

Real-World Effectiveness of Pharmacologic Treatments for the Prevention of Rehospitalization in a Finnish Nationwide Cohort of Patients With Bipolar Disorder

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IMPORTANCE Mood stabilizers and antipsychotics are the main maintenance treatments for bipolar disorder. Lithium is considered to be the most effective mood stabilizer, but very little is known about overall health outcomes associated with specific treatments and the comparative long-term effectiveness of specific psychotropics or routes of administration in the prevention of rehospitalizations.

OBJECTIVE To study the comparative effectiveness of pharmacologic treatments in the prevention of rehospitalization in a nationwide cohort of patients with bipolar disorder.

DESIGN, SETTING, AND PARTICIPANTS This cohort study examined the risk of psychiatric, cardiovascular, and all-cause hospitalization from January 1, 1987, to December 31, 2012, among all patients in Finland who had been hospitalized for bipolar disorder (N = 18 018; mean follow-up time, 7.2 years) using prospectively gathered nationwide databases for hospitalization and dispensed medications. The primary analysis was within-individual analysis, in which each individual was used as his or her own control to eliminate selection bias. The study adjusted for the effect of concomitant psychotropic medications, duration of illness, and the temporal orders of exposure and nonexposure periods. Statistical analysis was conducted from January 1, 1996, to December 31, 2012.

MAIN OUTCOMES AND MEASURES Adjusted hazard ratios (HRs) for rehospitalization were calculated.

RESULTS Among the cohort (9558 women and 8460 men; mean [SD] age, 46.6 [17.0] years), 9721 patients (54.0%) had at least 1 psychiatric rehospitalization. In comparison between use and no use among specific agents reaching nominal statistical significance, risperidone long-acting injection (HR, 0.58 [95% CI, 0.34-1.00]), gabapentin (HR, 0.58 [95% CI, 0.44-0.77]), perphenazine long-acting injection (HR, 0.60 [95% CI, 0.41-0.88]), and lithium carbonate (HR, 0.67 [95% CI, 0.60-0.73]) were associated with the lowest risk of psychiatric rehospitalization. Concerning all-cause hospitalization, lithium (HR, 0.71 [95% CI, 0.66-0.76]) was associated with the lowest risk. The most frequently used antipsychotic treatment, quetiapine fumarate, showed only modest effectiveness (risk of psychiatric rehospitalization: HR, 0.92 [95% CI, 0.85-0.98]; risk of all-cause hospitalization: HR, 0.93 [95% CI, 0.88-0.98]). Long-acting injections were associated with substantially better outcomes compared with identical oral antipsychotics (risk of psychiatric rehospitalization: HR, 0.70 [95% CI, 0.55-0.90]; risk of all-cause hospitalization: HR, 0.70 [95% CI, 0.57-0.86]). Results from sensitivity analyses showed consistent beneficial effects only for lithium and for long-acting injections compared with their oral counterparts.

CONCLUSIONS AND RELEVANCE Lithium was the most effective mood stabilizer, and long-acting injections the most effective antipsychotics, in preventing hospitalization due to mental or physical illness.

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← Editorial

+ Supplemental content

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Bipolar disorder is a serious, often debilitating, and recurring chronic psychiatric disorder,¹ although individual disease courses may vary. Bipolar disorder is rated as the sixth most common cause of disability in the world by the World Health Organization, accounting for more loss of disability-adjusted life years than all cancers combined.² Long-term medication is often required to attain remission and prevent relapses, although, even with advanced treatment protocols, rates of remission remain low.³ Many randomized clinical trials and their meta-analyses have been performed to discover the most efficacious treatment forms for prevention of relapse; some more recent trials also included antipsychotics in long-acting injectable (LAI) form.^{4,5} However, these studies did not include oral antipsychotics, and the comparative effectiveness of LAI vs oral antipsychotics has remained unknown.

