, depressive episodes (F32) from 13.9 % to 2.9 %, and recurrent depression (F33) from 22.0 % to 6.1 % (▶ **Fig. 2**, **Table S3**). Relative reductions were 34 % for F31, 38 % for F25, 79 % for F32, and 72 % for F33. Detailed information is in the supplement (**table S3**).

This figure shows the evolution of the percentage of patients prescribed lithium for the clinically most relevant diagnoses. We aggregated the prescriptions for two consecutive years and performed a linear regression. The slope of the regression of the four diagnoses yielded statistically significant results ($p < 0.01$; Coeff (f): F25: − 0.6 (39), F31: − 0.7 (36), F32:-0.4 (35), F33: − 0.8 (70)).

Discussion

Our large-scale data provide valuable insights into inpatient lithium prescription patterns over more than 20 years. Consistent with previous cohorts of patients with bipolar disorders [8, 17, 18], we found a gradual decline in lithium use. This trend may be due to the emergence of newer antipsychotic drugs, especially SGAs (which

▶ **Table 2** Lithium prescriptions in different diagnostic groups with schizophrenia spectrum disorders compared between 1994–2000 vs. 2001–2017.

ICD-10	Prescriptions filled during 1994–2000			Prescriptions filled during 2001–2017			p-value
	Lithium-treated	Total	%	Lithium-treated	Total	%	
F20**	256	7'431	3.45	639	31'366	2.04	**<0.001**
F21	3	40	7.50	2	165	1.21	0.10
F22	5	307	1.63	15	1'359	1.10	0.64
F23	5	219	2.28	25	1'912	1.31	0.40
F24	0	5	0.00	0	33	0.00	NA
F25**	478	1'719	27.81	1'535	8'847	17.35	**<0.001**
F28	1	5	20.00	6	51	11.76	1.00

**statistical significance p<0.001. ICD-10: International Classification of Diseases; NA: not applicable; F2: Schizophrenia, schizotypal and delusional disorders; F20: Schizophrenia; F21: Schizotypal disorder; F22: Persistent delusional disorders; F23: Acute and transient psychotic disorders; F24: Induced delusional disorders; F25: Schizoaffective disorders; F28: Other nonorganic psychotic disorders.

▶ **Table 3** Lithium prescriptions in different diagnostic groups with affective disorders compared between 1994–2000 vs. 2001–2017.

ICD-10	Prescriptions filled during 1994–2000			Prescriptions filled during 2001–2017			p-value
	Lithium-treated	Total	%	Lithium-treated	Total	%	
F30	173	805	21.49	88	421	20.90	0.90
F31**	414	1'002	41.32	2'392	7'703	31.05	**<0.001**
F32**	245	3'041	8.06	646	18'995	3.40	**<0.001**
F33**	351	1'959	17.92	1'833	24'565	7.46	**<0.001**
F34	26	385	6.75	13	268	4.85	0.43
F38	0	6	0.00	4	30	13.33	0.88
F39	0	13	0.00	0	27	0.00	-

**statistical significance p<0.001; ICD-10: International Classification of Diseases; NA: not applicable; F3: Mood [affective] disorders; F30: Manic episode; F31: Bipolar affective disorder; F32: Depressive episode; F33: Recurrent depressive disorder; F34: Persistent mood [affective] disorders; F38: Other mood [affective] disorders; F39: Unspecified mood [affective] disorder.

