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ORIGINAL ARTICLE

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Comprehensive comparison of monotherapies for psychiatric hospitalization risk in bipolar disorders

Anastasiya Nestsiarovich[1] | Aurélien J Mazurie[2] | Nathaniel G Hurwitz[3] | Berit Kerner[4,5] | Stuart J Nelson[6,7] | Annette S Crisanti[8] | Mauricio Tohen[8] | Ronald L Krall[9] | Douglas J Perkins[1] | Christophe G Lambert[1,7]

[1]Center for Global Health, Department of Internal Medicine, University of New Mexico Health Sciences Center, Albuquerque, NM, USA

[2]TwoFoldChange Consulting, Bozeman, MT, USA

[3]New Mexico Behavioral Health Institute, Las Vegas, NM, USA

[4]Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine, University of California, Los Angeles, CA, USA

[5]Witten/Herdecke University, Witten, Germany

[6]University of New Mexico Health Sciences Library and Informatics Center, Albuquerque, NM, USA

[7]Division of Translational Informatics, Department of Internal Medicine, University of New Mexico Health Sciences Center, Albuquerque, NM, USA

[8]Department of Psychiatry & Behavioral Sciences, University of New Mexico Health Sciences Center, Albuquerque, NM, USA

[9]University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Correspondence
Christophe G. Lambert, Department of Internal Medicine, Center for Global Health and Division of Translational Informatics, University of New Mexico Health Sciences Center, MSC10-5550, 915 Camino de Salud NE, Albuquerque, NM 87131, USA.
Email: cglambert@unm.edu

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Objectives: This study compared 29 drugs for risk of psychiatric hospitalization in bipolar disorders, addressing the evidence gap on the >50 drugs used by US patients for treatment.

Methods: The Truven Health Analytics MarketScan® database was used to identify 190 894 individuals with bipolar or schizoaffective disorder who filled a prescription for one of 29 drugs of interest: lithium, first- or second-generation antipsychotics, mood-stabilizing anticonvulsants, and antidepressants. Competing risks regression survival analysis was used to compare drugs for risk of psychiatric hospitalization, adjusting for patient age, sex, comorbidities, and pretreatment medications. Other competing risks were ending monotherapy and non-psychiatric hospitalization.

Results: Three drugs were associated with significantly lower risk of psychiatric hospitalization than lithium: valproate (relative risk [RR] = 0.80, $P = 3.20 \times 10^{-4}$), aripiprazole (RR = 0.80, $P = 3.50 \times 10^{-4}$), and bupropion (RR = 0.80, $P = 2.80 \times 10^{-4}$). Eight drugs were associated with significantly higher risk of psychiatric hospitalization: haloperidol (RR = 1.57, $P = 9.40 \times 10^{-4}$), clozapine (RR = 1.52, $P = .017$), fluoxetine (RR = 1.17, $P = 3.70 \times 10^{-3}$), sertraline (RR = 1.17, $P = 3.20 \times 10^{-3}$), citalopram (RR = 1.14, $P = .013$), duloxetine (RR = 1.24, $P = 5.10 \times 10^{-4}$), venlafaxine (RR = 1.33; $P = 1.00 \times 10^{-6}$), and ziprasidone (RR = 1.25; $P = 6.20 \times 10^{-3}$).

Conclusions: This largest reported retrospective observational study on bipolar disorders pharmacotherapy to date demonstrates that the majority of patients end monotherapy within 2 months after treatment start. The risk of psychiatric hospitalization varied almost two-fold across individual medications. The data add to the evidence favoring lithium and mood stabilizer use in short-term bipolar disorder management. The findings that the dopaminergic drugs aripiprazole and bupropion had better outcomes than other members of their respective classes and that antidepressant outcomes may vary by baseline mood polarity merit further investigation.

KEYWORDS
bipolar disorder, comparative effectiveness, competing risks, drug, hospitalization, schizoaffective

1 | INTRODUCTION

Hospitalization in bipolar disorder (BD) is a high-incidence outcome of great clinical and socioeconomic importance.[1] Hospital admission due to a severe mood episode occurs in 17%-40% of patients within the first year following BD acute phase treatment,[2] in 50% of patients within 4 years,[3] and in 79% of patients within 15 years.[4] The evidence on drug-dependent risk of hospitalization in BD is incomplete and contradictory. The majority of published comparative effectiveness studies of BD drugs have focused on symptom reduction and rates of remission achievement, relapses and recurrences, rather than on psychiatric hospitalization.[5] Comparison is usually made for just a few agents (e.g. lithium, valproate, lamotrigine, quetiapine, imipramine and olanzapine), with relatively scarce data on other medications.[6] Sample sizes have been <36 000 cases, and often studies have been restricted to only outpatient visits with BD type I diagnosis.

This study on BD monotherapies compared 29 drugs from different pharmacological groups, had a sample size of 190 894 cases, and included both inpatient and outpatient adults with BD type I/II/not otherwise specified, as well as schizoaffective disorder (SCAD) to account for lack of clinical distinction between the two diseases. Moreover, this study used competing risks regression to distinguish between psychiatric and non-psychiatric hospitalization outcomes, as well as drug switching/ending to better verify that patients were consistently on therapy, versus an "intent-to-treat" model.

Being the first in a series of observational studies on a large population of insured US individuals with BD, this study specifically focused on monotherapies, while subsequent analyses are planned to address more complex treatment regimens. The choice of the outcome of interest indicative of BD treatment response was partially driven by the challenges of administrative claims data analysis such as lack of data granularity to assess residual symptoms and cognitive impairment, and inability to distinguish between outpatient relapse management and maintenance therapy. We consider psychiatric hospitalization as a robust indicator of BD relapse, which is presumably associated with subjectively unbearable psychiatric complaints and/or prominent social dysfunction requiring monitored pharmaceutical intervention and observation.