Some meta-analyses have shown clinically meaningful differences between pharmacotherapies in their comparative effectiveness of acute treatment,⁶⁻⁸ but treatment guidelines until recently did not recognize such differences.^{9,10} However, as has been noted in the field of depression research, randomized clinical trials often have stringent inclusion and exclusion criteria and limited follow-up times, which may impair their ability to reflect the real-world effectiveness of therapies in their actual clinical application.¹¹ Randomized clinical trials usually exclude patients with the most comorbidities and the highest severity of illness (eg, propensity to suicide). Furthermore, many efficient medications might cause adverse effects on a very long time scale. Thus, the most efficient way to obtain a good estimate on the overall real-world effectiveness of therapies for bipolar disorder may be through observational studies.¹² One such recent study by Hayes et al¹³ indicated that lithium appears to be more successful as monotherapy maintenance treatment for bipolar disorder than valproate sodium, olanzapine, or quetiapine fumarate. Similar findings on the superiority of lithium compared with other pharmacologic treatments in bipolar disorder have been reported by Kessing et al¹⁴ in a 2011 registry study from Denmark and by Simhandl et al¹⁵ in a 4-year naturalistic follow-up study from Austria in 2014. Joas et al¹⁶ suggested that lithium is more effective than both quetiapine and olanzapine in prevention of relapse in bipolar disorder, and a study by Song et al¹⁷ suggested that lithium is superior to valproate sodium in preventing suicidal behavior in bipolar patients.

However, these studies were limited to only a few pharmacologic agents. To our knowledge, no studies have investigated the comparative effectiveness of long-acting antipsychotic injections vs identical oral agents. This investigation aimed to overcome these shortcomings in the largest and most complete register-based, real-world effectiveness study of pharmacotherapies for bipolar disorder to date.

Methods

Study Design and Data Acquisition

Finnish nationwide databases were used to combine prospectively collected registry data to conduct a population-based co-

Key Points

Question What is the comparative effectiveness of pharmacologic treatments in the prevention of rehospitalization in bipolar disorder?

Findings In this Finnish nationwide cohort study of 18 018 patients, lithium use was associated with the lowest risk of rehospitalization because of mental or somatic disorder. The risk of rehospitalization was about 30% lower during treatment with long-acting injections compared with treatment with their oral counterparts.

Meaning In bipolar disorder, lithium should remain the first line of treatment, and long-acting injections might offer a safe, effective option for patients in whom lithium is not suitable.

hort study of patients hospitalized for bipolar disorder. The registers were used to identify the study cohort (patients hospitalized for bipolar disorder between January 1, 1987, and December 31, 2012); to determine the incidences, durations, and reasons for rehospitalizations; to obtain information on reimbursed medications dispensed from pharmacies (all psychotropic medications except small packages of benzodiazepines were reimbursed in this indication); and to retrieve information on deaths. The databases and their use have been described in more detail in previous pharmacoepidemiologic studies.¹⁸⁻²¹ For details, see the eAppendix in the [Supplement](#). The cohorts are described in detail in the [Table](#). This research project was approved by the Ethics Committee of the Finnish National Institute for Health and Welfare. Further permissions were granted by pertinent institutional authorities at the Finnish National Institute for Health and Welfare (permission THL/1466/6.02.00/2013), the Social Insurance Institution of Finland (34/522/2013), and Statistics Finland (TK53-305-13). Informed consent is not required for register-based studies using anonymized data.

Exposure

The PRE2DUP (Prescription drug purchases to Drug Use Periods) method was used to define exposure and nonexposure periods for medications.¹⁸⁻²¹ The PRE2DUP method calculates the current dose with a sliding mean, uses package information (eg, number of tablets and administration intervals for injections), and takes into account stockpiling when constructing time periods of continuous use. Previous publications on the validation of the method indicate that PRE2DUP is the most precise method currently available to estimate drug use, and it gives highly accurate drug use periods for most drug classes, especially those meant for long-term use.^{19,20} As variation in dose is allowed within the method, no artificial grace periods are used. Thus, the risk is attributed to the ongoing treatment(s) according to the PRE2DUP method for each day. Concerning switching and cross-titration of treatments, the exposure of the first drug is defined to last until the whole amount of the purchased drug would be used as calculated with PRE2DUP, usually overlapping the use of the second drug. Therefore, if the hospitalization takes place within a few weeks