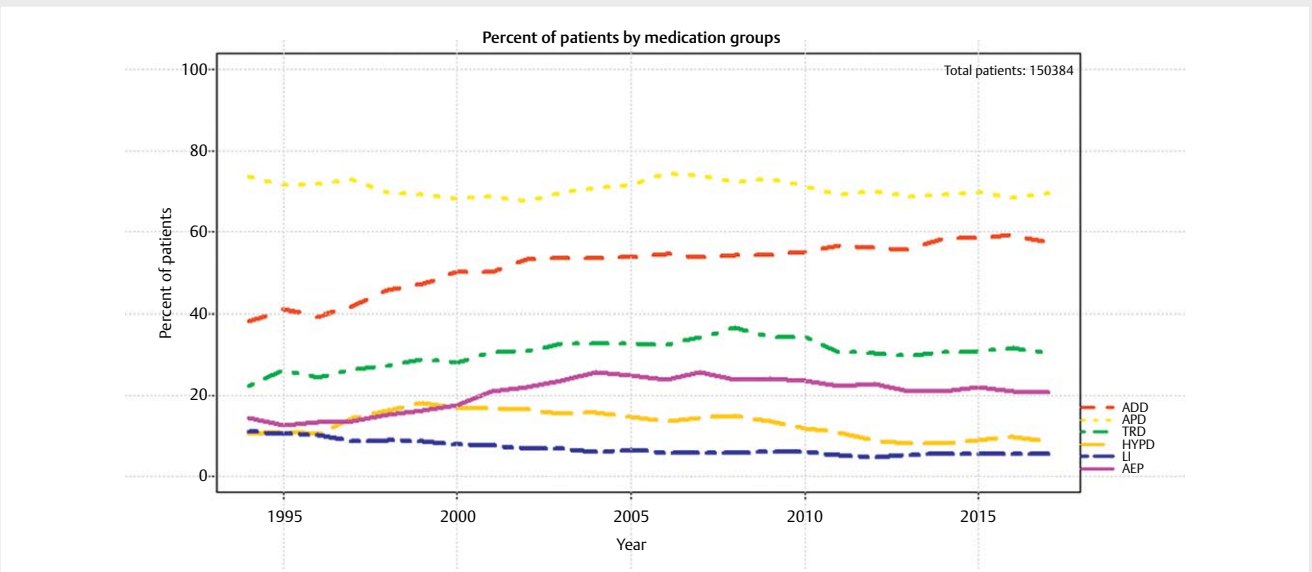
▶ **Table 4** Lithium prescriptions in different diagnostic groups with disorders of adult personality and behaviour compared between 1994–2000 vs. 2001–2017.

ICD-10	Prescriptions filled during 1994–2000			Prescriptions filled during 2000–2017			p-value
	Lithium-treated	Total	%	Lithium-treated	Total	%	
F60*	52	1'039	5.00	204	5'736	3.56	**0.04**
F61	1	45	2.22	32	663	4.83	0.69
F62	0	6	0.00	3	60	5.00	1.00
F63	0	11	0.00	5	124	4.03	1.00

statistical significance p<0.05. ICD-10: International Classification of Diseases; F6: Disorders of adult personality and behaviour; F60: Specific personality disorders; F61: Mixed and other personality disorders; F62: Enduring personality changes, not attributable to brain damage and disease; F68: Other disorders of adult personality and behaviour; F69: Unspecified disorder of adult personality and behaviour; Note: F60.3: Emotionally unstable personality disorder, decrease from 6.3 % (n = 37) between 1994–2000 to 3.9 % (n = 186) between 2001–2017 (p = 0.01). F60: Specific personality disorders; F60.0: Paranoid personality disorder; F60.1: Schizoid personality disorder; F60.2: Dissocial personality disorder; F60.3: Emotionally unstable personality disorder; F60.4: Histrionic personality disorder; F60.5: Anankastic personality disorder; F60.6: Anxious [avoidant] personality disorder; F60.7: Dependent personality disorder; F60.8: Other specific personality disorders.

replace lithium), safety concerns [19], and burdensome laboratory monitoring [20]. Consequently, clinicians must be trained to manage lithium-related safety concerns in order to adhere to current treatment guidelines [1, 20]. Predicting future trends in lithium use remains challenging, as its decline has stabilized in some cohorts [8, 11, 13].

Our analysis extends previous findings by showing a decrease in lithium use not only in bipolar disorder but also in schizophrenia spectrum disorders, such as schizoaffective disorder. Despite guidelines not strongly recommending lithium for schizophrenia spectrum disorders, large studies suggest it may reduce hospitalization risk due to psychosis [21]. The high rates of lithium use in schizoaffective disorders, ranging from 27 % at the beginning of the study to 16 % in recent years, should be emphasized. The guidelines emphasize the importance of SGAs in the treatment of the disorder [1], but studies have shown that lithium is effective for the long-term treatment of schizoaffective disorders [22, 27]. Lithium use also dropped in patients with borderline personality disorders, whereas it has remained stable in other countries [23]. A previous study with data from the AMSP project showed that psychotropic



▶ **Fig. 1** Lithium prescriptions from 1994 to 2017 for various groups of psychotropic drugs. Legend: To study the evolution of psychotropic prescriptions in our study population, we grouped the prescribed drugs into antidepressant drugs (ADD), antipsychotic drugs (APD), tranquilizing drugs (TRD), hypnotic drugs (HYPD), lithium (LI), and antiepileptic drugs (AEP). For each of these groups, we calculated the number of patients who received a prescription. The exact values for the figure can be found in the supplement material (**Table S3**).

drugs are very frequently used in hospitalized patients with borderline personality disorder, even though they are not recommended in guidelines [14].