2 | PATIENTS AND METHODS

This retrospective observational study utilized the Truven Health Analytics MarketScan® administrative claims database on 1.3 million commercially insured US patients with BD spanning the years 2003-2015.[7] The data contain records of visits, diagnoses, procedures, outpatient prescription fills, laboratory test orders (but not results), and patient age, sex, and state of residence. The study protocol was approved by the University of New Mexico Human Research Review Committee (Institutional Review Board number 16-243). Data were transformed to the Observational Medical Outcomes Partnership (OMOP) common data model version 5.0.1,[8] using the OHDSI ETL-CDM Builder tool (https://github.com/OHDSI/ETL-CDMBuilder). Data were retrieved using custom PostgreSQL queries, and analyzed for 190 894 adults (age 18-64 years) in both outpatient (n = 171 434) and inpatient (n = 19 460) settings who had two or more ICD-9-CM/ICD-10-CM diagnostic codes for BD (296.[0-1]*, 296.[4-8]*, F30* and F31*) or SCAD (295.7* and F25*) during the observation period 2003-2015, and were newly given one of 29 drugs of interest, including lithium, mood-stabilizing anticonvulsants (MSAs), first-generation antipsychotics (FGAs), second-generation antipsychotics (SGAs), and antidepressants (ADs) (Supporting Information Table S1). Each drug of interest had at least 250 observations that met study design criteria. Patients diagnosed with schizophrenia, chronic delusional disorders, intellectual disabilities, autism-spectrum disorders, organic mental disorders, and Parkinson's disease prior to or on the date of treatment start were excluded from the sample, as well as those given anti-dementia drugs (cholinesterase inhibitors and memantine) (Supporting Information Table S2). The onset of excluded conditions/drugs after treatment initiation was considered as a censoring event in the competing risks regression.

The following sequence of events (Figure 1) was a necessary condition to include a patient in the analysis: (i) a 12-month "washout" period with no drugs of interest and no hospitalization/emergency room (ER) visit with primary psychiatric code; (ii) an outpatient (cohort A) or inpatient (cohort B) mood episode meta-visit ("index visit") defined as a consecutive sequence of visits, at least one of which had a primary psychiatric diagnosis and non-remission code for BD, SCAD or major depressive disorder (MDD); (iii) the filled prescription of the drug of interest ("index fill") defined as the prescription filled on or before the 4th day after visit/discharge; and (iv) a competing risk event: hospitalization/ER meta-visit with psychiatric code, hospitalization/ER meta-visit without psychiatric code, ending monotherapy (adding/switching to a new drug of interest or stopping therapy), or right censoring. Stopping therapy of interest was defined as a ≥ 30-day gap between the expected date of drug supply ending and subsequent refill. Right censoring events included death, end of data, or onset of excluded conditions. Note that the index meta-visit allowed an MDD code alone, given the fact that all patients in our sample were diagnosed with BD/SCAD at least twice during the observation period, before or after the index visit, and thus were classified as having a bipolar spectrum disorder. If more than one event sequence satisfied the above conditions during the period 2003-2015, only the first one was analysed as part of the study.

Competing risks regression[9] survival analysis with lithium as a reference was used to compare 29 monotherapies with respect to the risk of the first event of interest after the index fill: psychiatric hospitalization/ER visit, non-psychiatric hospitalization/ER visit, or ending monotherapy. The last two events preclude the risk of psychiatric hospitalization/ER visit: medication side effects can trigger a medical emergency or non-adherence. Lumping any of these events with censoring could result in risk overestimation for the outcome of interest.[10] A similar competing risks design was used

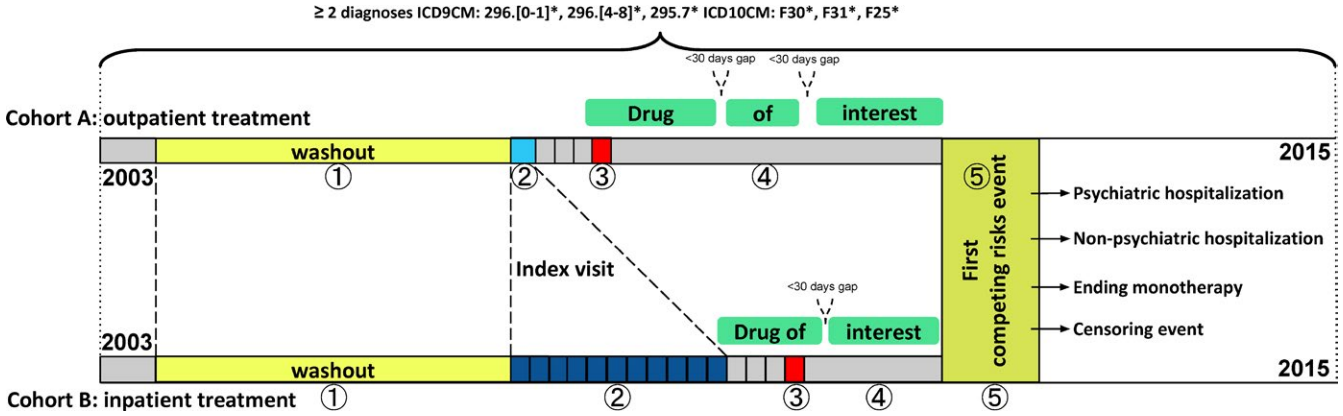

FIGURE 1 Sequence of events of interest in two cohorts (outpatient or inpatient meta-visits). (1) One-year "washout"; (2) index visit: cohort A—outpatient mood episode meta-visit; cohort B—mood episode hospitalization; (3) index fill: drug of interest active on the 4th day after, cohort A—outpatient visit; cohort B—inpatient discharge; (4) time to psychiatric hospitalization/emergency room visit with competing risks of other events; (5) outcome: one of three competing risk events or censoring event

in a recent study assessing hypothyroidism risk on bipolar disorder medications.[11]