Table. Characteristics of Study Cohorts

Covariate	Patients, No. (%)	
	Total Cohort (N = 18 018)	Incident Cohort (n = 2074)
Sex		
Male	8460 (47.0)	1111 (53.6)
Female	9558 (53.0)	963 (46.4)
Age at cohort entry date, y		
<30	3345 (18.6)	588 (28.4)
30-49	7121 (39.5)	689 (33.2)
50-69	5577 (31.0)	534 (25.8)
≥70	1975 (11.0)	263 (12.7)
Calendar year of cohort entry date		
1996-1999	5107 (28.3)	343 (16.5)
2000-2003	3102 (17.2)	501 (24.2)
2004-2007	4280 (23.8)	573 (27.6)
2008-2012	5529 (30.7)	657 (31.7)
Patients remaining in cohort after censoring hospitalizations longer than 30.5 d		
No	105 (0.6)	13 (0.6)
Yes	17 913 (99.4)	2061 (99.4)
Patients remaining in cohort after censoring hospitalizations longer than 0 d		
No	141 (0.8)	22 (1.1)
Yes	17 877 (99.2)	2052 (98.9)
Time since diagnoses at cohort entry date, y		
0-5	16 531 (91.8)	2074 (100.0)
>5-10	1472 (8.2)	0
>10	15 (0.1)	0
Time since diagnoses at end of follow-up, y		
0-5	7120 (39.5)	870 (42.0)
>5-10	5357 (29.7)	669 (32.3)
>10	5541 (30.8)	535 (25.8)
Two-year history of all-cause hospitalizations at cohort entry date		
0	1364 (7.6)	0
1-2	12 129 (67.3)	1872 (90.3)
>2	4525 (25.1)	202 (9.7)
Two-year history of all-cause hospitalizations at end of follow-up		
0	7321 (40.6)	1055 (50.9)
1-2	6756 (37.5)	765 (36.9)
>2	3941 (21.9)	254 (12.3)
Two-year history of any psychiatric hospitalizations before cohort entry date		
0	1777 (9.9)	2074 (100.0)
1-2	14 097 (78.2)	0
>2	2144 (11.9)	0
Two-year history of any psychiatric hospitalizations at end of follow-up		
0	10 997 (61.0)	1435 (69.2)
1-2	5312 (29.5)	574 (27.7)
>2	1709 (9.5)	65 (3.1)
Use of benzodiazepines during follow-up		
No	8580 (47.6)	1466 (70.7)
Yes	9438 (52.4)	608 (29.3)
Use of sedatives during follow-up		
No	8069 (44.8)	1306 (63.0)
Yes	9949 (55.2)	768 (37.0)
Use of mood stabilizers during follow-up		
No	4749 (26.4)	827 (39.9)
Yes	13 269 (73.6)	1247 (60.1)

(continued)

Table. Characteristics of Study Cohorts (continued)

Covariate	Patients, No. (%)	
	Total Cohort (N = 18 018)	Incident Cohort (n = 2074)
Use of antidepressants during follow-up		
No	4832 (26.8)	1182 (57.0)
Yes	13 186 (73.2)	892 (43.0)
Use of antipsychotics during follow-up		
No	3413 (18.9)	603 (29.1)
Yes	14 605 (81.1)	1471 (70.9)

after a change in medication status, the rehospitalization is typically attributed to both treatments. Antipsychotics were defined as Anatomical Therapeutic Chemical code N05A except for lithium carbonate (N05AN01); antidepressants as N06A, mood stabilizers as N03AF, N03AG, N03AX, and N05AN01 (lithium); benzodiazepines as N05BA; and sedatives as N05C. Antipsychotics were modeled according to drug form (ie, oral and LAIs separately) based on package information recorded for each filling of a prescription.