The very pronounced decline in the prescription of lithium over time in the treatment of depressive episodes may indicate that augmentation therapy with lithium in treatment-resistant depression is increasingly being replaced by augmentation with alternative drugs, especially SGAs. Lithium is effective in the long-term treatment of recurrent unipolar depression [24, 25], although lithium also appears to be increasingly replaced by other options, predominantly antidepressant drugs. In schizoaffective disorders, first-line treatment includes antipsychotic drugs and not lithium and anticonvulsants [26]. Thus, the declining prescription found in the present study is consistent with the current state of the art [1, 27]. On the other hand, the large decline of 37 % with respect to prescriptions of lithium in patients with bipolar disorder (which is the main indication for lithium) is worrisome. As our prescription data refer to inpatients, we are concerned that the phenomenon of the declining prescription of lithium may be even more pronounced within the outpatient setting. However, we found no further decrease in lithium prescriptions in bipolar disorder in the last two periods, T2 versus T3, from 31.7 % to 30 % (not significant), i. e., from 2002 onwards. This is in agreement with a new paper published while the present manuscript was being written [28], reporting no change in bipolar disorder from 2014 onwards, in about 30 % of the patients.

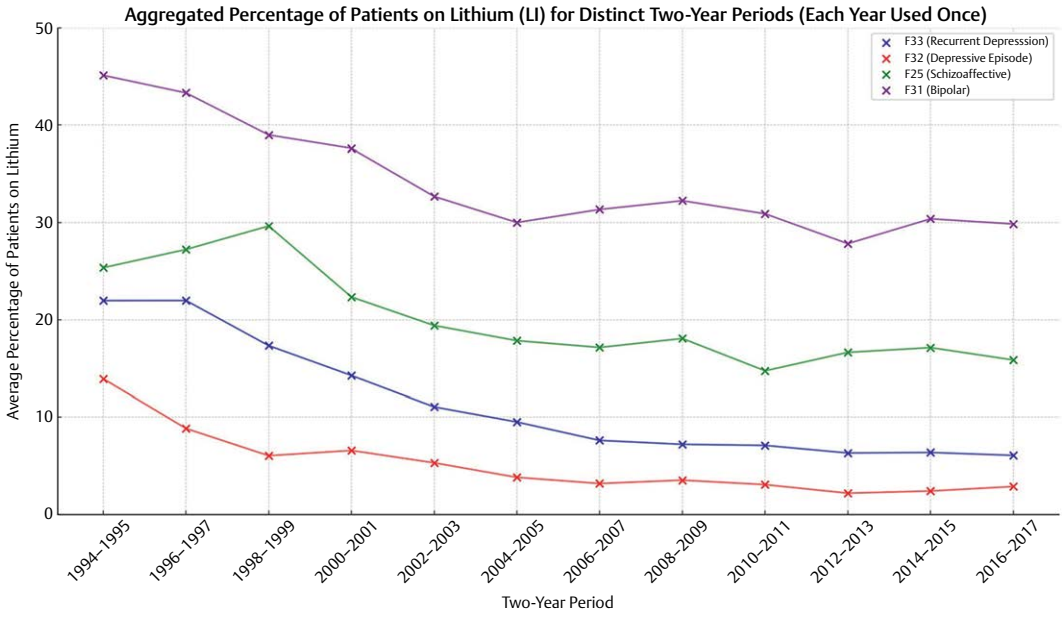
When analyzing the temporal course of the different groups of drugs, the increase and then the decrease in prescriptions of anticonvulsants over time is particularly noticeable. It implies that this group of drugs may have experienced a short-lived hype in the treatment of psychiatric disorders until the year 2007, subsequently overshadowed by newer antipsychotics. The distinct increase in antidepressant prescriptions is in line with an official German drug prescription report [29].

▶ **Table 5** Combination with lithium. N with Lithium, then percent within Lithium, N total, Percent within total. (N_LI = 9940, N_tot = 158'384). Psychotropic Medications (Top 10 in regard of N (with LI)).