The following covariates were initially included in the analysis: patient age, sex, inpatient/outpatient meta-visit, number of patient visit days to any health care provider 1 year prior to the index visit, length of index visit, index episode characteristics (BD/SCAD/MDD diagnosis, BD subtype, polarity, severity, and psychotic features), procedures related to mental health and injuries as well as procedures potentially influencing the central nervous system (general anesthesia, brain surgeries, and apnea-related procedures), and 55 mental and somatic comorbidities (Tables S3-5). The analysis also included 35 classes of medications other than drugs of interest for which the prescription was filled 1 year before and/or on the index fill date. These medications comprised a diverse range of pharmacological groups and medical indications that could contribute to indication bias. A forward stepwise selection procedure was performed to determine the final model covariates, applying a Bonferroni-corrected *P*-value threshold of 5×10^{-4} for inclusion, to account for multiple testing with 100 potential covariates. Covariates with significant mutual correlation were united before being added into the regression model, in particular: (i) "depressive mood episode" included diagnosis of MDD or a BD episode with depressive polarity; (ii) "other drugs acting on central nervous system" included analgesics, non-mood-stabilizing anticonvulsants, anxiolytics, and sedatives. The analgesics group included amitriptyline due to its common use for neuropathic pain management, despite it being classified as a tricyclic AD. Topiramate was classified as a non-mood-stabilizing anticonvulsant and pregabalin and gabapentin were classified as anti-anxiety agents.

To account for possible indication biases, the same regression covariates were used to run psychiatric hospitalization models on sample subsets: patients with and without index depressive mood episode, index manic episode, index psychotic features (including SCAD and acute psychoses), and comorbid drug abuse/dependence, and with inpatient versus outpatient meta-visit. Regression analysis with drugs of interest united into classes was also conducted to explore inter-class variability of outcomes using the same covariates as the main model. This analysis was reproduced in subgroups of patients with index depressive and non-depressive mood episode.

One benefit of our design over an intent-to-treat approach is that it allows modeling of a continuous drug exposure, requiring prescription refills, which is important given adherence issues and high rates of psychiatric drug switching.

The following software was used in the study: PostgreSQL version 9.2 (PostgreSQL Global Development Group) and R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria) including the cmprsk (2.2-7) and aod (1.1-32) packages. All hypothesis tests were two-sided.

3 | RESULTS

The majority of patients were female (62.4%), with most (73.9%) of the population aged ≤45 years. A diagnosis of BD was present in 74.6% of all index meta-visits: type I (32.8%), type II (12.8%) and not otherwise specified (29.0%). A diagnosis of MDD was present in 44.7% of all index meta-visits, and SCAD only in 2.2%. In some cases, the index meta-visit included several codes related to different diagnostic categories and different polarities of mood episode; thus, the percentages shown above will sum up to >100%. Among the cases with known mood polarity, 73.3% were depressive. Psychotic features were present in 7.5% of all index meta-visits. Prescriptions of drugs of interest were predominantly filled after an outpatient meta-visit (89.8%). ADs were the most commonly used drug class (50.2%), with the highest number of prescriptions filled for sertraline (17.6% of all AD fills). MSAs accounted for 23.0% of prescription fills, with the top-filled drug being lamotrigine (58.5% of all MSAs). SGAs were filled following 21.3% of meta-visits, with quetiapine being the most common (36.2% of all SGAs). The fraction of patients who started on lithium or FGAs was 5.1% and 0.41%, respectively. Benzodiazepines

were prescribed in 27.0% of cases within 1 year prior to and on the date of treatment start.

Among patients with index manic or mixed mood episode (n = 59 310), almost a quarter (24.4%) were treated with ADs, among which the most commonly used drug was bupropion (17.9%), followed by sertraline (15.6%), escitalopram (15.0%), fluoxetine (14.3%), citalopram (12.1%) and venlafaxine (9.8%). Among patients with index manic/hypomanic BD episode, 49.8% (9159 out of 18 378) were prescribed ADs, of which the most commonly used were escitalopram, citalopram, bupropion and fluoxetine.

The average length of meta-visits was 2.0 days for outpatients and 11.2 days for inpatients. The duration of observation ranged from 1 to 3683 days (10 years), with mean 94.0 days, median 32 days and standard deviation 157.2 days. The shortest average times until the first competing risks event were observed in patients on asenapine (52.7 days), doxepin (54.38 days) and lurasidone (56.63 days), and the longest times were observed in patients on clozapine (190.4 days), paroxetine (125.2 days), and venlafaxine (119.8 days) (Table S1).

One of the pre-specified competing risk events occurred in 50.0% of patients by day 32, in 73.2% of patients by the third month, in 95.1% of patients by year 1, and in 99.9% of patients by year 4. Therefore, results are reported up to 4 years from the start of monotherapy due to the paucity of longer term observations.

Ending monotherapy was the most common competing risk event by the end of the observation period, whereas psychiatric and non-psychiatric hospitalizations occurred in only 6.4% and 4.8% of cases, respectively (Table S6). The majority of patients (53.7%) ended monotherapy within 2 months (30.5% failed to make a refill and 23.1% added/changed to a new drug), and more than two-thirds of patients (67.8%) "dropped out" of monotherapy within 4 months.