Statistical Analysis

Statistical analysis was conducted from January 1, 1996, to December 31, 2012. Three analyses were performed on the cohorts using within-individual Cox proportional hazards regression analysis. First, rehospitalization owing to any mental disorder (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision [ICD-10]*, diagnosis codes beginning with the letter *F*) was investigated as a proxy marker for treatment failure (effectiveness; primary analysis). Second, all-cause hospitalization (including for somatic reasons) was used as a proxy marker for effectiveness vs tolerability of treatments (ie, taking into account the hospitalizations owing to severe adverse effects; secondary analysis). Third, hospitalization owing to cardiovascular diseases (*ICD-10* diagnosis codes beginning with the letter *I*) was used as a proxy for cardiovascular tolerability (secondary analysis). In addition, an analysis for rehospitalization for somatic reasons was performed for lithium, valproic acid, and quetiapine, the 3 most frequently used medications.

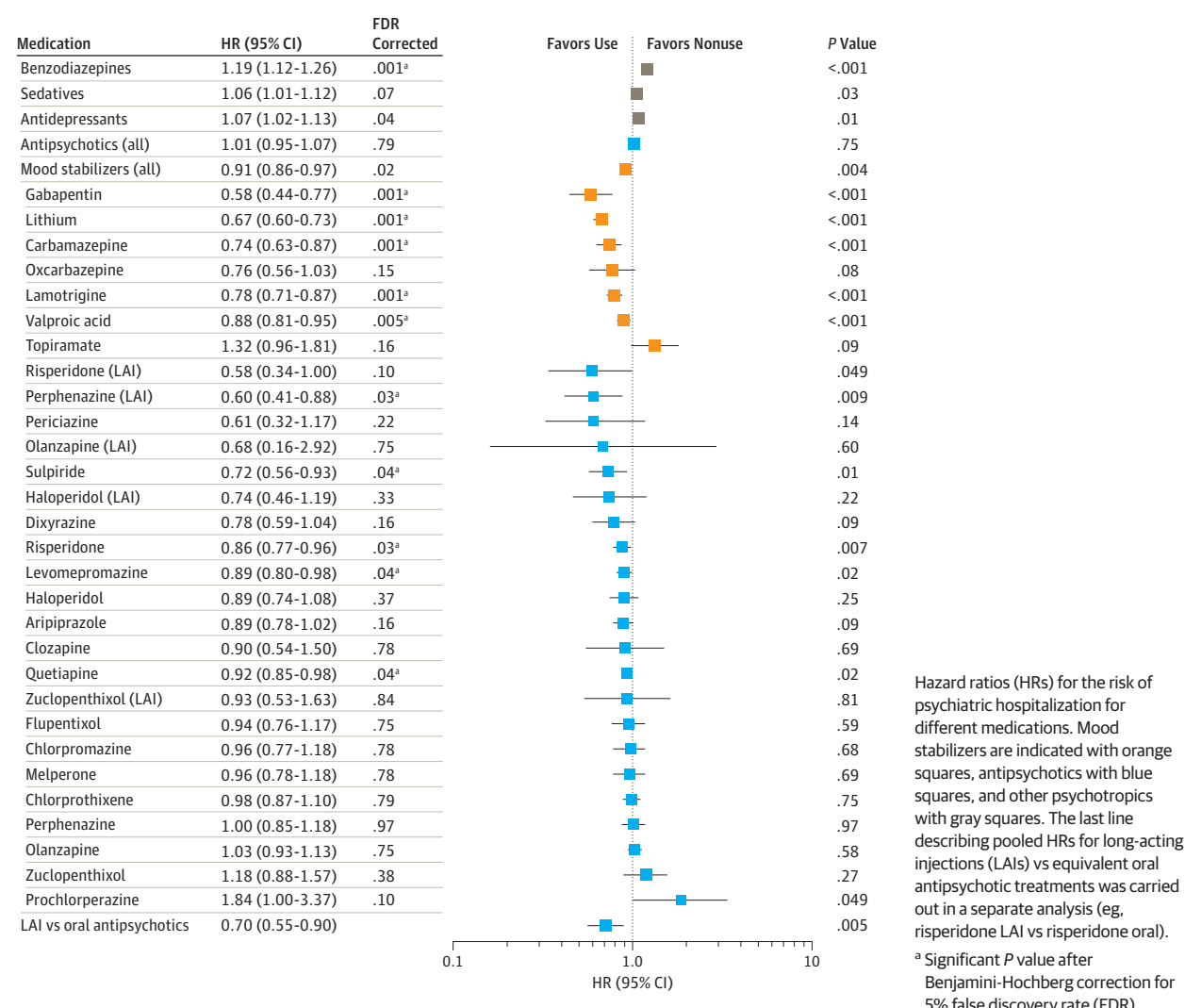
The analyses used the within-individual Cox proportional hazards regression model in which each individual is assigned his or her own stratum and the follow-up time is reset at the initiation of a new treatment, thus eliminating selection bias (eFigure in the [Supplement](#)).²¹ Other time-dependent adjusting variables considered to increase the reliability of the analysis are detailed in eTables 1 and 2 in the [Supplement](#) (for all analyses: the effect of time since diagnosis, order of treatments, current use of other treatments, and polypharmacy; for the traditional analysis models: number of rehospitalizations within 2 years prior to index date [indicator of inherent risk of relapse], age at index date, sex, and calendar year of index date). $P < .05$ was considered significant. The P values shown in the figures were corrected for multiple comparisons using the Benjamini-Hochberg false discovery rate method. The P values shown in the eTables have not been corrected for multiple comparisons. The antipsychotic thioridazine hydrochloride was included in the original analyses. However, since it was withdrawn from the market in the middle of the observation period in 2006, no data for thioridazine are shown because they might be skewed. The analyses for thioridazine were incorporated into the multiple comparisons corrections, so as to not underestimate type I error.