Medication	N (with LI)	Percent (in LI)	N (total)	Perc (of total)
Quetiapine*	2096	21.1	27032	16.3
Lorazepam	2052	20.6	30042	18.1
Olanzapine*	1513	15.2	20232	12.2
Venlafaxine*	1361	13.7	15454	9.3
Mirtazapine	1172	11.8	21205	12.8
Valproic Acid	1050	10.6	14116	8.5
Clozapine*	977	9.8	12267	7.4
Diazepam	894	9.0	11837	7.1
Risperidone	889	8.9	18601	11.2
Biperiden	674	6.8	10155	6.1

*Medications statistically overrepresented in combination with Lithium ($p < 0.01$).

Our findings need to be considered in light of some limitations. First, the lack of data regarding clinical response to pharmacotherapy and adverse drug reactions may hamper conclusions on effectiveness and tolerability. Second, we only reported prescription rates in hospitalized patients, and it may be difficult to extrapolate these findings to outpatient treatment settings. In fact, patients treated as inpatients may suffer from more severe symptoms and/or comorbidities [30]. Third, as diagnoses were extracted from the medical records, including chart reviews, they may be less reliable compared to structured interviews. Fourth, although we know the



▶ **Fig. 2** Lithium prescriptions from 1994 to 2017 for various diagnoses: F25, F31, F32, F33. Legend:This figure shows the evolution of the percentage of patients prescribed lithium for the clinically most relevant diagnoses. We aggregated the prescriptions for two consecutive years and performed a linear regression. The slope of the regression of the four diagnoses yielded statistically significant results ($p<0.01$; Coeff (f): F25: −0.6 (39) , F31: −0.7 (36), F32: −0.4 (35), F33: −0.8 (70)).

diagnoses, we do not know the exact indication for the prescription of lithium, such as to alleviate acute symptoms, to augment existing medication, or for prophylaxis. We only use the main diagnoses; the use of lithium could also be indicated by comorbidity. In addition to the large data set, a further strength of the study is that prescriptions correspond to the actual use of the medication, as the data is based on inpatients.

Conclusions

Our analysis provides a comprehensive review of lithium prescriptions over nearly 25 years across hospitals in Germany, Austria, and Switzerland. We observed a concerning decrease in lithium prescriptions for bipolar disorder, but also for other psychiatric illnesses, including schizoaffective psychosis, depressive episodes, and recurrent depression. This trend underscores the need for clinician training on lithium use. Further studies should compare the efficacy of lithium and alternative drugs, such as SGAs, and of combinations with lithium in schizoaffective disorder, bipolar disorder, and unipolar depression augmentation. This could clarify whether current prescribing practices are justified by clinical experience.

Ethics approval and consent to participate

Assessments based on the AMSP database have been approved by the Ethics Committee of the University of Munich and the Ethics Committee of the Hannover Medical School (Nr. 8100_BO_S_2018). This study adheres to the Declaration of Helsinki and its later amendments. The AMSP program is a continuous observational post-marketing drug surveillance program and does not interfere with the ongoing clinical treatment of the patients under surveillance (see Methods: Data source).

Availability of data and materials

The datasets used and/or analyszed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

W.G. and G. Sch. initiated the study. G. Sch., W.G. and M.deB. wrote the main manuscript. M.deB. conducted the statistical analyses and prepared figures and tables. N.N. undertook the literature research. J.S., S.T. and R.G. gave suggestions for improving various versions of the manuscript. All authors proofread the definite manuscript and reviewed and accepted the final version.

Acknowledgement

The authors would like to thank all psychiatric hospitals participating in the AMSP project, in particular the drug monitors, for their continuous support in data collection.

Conflict of Interest

Competing interests S. Toto is the project manager of the AMSP program and a member of the advisory board for Otsuka and Janssen-Cilag and has received speaker's honoraria from Janssen-Cilag, Lundbeck/Otsuka, Recordati Pharma GmbH, ROVI, and Servier. G. Schoretsanitis has served as a consultant for Dexcel Pharma, HLS Therapeutics, Saladax and Thermo Fisher and has received speaker's fees from HLS Therapeutics and Saladax. M. de Bardeci is Co-Founder and member of the board of directors of the company DeepPsy AG. All other authors state they have no conflicts of interest to declare.