The uncorrected cumulative incidence curves for the three competing risks are shown in Figures S1-3. The covariate-adjusted cumulative incidence of psychiatric hospitalization for all 29 drugs of interest indicated that MSAs performed comparably to or better than lithium, with valproate being associated with significantly lower risk of hospitalization (Table 1, Figure 2). Among antipsychotics, clozapine, haloperidol and ziprasidone had significantly higher risk of hospital admission than lithium, while aripiprazole had significantly lower risk. Among ADs, three selective serotonin reuptake inhibitors (citalopram, fluoxetine, and sertraline), as well as two serotonin-norepinephrine reuptake inhibitors (duloxetine and venlafaxine), were associated with significantly higher risk of hospitalization than lithium; the norepinephrine-dopamine reuptake inhibitor bupropion showed a significantly lower risk.

Out of 100 non-treatment covariates tested, 13 were significantly associated with the risk of psychiatric hospitalization in the model: eight of them had elevated risk (inpatient meta-visit, baseline depression and psychosis, comorbid drug abuse/dependence, pulmonary and cardiovascular disorders, loop diuretics, and other drugs acting on the central nervous system) and five had reduced risk (age, antibacterial and non-steroid anti-inflammatory agents, and BD subtypes I and II) (Table 1).

Significant risk differences between drug categories were found for a regression model with the same covariates, but with drugs united into classes (Table S7). Compared to lithium, ADs and FGAs were associated with 1.12 and 1.32 times higher risk of psychiatric hospitalization (P = .017 and .026, respectively), whereas MSAs had a reduced risk (relative risk [RR] = 0.89, 95% confidence interval [CI] 0.80–0.98, P = .014). SGAs were not significantly different as a class from lithium (RR = 1.01, P = .89).

Regression analysis in sample subgroups with and without index depressive episode showed that drug associations significant in the main model kept the same direction in both subgroups, except for three ADs (sertraline, fluoxetine and citalopram) non-significantly associated with lower hospitalization risk in non-depressed patients (Table 2). Many of the P-values related to other drugs were not significant in the subgroups either.

The direction of drug associations significant in the main model stayed the same in subgroups of patients with and without comorbid substance use disorder (Tables S8 and S9), and also among patients in cohorts A (outpatient treatment) and B (inpatient treatment) (Supporting Information Tables S13 and 14). Again, many of these associations were non-significant. For groups of patients with either an index manic or psychotic episode, sample sizes were too small to derive definitive conclusions about the direction of the factors' associations (Tables S10-S12). Non-drug factors identified in the primary regression model mainly retained their direction of association in all studied subgroups.

The regression models with drugs united into classes showed that ADs were associated with higher risk of hospitalization in patients with depressive index mood episode, whereas no significant association was observed for ADs in the non-depressed cohort. The risk of psychiatric hospitalization was not significantly different from lithium for SGAs in both depressed and non-depressed subgroups (Supporting Information Tables S15, S16).

4 | DISCUSSION

Despite an extensive observation period covering the years 2003-2015, the data on drug-dependent hospitalization risk could only be assessed short term, as few patients stayed on a monotherapy for >4 months. Moreover, the data show that one-third of patients failed to make a refill within 60 days after the end of supply. This finding reflects a disturbing trend in mental health care of poor medication adherence among the BD population and unsatisfactory response to first-line monotherapy. Additional qualitative studies are required to shed light on the reasons behind drug switching/ending, whether it is due to clinicians' views on polypharmacy, low patient acceptability or tolerability of the drugs, lack of the actual therapeutic effect of the medication, or other factors.

Given the high rates of patient "dropout" from monotherapy, the associations revealed between drug prescription fill and the risk of psychiatric hospitalization can be biased by enrichment from acute-phase treatment. Thus, caution should be used in extrapolating these

TABLE 1 Competing risks regression model of psychiatric hospitalization in bipolar disorders (n = 190 894)

Variable	N	Relative risk of hospitalization	95% confidence interval	*P*-value
First-generation antipsychotics				
Haloperidol	**529**	**1.57**	**1.19-2.06**	**9.40×10^{-4}**
Perphenazine	253	0.78	0.44-1.37	.37
Second-generation antipsychotics				
Clozapine	**410**	**1.52**	**1.07-2.16**	**.017**
Paliperidone	369	1.26	0.87-1.83	.22
Ziprasidone	**3014**	**1.25**	**1.06-1.46**	**6.20×10^{-3}**
Asenapine	258	1.24	0.76-2.00	.38
Risperidone	6373	1.12	0.98-1.27	.083
Quetiapine	14 704	1.05	0.94-1.17	.41
Olanzapine	4808	0.98	0.84-1.13	.75
Lurasidone	649	0.98	0.69-1.39	.89
Aripiprazole	**10 080**	**0.80**	**0.70-0.90**	**3.50×10^{-4}**
Antidepressants				
Venlafaxine	**8944**	**1.33**	**1.18-1.49**	**1.00×10^{-6}**
Duloxetine	**6943**	**1.24**	**1.09-1.40**	**5.10×10^{-4}**
Paroxetine	521	1.20	0.86-1.68	.27
Fluvoxamine	419	1.20	0.83-1.74	.31
Sertraline	**16 890**	**1.17**	**1.05-1.30**	**3.20×10^{-3}**
Fluoxetine	**13 076**	**1.17**	**1.05-1.31**	**3.70×10^{-3}**
Citalopram	**14 537**	**1.14**	**1.03-1.27**	**.013**
Escitalopram	16 269	1.11	0.99-1.23	.062
Mirtazapine	2847	1.09	0.93-1.28	.28
Desvenlafaxine	1535	1.06	0.85-1.31	.62
Doxepin	407	1.04	0.71-1.54	.83
Bupropion	**13 160**	**0.80**	**0.71-0.91**	**2.80×10^{-4}**
Vilazodone	341	0.64	0.37-1.09	.093
Mood-stabilizing anticonvulsants				
Lamotrigine	25 637	0.94	0.84-1.04	.23
Oxcarbazepine	4013	0.87	0.73-1.03	.096
Carbamazepine	1826	0.84	0.66-1.06	.13
Valproate	**12 380**	**0.80**	**0.71-0.91**	**3.20×10^{-4}**
Factors not related to drugs				
Inpatient prescription mode	**19 460**	**1.68**	**1.59-1.79**	**$<2.23 \times 10^{-308}$**
Drug abuse/dependence	**21 661**	**1.38**	**1.31-1.46**	**$<2.23 \times 10^{-308}$**
Loop diuretics	**2172**	**1.35**	**1.17-1.56**	**2.30×10^{-5}**
Other drugs acting on central nervous system	**111 406**	**1.31**	**1.26-1.37**	**$<2.23 \times 10^{-308}$**
Index depressive mood episode	**101 525**	**1.24**	**1.19-1.30**	**$<2.23 \times 10^{-308}$**
Index psychotic features	**14 341**	**1.22**	**1.14-1.30**	**5.80×10^{-9}**
Pulmonary diseases	**5461**	**1.22**	**1.11-1.34**	**1.70×10^{-5}**
Cardiovascular diseases	**37 951**	**1.11**	**1.06-1.16**	**1.60×10^{-5}**
Male sex	71 790	1.03	0.99-1.07	.20
Age at index meta-visit start	**190 894**	**0.99**	**0.99-1.00**	**4.90×10^{-13}**
Antibacterial agents	**56 650**	**0.92**	**0.89-0.96**	**1.50×10^{-4}**