As observational studies are prone to bias and confounding, a number of sensitivity analyses were performed. As a general sensitivity analysis, the within-individual Cox proportional hazards regression analyses for risk of psychiatric and all-cause rehospitalization were also performed by doing time resets at outcome (hospitalization) rather than at initiation of a new treatment (eTables 3 and 4 in the [Supplement](#)). To account for putative survival bias (selective mortality owing to previous treatments) for the primary analysis, the primary analysis for psychiatric rehospitalization was also performed in the incident cohort (eTable 5 in the [Supplement](#)). A total of 8714 patients did not have psychiatric rehospitalizations, 4609 did not have all-cause hospitalizations, and 15 662 did not have cardiovascular hospitalizations or variation in the exposure and, therefore, did not contribute to the corresponding within-individual analysis. To test for generalizability in the total cohort population (also including patients without any outcome incidents or any changes in their medication during follow-up), traditional between-groups Cox proportional hazards regression analyses were also performed for all primary and secondary outcomes (psychiatric hospitalization, all-cause hospitalization, and cardiovascular hospitalization) (eTables 6-8 in the [Supplement](#)).

Results

The mean (SD) age of the cohort was 46.6 (17.0) years, and the cohort included 9558 women and 8460 men. A total of 9721 patients (54.0%) had at least 1 psychiatric rehospitalization. The sociodemographic, clinical, and treatment characteristics of the total cohort and the incident cohorts are shown in the Table. The study cohort consisted of 18 018 individuals with a total observation time of 128 353 person-years, with a mean observation (follow-up) time of 7.2 years (range, 1 day-17.0 years). Since 141 patients were hospitalized during their entire follow-up, 17 877 patients were at risk for rehospitalization. During this period, we observed a total of 82 858 hospitalizations (for any cause; approximately 4.6 per individual), of which 36 131 were psychiatric hospitalizations (approx-