Role of the funding source

The authors did not receive any specific grants or funding for the present study. The AMSP drug safety program is facilitated by nonprofit associations in Germany, Austria and Switzerland. The AMSP program has been supported with unrestricted educational and research grants since 1993 by the following companies: Austrian companies: Astra Zeneca Österreich GmbH, Boehringer Ingelheim Austria, Bristol-Myers Squibb GmbH, CSC Pharmaceuticals GmbH, Eli Lilly GmbH, Germania Pharma GmbH, GlaxoSmithKline Pharma GmbH, Janssen-Cilag Pharma GmbH, Lundbeck GmbH, Novartis Pharma GmbH, Pfizer Med Inform and Wyeth Lederle Pharma GmbH; German companies: Abbott GmbH & Co. KG, Aristo Pharma, AstraZeneca GmbH, Aventis Pharma Deutschland GmbH GE–O/R/N, Bayer Vital GmbH, Boehringer Mannheim GmbH, Bristol-Myers-Squibb, Ciba Geigy GmbH, Desitin Arzneimittel GmbH, Duphar Pharma GmbH & Co. KG, Eisai GmbH, Esparma GmbH Arzneimittel, GlaxoSmithKline Pharma GmbH & Co. KG, Hoffmann-La Roche AG Medical Affairs, Janssen-Cilag GmbH, Janssen Research Foundation, Knoll Deutschland GmbH, Lilly Deutschland GmbH Niederlassung Bad Homburg, Lundbeck GmbH & Co. KG, Novartis Pharma GmbH, Nordmark Arzneimittel GmbH, Organon GmbH, Otsuka-Pharma Frankfurt, Pfizer GmbH, Pharmacia & Upjohn GmbH, Promonta Lundbeck Arzneimittel, Recordati Pharma GmbH, Rhone-Poulenc Rohrer, ROVI, Sanofi-Synthelabo GmbH, Sanofi-Aventis Deutschland, Schering AG, Smith-KlineBeecham Pharma GmbH, Solvay Arzneimittel GmbH, Synthelabo Arzneimittel GmbH, Dr. Wilmar Schwabe GmbH & Co., Thiemann Arzneimittel GmbH, Troponwerke GmbH & Co. KG, Upjohn GmbH, Wander Pharma GmbH and Wyeth-Pharma GmbH; Swiss companies: AHP (Schweiz) AG, AstraZeneca AG, Bristol-Myers Squibb AG, Desitin Pharma GmbH, Eli Lilly (Suisse) S.A., Essex Chemie AG, GlaxoSmith-Kline AG, Janssen-Cilag AG, Lundbeck (Suisse) AG, Organon AG, Pfizer AG, Pharmacia, Sanofi-Aventis (Suisse) S.A., Sanofi-Synthelabo SA, Servier SA, SmithKlineBeecham AG, Solvay Pharma AG, Wyeth AHP (Suisse) AG and Wyeth Pharmaceuticals AG.

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: 97–170

[2] Ercis M, Ozerdem A, Singh B. When and how to use lithium augmentation for treating major depressive disorder. J Clin Psychiatry 2023; 84: 23ac14813

[3] Leucht S, Helfer B, Dold M et al. Lithium for schizophrenia. Cochrane Database Syst Rev 2015; 2015: CD003834

[4] Antolin-Concha D, Lahteenvuo M, Vattulainen P et al. Suicide mortality and use of psychotropic drugs in patients hospitalized due to bipolar disorder: A Finnish nationwide cohort study. J Affect Disord 2020; 277: 885–892

[5] Lewitzka U, Severus E, Bauer R et al. The suicide prevention effect of lithium: More than 20 years of evidence-a narrative review. Int J Bipolar Disord 2015; 3: 32

[6] Queissner R, Lenger M, Birner A et al. The association between anti-inflammatory effects of long-term lithium treatment and illness course in Bipolar Disorder. J Affect Disord 2020; 281: 228–234

[7] Forlenza OV, Diniz BS, Radanovic M et al. Disease-modifying properties of long-term lithium treatment for amnestic mild cognitive impairment: Randomised controlled trial. Br J Psychiatry 2011; 198: 351–356

[8] Rhee TG, Olfson M, Nierenberg AA et al. 20-Year Trends in the pharmacologic treatment of bipolar disorder by psychiatrists in outpatient care settings. Am J Psychiatry 2020; 177: 706–715

[9] Kessing LV, Vradi E, Andersen PK. Nationwide and population-based prescription patterns in bipolar disorder. Bipolar Disord 2016; 18: 174–182