(Continues)

TABLE 1 (Continued)

Variable	N	Relative risk of hospitalization	95% confidence interval	*P*-value
Non-steroid anti-inflammatory drugs	**32 795**	**0.88**	**0.84-0.93**	**6.10×10^{-7}**
Bipolar type I at index visit	**62 612**	**0.74**	**0.71-0.78**	**$<2.23 \times 10^{-308}$**
Bipolar type II at index visit	**24 373**	**0.74**	**0.69-0.79**	**$<2.23 \times 10^{-308}$**

The model includes 29 drugs with lithium (n = 9702) as a reference, as well as age, sex and other variables that were significant during the stepwise selection procedure. Statistically significant factors are shown in bold.

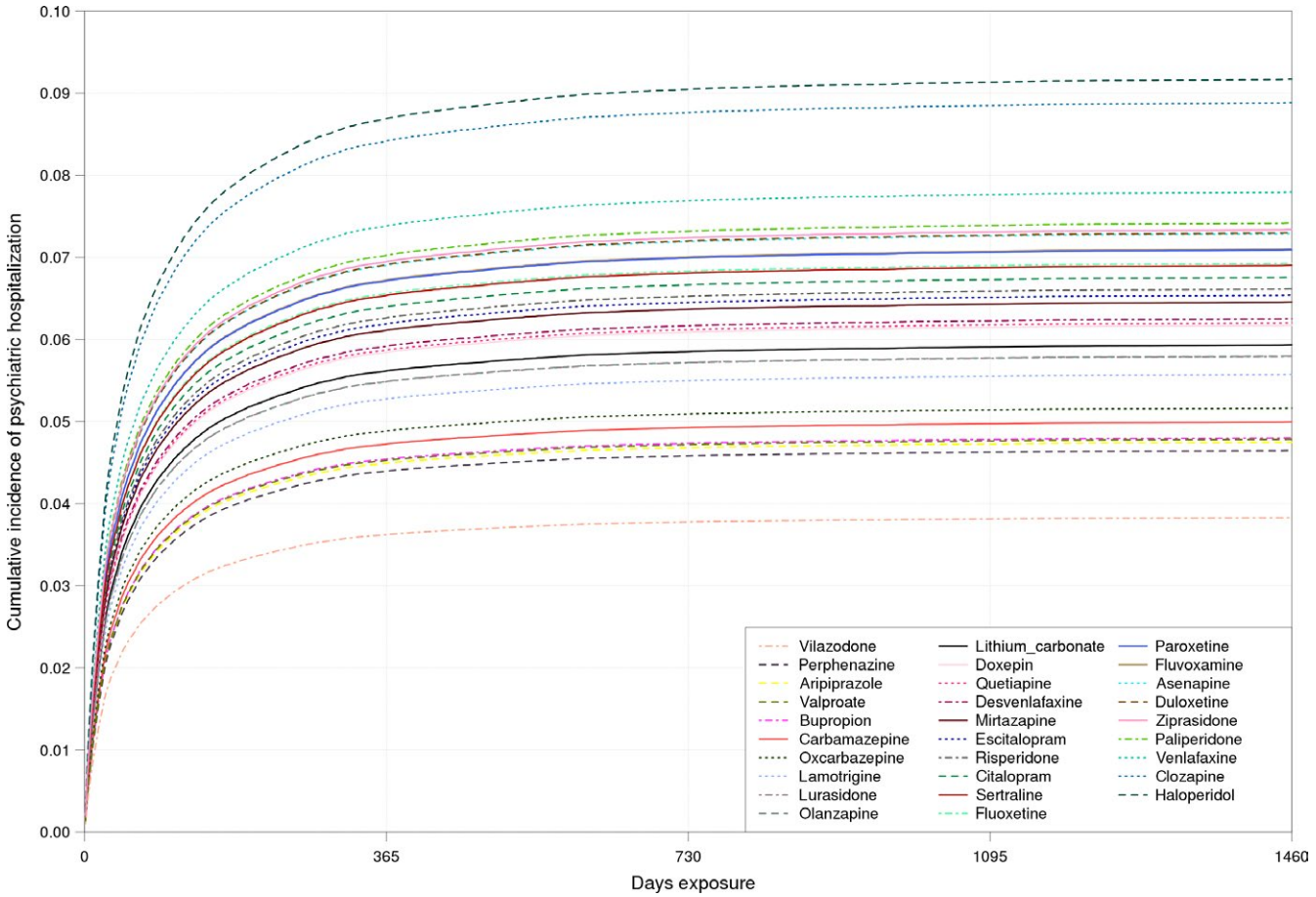

FIGURE 2 The cumulative incidence of psychiatric hospitalization for all 29 monotherapies based on the regression model at the average value of non-drug covariates. Drugs in the key are sorted from lowest to highest risk

results to long-term maintenance pharmacotherapy of patients with BDs.

Overall, our findings indicate that, despite the risk differences between individual members of drug classes, all studied MSAs were associated with a lower or non-significantly different risk of psychiatric hospitalization as compared to lithium, and all of the significantly higher risk drugs were antipsychotics and ADs. These correlations may reflect the pharmacological effectiveness of the studied drug classes, but could also result from biological, psychosocial, economic and health care factors unrelated to pharmacotherapy. Moreover, for many of the comparison drugs, the sample size or magnitude of the difference was not large enough to reveal significant associations.

Better clinical outcomes associated with lithium and MSAs versus antipsychotics are supported by data from a retrospective cohort study by Guo et al.: BD patients receiving SGAs had higher risks of hospitalization (RR = 1.44, 95% CI 1.33-1.56) and ER visits (RR = 1.15, 95% CI 1.04-1.27) as compared to those on SGA + MSA or MSA alone.[12] Bauer and colleagues showed that intent to treat with either lithium or valproate was associated with a lower risk of all-cause and psychiatric hospitalization in BD as compared to SGA monotherapy and the combinations SGA + lithium and SGA + valproate.[13] Nevertheless, a large Swedish observational study showed that both MSAs (lithium, valproate, and lamotrigine), and some SGAs (quetiapine and olanzapine) substantially decreased the risk of admissions to hospital in patients with BD compared to times off-drug.[14]

TABLE 2 Competing risks regression models of psychiatric hospitalization in patients with depressive (n = 101 525) and non-depressive (n = 89 369) index mood episode

Depressive mood episode					Non-depressive mood episode			
Variable	N	RR of hospitalization	95% CI	*P*-value	N	RR of hospitalization	95% CI	*P*-value
First-generation antipsychotics								
Haloperidol	176	1.35	0.83-2.19	.22	**353**	**1.60**	**1.15-2.22**	**4.50×10^{-3}**
Perphenazine	106	0.50	0.18-1.40	.18	147	1.06	0.54-2.08	.85
Second-generation antipsychotics								
Clozapine	68	1.44	0.57-3.62	.43	**342**	**1.49**	**1.01-2.19**	**.041**
Paliperidone	125	1.15	0.59-2.23	.68	244	1.26	0.80-1.99	.30
Ziprasidone	**1108**	**1.45**	**1.13-1.86**	**2.70×10^{-3}**	1906	1.09	0.88-1.35	.43
Asenapine	79	1.50	0.69-3.24	.30	179	1.10	0.59-2.04	.76
Risperidone	2342	1.12	0.91-1.38	.29	4031	1.10	0.93-1.29	.27
Quetiapine	583	1.17	0.98-1.40	.07	8867	0.98	0.84-1.13	.73
Olanzapine	1663	1.03	0.81-1.31	.79	3145	0.90	0.75-1.08	.26
Lurasidone	231	0.93	0.52-1.66	.80	418	1.02	0.66-1.58	.94
Aripiprazole	3715	0.86	0.70-1.05	.14	**6365**	**0.76**	**0.64-0.89**	**7.90×10^{-4}**
Antidepressants								
Venlafaxine	**6558**	**1.47**	**1.24-1.75**	**5.80×10^{-6}**	2386	1.06	0.86-1.31	.57
Duloxetine	**5038**	**1.37**	**1.15-1.64**	**3.30×10^{-4}**	1905	1.01	0.80-1.27	.92
Paroxetine	371	1.25	0.84-1.85	.27	150	1.25	0.64-2.43	.50
Fluvoxamine	**251**	**1.55**	**1.01-2.38**	**.040**	168	0.69	0.30-1.56	.36
Sertraline	**12 369**	**1.28**	**1.09-1.50**	**2.70×10^{-3}**	4521	0.99	0.83-1.18	.93
Fluoxetine	**9437**	**1.32**	**1.12-1.56**	**8.10×10^{-4}**	3639	0.87	0.72-1.06	.16
Citalopram	**10 852**	**1.28**	**1.08-1.50**	**3.20×10^{-3}**	3685	0.86	0.71-1.05	.12
Escitalopram	**12 059**	**1.23**	**1.04-1.45**	**.013**	4210	0.85	0.71-1.03	.093
Mirtazapine	2114	1.18	0.96-1.46	.12	733	1.04	0.73-1.46	.84
Desvenlafaxine	1106	1.12	0.85-1.46	.41	429	1.03	0.66-1.62	.88
Doxepin	250	1.13	0.70-1.81	.61	157	0.96	0.47-1.96	.92
Bupropion	8741	0.84	0.71-1.01	.05	**4419**	**0.80**	**0.66-0.96**	**.016**
Vilazodone	257	0.71	0.40-1.28	.25	84	0.47	0.11-1.94	.29
Mood-stabilizing anticonvulsants								
Lamotrigine	7833	0.94	0.79-1.12	.49	17 804	0.95	0.83-1.09	.44
Oxcarbazepine	1234	0.98	0.74-1.29	.86	2779	0.81	0.65-1.01	.054

(Continues)

TABLE 2 (Continued)