[10] Mandal S, Mamidipalli SS, Mukherjee B et al. Perspectives, attitude, and practice of lithium prescription among psychiatrists in India. Indian J Psychiatry 2019; 61: 451–456

[11] Parabiaghi A, Barbato A, Risso P et al. Lithium use from 2000 to 2010 in Italy: A population-based study. Pharmacopsychiatry 2015; 48: 89–94

[12] Poranen J, Koistinaho A, Tanskanen A et al. Twenty-year medication use trends in first-episode bipolar disorder. Acta Psychiatr Scand 2022; 146: 583–593

[13] Shafiq S, Ronksley PE, Scory TD et al. Ten-year trends in lithium prescribing in Alberta, Canada. Can J Psychiatry 2023; 69: 13–20. DOI: 10.1177/07067437231176905

[14] Bridler R, Haberle A, Muller ST et al. Psychopharmacological treatment of 2195 in-patients with borderline personality disorder: A comparison with other psychiatric disorders. Eur Neuropsychopharmacol 2015; 25: 763–772

[15] Glocker C, Grohmann R, Burkhardt G et al. Antipsychotic drug-induced neutropenia: Results from the AMSP drug surveillance program between 1993 and 2016. J Neural Transm (Vienna) 2023; 130: 153–163

[16] Seifert J, Maier HB, Fuhrmann F et al. Pharmacological treatment of major depressive disorder according to severity in psychiatric inpatients: Results from the AMSP pharmacovigilance program from 2001-2017. J Neural Transm (Vienna) 2022; 129: 925–944

[17] 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: 415–421

[18] Lin CH, Chan HY, Chen CC et al. Prescribing changes for bipolar patients discharged from two public psychiatric hospitals in Taiwan, 2006-2019. J Affect Disord 2022; 318: 386–392

[19] Greil W, de Bardeci M, Muller-Oerlinghausen B et al. Controversies regarding lithium-associated weight gain: Case-control study of real-world drug safety data. Int J Bipolar Disord 2023; 11: 34

[20] Malhi GS, Bell E, Jadidi M et al. Countering the declining use of lithium therapy: A call to arms. Int J Bipolar Disord 2023; 11: 30

[21] Puranen A, Koponen M, Lahteenvuo M et al. Real-world effectiveness of mood stabilizer use in schizophrenia. Acta Psychiatr Scand 2023; 147: 257–266

[22] Baethge C, Gruschka P, Berghofer A et al. Prophylaxis of schizoaffective disorder with lithium or carbamazepine: Outcome after long-term follow-up. J Affect Disord 2004; 79: 43–50

[23] Martin-Blanco A, Ancochea A, Soler J et al. Changes over the last 15 years in the psychopharmacological management of persons with borderline personality disorder. Acta Psychiatr Scand 2017; 136: 323–331

[24] Greil W, Ludwig-Mayerhofer W, Erazo N et al. Comparative efficacy of lithium and amitriptyline in the maintenance treatment of recurrent unipolar depression: A randomised study. J Affect Disord 1996; 40: 179–190

[25] Coppen A, Abou-Saleh MT. Lithium in the prophylaxis of unipolar depression: A review. J R Soc Med 1983; 76: 297–301

[26] Barnes TR, Drake R, Paton C et al. Evidence-based guidelines for the pharmacological treatment of schizophrenia: Updated recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2020; 34: 3–78

[27] Greil W, Ludwig-Mayerhofer W, Erazo N et al. Lithium vs carbamazepine in the maintenance treatment of schizoaffective disorder: A randomised study. Eur Arch Psychiatry Clin Neurosci 1997; 247: 42–50

[28] Kriner P, Severus E, Korbmacher J et al. Lithium prescription trends in psychiatric inpatient care 2014 to 2021: Data from a Bavarian drug surveillance project. Int J Bipolar Disord 2023; 11: 40

[29] Lohse MJ, Müller-Oerlinhausen B. Psychopharmaka. In: Schwabe U, Paffrath D, Ludwig WD, Klauber J eds, Arzneiverordnungs-Report 2018. Berlin: Springer; 2018: 733–762

[30] Tokumitsu K, Yasui-Furukori N, Adachi N et al. Predictors of psychiatric hospitalization among outpatients with bipolar disorder in the real-world clinical setting. Front Psychiatry 2023; 14: 1078045