	Depressive mood episode				Non-depressive mood episode			
Variable	**N**	**RR of hospitalization**	**95% CI**	***P*-value**	**N**	**RR of hospitalization**	**95% CI**	***P*-value**
Carbamazepine	626	0.71	0.47-1.06	.09	1200	0.94	0.70-1.25	.64
Valproate	3948	0.84	0.68-1.03	.08	**8432**	**0.79**	**0.68-0.92**	**2.30×10^{-3}**
Factors not related to drugs								
Inpatient prescription mode	—	**1.63**	**1.52-1.75**	**$<2.23 \times 10^{-308}$**	—	**1.88**	**1.68-2.11**	**$<2.23 \times 10^{-308}$**
Drug abuse/ dependence	—	**1.34**	**1.26-1.44**	**$<2.23 \times 10^{-308}$**	—	**1.49**	**1.35-1.63**	**$<2.23 \times 10^{-308}$**
Loop diuretics	—	**1.40**	**1.18-1.66**	**7.70×10^{-5}**	—	1.25	0.96-1.62	.086
Other drugs acting on central nervous system	—	**1.34**	**1.27-1.41**	**$<2.23 \times 10^{-308}$**	—	**1.27**	**1.19-1.36**	**3.20×10^{-12}**
Index psychotic features	—	**1.11**	**1.01-1.22**	**.03**	—	**1.38**	**1.24-1.53**	**7.50×10^{-10}**
Pulmonary diseases	—	**1.18**	**1.05-1.32**	**3.40×10^{-3}**	—	**1.34**	**1.14-1.59**	**3.40×10^{-4}**
Cardiovascular diseases	—	**1.10**	**1.04-1.16**	**1.10×10^{-3}**	—	**1.13**	**1.04-1.23**	**3.10×10^{-3}**
Male sex	—	**1.10**	**1.04-1.15**	**1.30×10^{-4}**	—	**0.91**	**0.85-0.97**	**2.00×10^{-3}**
Age at index meta-visit start	—	**0.99**	**0.99-1.00**	**5.30×10^{-10}**	—	**1.00**	**0.99-1.00**	**2.30×10^{-4}**
Antibacterial agents	—	**0.93**	**0.89-0.98**	**4.90×10^{-3}**	—	**0.90**	**0.83-0.96**	**2.90×10^{-3}**
Non-steroid anti-inflammatory drugs	—	**0.86**	**0.80-0.91**	**6.20×10^{-7}**	—	0.93	0.85-1.02	.094
Bipolar type I at index visit	—	**0.66**	**0.62-0.71**	**$<2.23 \times 10^{-308}$**	—	**0.91**	**0.85-0.97**	**6.00×10^{-3}**
Bipolar type II at index visit	—	**0.73**	**0.62-0.85**	**6.80×10^{-5}**	—	**0.84**	**0.77-0.92**	**6.50×10^{-5}**

Both models include 29 drugs with lithium (n = 3031 and 6671, respectively) as a reference, as well as age, sex and other variables that were significant during the stepwise selection procedure. Statistically significant factors are shown in bold.
RR, relative risk; CI, confidence interval.

The possibility of indication biases should be recognized when interpreting the data. First, antipsychotics could be prescribed to more severely ill patients, presenting with psychosis, a complex/atypical symptom profile or a previous history of drug resistance, potentially reflecting predisposition to a more deleterious BD course. For example, clozapine is often prescribed to patients who were non-responders to other therapies.[15] However, the finding that the SGA aripiprazole performed favorably counters the argument that the evidence for the poorly performing antipsychotics is predominantly an artifact of confounding by indication. Second, as both the baseline depression and AD monotherapy were associated with higher risk of psychiatric hospitalization, it could be inferred that the symptoms rather than the medication could drive the worse outcomes. While subgroup regression with 29 drugs in depressive and non-depressive cohorts gave inconclusive results due to insignificant *P*-values, the model with drugs united into classes confirmed an AD-associated risk of psychiatric hospitalization only in the depressed subgroup. Although it is challenging to differentiate the contribution of depression and ADs to the worse BD outcomes, our data add to the evidence that pharmacologically treated depression may lead to a higher risk of psychiatric hospitalization if ADs are used.

An important insight from our findings is that heterogeneity exists within the studied drug classes with regard to hospitalization risk—individual members can be better or worse than lithium, perhaps due to the unique receptor profile and mechanism of action of each medication.

Three drugs were associated with significantly lower risk of psychiatric hospitalization than lithium: valproate, and the two dopamine system-targeting agents: aripiprazole and bupropion. Previous studies comparing the effectiveness of BD acute-phase and maintenance treatment with valproate versus lithium (as monotherapies or adjuncts) showed contradictory results.[2,16-19] Aripiprazole has been consistently reported to have the most favorable hospitalization outcomes among SGAs in retrospective studies,[1,13,20,21] whereas a recent review of BD randomized controlled trials on adjunctive antipsychotics showed only one study with an SGA superior to lithium, namely quetiapine.[22]

The literature on bupropion suggests that it has equivalent effectiveness to other ADs in treatment of depressive states,[23-25] with contradictory data on manic switch risk.[25-27] Our findings on the reduced risk of hospitalization associated with bupropion were unexpected, since psychostimulants are known to significantly increase the probability of psychiatric hospitalization due to psychoses and mania.[28] The observation of bupropion's lower risk might be dose-dependent or relevant to certain subgroups of patients in their early course of BD/SCAD. In a subgroup analysis of patients with substance use disorder, the direction of bupropion's risk remained the same, but was not statistically significant, due to the small sample size (Table S8). Also, bupropion was associated with reduced hospitalization risk compared to lithium in patients without a depressive index episode, which negates the hypothesis that its observed role is explained only by alleviating depression through psychostimulation (Table 2).

Analysis of factors other than drugs of interest showed that the inpatient meta-visit had an RR of 1.68 over the outpatient meta-visit for psychiatric hospitalization ($P < 2.23 \times 10^{-308}$), supporting the evidence that previous hospitalization is a strong predictor of subsequent hospital admission in patients with BD.[29-33] Consistent with our data, baseline substance use disorder, psychosis, and use of anticonvulsants and anxiolytics were previously reported to be risk factors for hospitalization in BD.[30] The findings on the reduced risk of psychiatric hospitalizations for patients on antibiotics and non-steroidal anti-inflammatory drugs contribute to the evidence suggesting the importance of immune alterations, inflammation, and the microbiome in BDs.[34]

It is important to consider some additional limitations of the study, including its observational nature. A non-randomized assignment of patients to treatment groups, non-standardization of diagnostic decisions, and non-uniform quality of data collection are inherent in observational studies of administrative claims data. Indication bias can still result from factors not recorded in the Truven dataset, such as symptom profile, complexity of clinical picture, lifelong history of disease and pharmacotherapy, adverse drug effects, and drug resistance. To address these challenges, we deployed adjustment procedures suitable for this particular design to correct for baseline mood episode characteristics, comorbidities and other drugs in use. Also, based on a prespecified 1-year "washout" defined by no psychiatric hospitalizations and no drugs of interest, many of the patients could have been in the early stages of disease with relatively unchanged neural substrate and preserved compensatory mechanisms, favoring better medication response and short-term prognosis, compared to chronically ill patients with more progressed disease. It is worth noting that a lower risk of psychiatric hospitalization does not necessarily signify remission quality, but could result from lack of access to mental health services or avoiding psychiatric care. Finally, no correction was made for medication cost, dosage, route of administration, and release mechanism. Extended release and long-acting injectable drugs could be associated with better adherence and thus better outcomes.

The relatively short-term observation after index prescription, the 1-year washout period, impeding the study of hospitalization risk in patients on second- and third-line treatment, as well as restriction of the performed analysis to monotherapies, as opposed to drug combinations, may preclude the generalizability of the findings to routine care.

Some additional findings from our study need to be emphasized and further explored. Our study indicates that a substantial proportion of BD patients (44.7%) were initially misdiagnosed with MDD. This finding can explain why AD monotherapy was the most commonly used treatment regimen and is of particular interest given the concerns about AD-induced risk of manic switch,[35] and potential contribution of the latter to treatment non-adherence. This highlights the challenges of the proper identification of BD in routine care settings and the negative sequelae of an incorrect diagnosis, given the significantly elevated risk for psychiatric hospitalization associated with this prescribing pattern. The other disturbing

finding is that one-quarter of patients initially diagnosed with manic or mixed mood episodes were prescribed ADs. This observation may be explained by the fact that the "mixed" category in our study covered both codes for manic and for depressive episodes, billed within the same meta-visit, and presumably reflects the attempt to target depressive symptoms. This may be due to a lack of coordination between providers to whom patients might present with different symptoms. Surprisingly, half of patients with an index manic/hypomanic BD episode were prescribed an AD. This observation may be due to mixed features being present during BD index episodes, but additional studies would be helpful to explain this finding.

Of interest is also the low rate of lithium treatment despite the fact that almost all major treatment recommendations and clinical guidelines suggest lithium as one of the first-line drugs, based on its effectiveness and safety.[36] This finding is supported by results from other recent studies on US inpatients with BD.[37,38]

Our study supports the data obtained in multiple randomized clinical studies favoring lithium and MSA use in BD management, suggesting their real-world applicability; nevertheless, we acknowledge that no causal inferences can be made based on the associations revealed.

5 | CONCLUSIONS

1. The majority of patients with BDs end monotherapy within 2 months after the treatment start either by switching to/adding another medication or by failing to make a refill.
2. The association of BD drugs with psychiatric hospitalization can differ significantly within one pharmacological group.
3. Treatment with aripiprazole, valproate and bupropion is associated with a lower risk of subsequent psychiatric hospitalization after treatment initiation as compared to lithium in BD/SCAD patients.
4. Treatment with haloperidol, clozapine, ziprasidone, duloxetine, fluoxetine, venlafaxine, sertraline, and citalopram is associated with a higher risk of subsequent psychiatric hospitalization as compared to lithium in BD/SCAD patients.
5. The fact that all the studied MSAs versus lithium were associated with better or comparable hospitalization outcomes, and that all the higher risk drugs were antipsychotics and ADs, contributes to the body of evidence which supports lithium and MSA preference in BD management.
6. The facts that the dopaminergic drugs aripiprazole and bupropion had better outcomes than other members of their respective classes, and that AD outcomes may vary by baseline mood polarity, merit further investigation.

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DISCLOSURES

Dr. Tohen was a full time employee at Lilly (1997-2008). He has received honoraria from, or consulted for, Abbott, Actavis, AstraZeneca, Bristol Myers Squibb, GlaxoSmithKline, Lilly, Johnson & Johnson, Otsuka, Merck, Sunovion, Forest, Gedeon Richter, Roche, Elan, Alkermes, Allergan, Lundbeck, Teva, Pamlab, Wyeth and Wiley Publishing. His spouse was a full-time employee at Lilly (1998-2013). Dr. Krall is a former employee and holds stock in GlaxoSmithKline, AstraZeneca, Abbott Labs, and Lorex Pharmaceuticals. Dr. Krall is a consultant to Takeda Pharmaceuticals and is Chairman of the Board of Pierian Biosciences. Drs. Nestsiarovich, Mazurie, Hurwitz, Kerner, Nelson, Crisanti, Perkins, and Lambert have no conflicts of interest to disclose.

ORCID

Anastasiya Nestsiarovich http://orcid.org/0000-0002-5558-2381

Mauricio Tohen http://orcid.org/0000-0001-8049-4351

Christophe G Lambert http://orcid.org/0000-0003-1994-2893

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