Figure 1. Within-Individual Analysis of Psychiatric Hospitalization

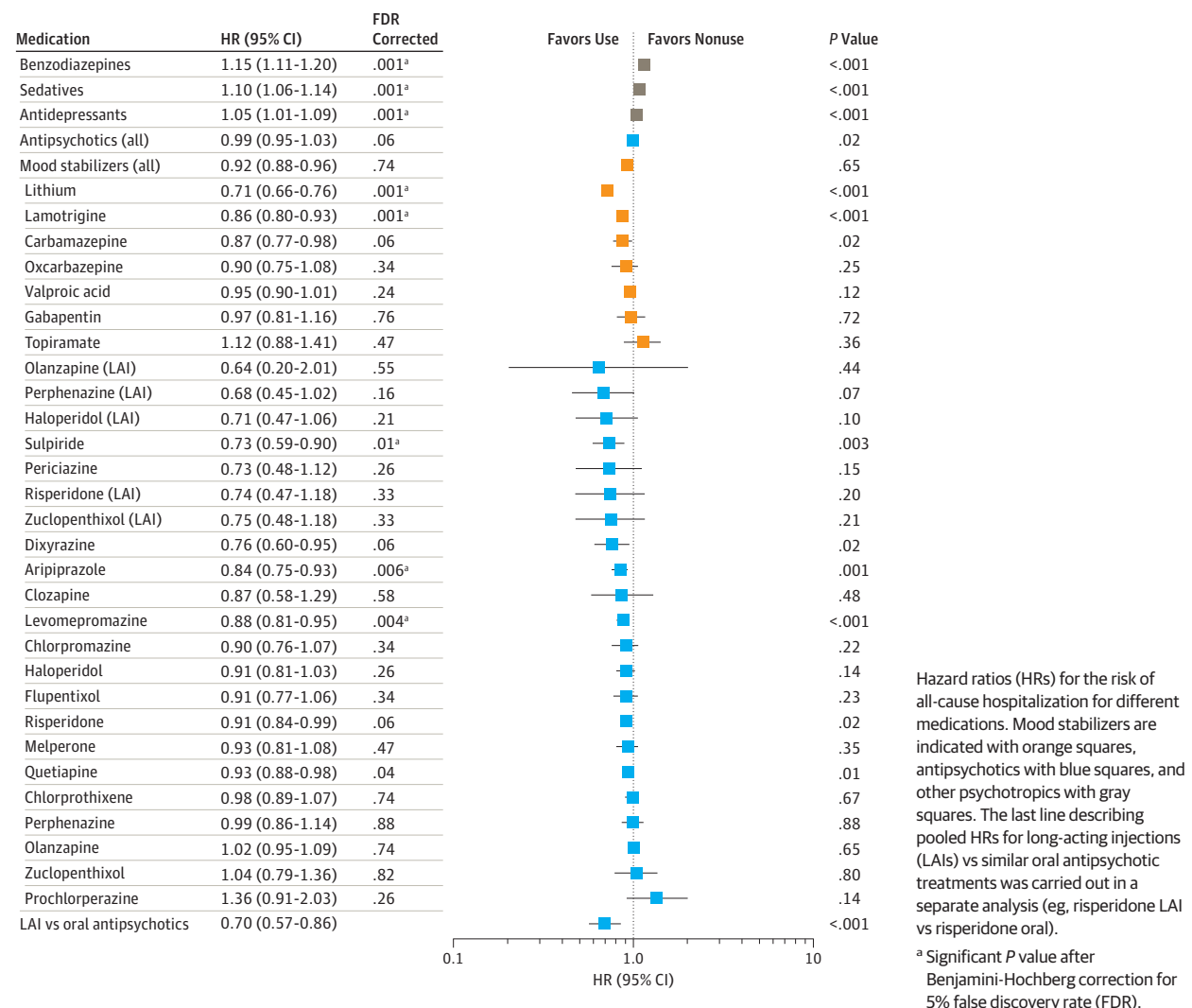


mately 2.0 per individual) and 4862 were for cardiovascular reasons (approximately 0.3 per individual). The person-years and events of rehospitalization are shown in eTables 3, 4, and 8 in the [Supplement](#).

Figure 1, Figure 2, and Figure 3 display hazard ratios (HRs) for hospitalization during use vs no use of specific psychopharmacologic treatments. The results for psychiatric rehospitalization are shown in Figure 1. As a therapeutic group, only mood stabilizers were associated with a decreased risk of relapse leading to psychiatric hospitalization, and the risk reduction remains modest (HR, 0.91 [95% CI, 0.86-0.97]). However, when comparing individual medications instead of therapeutic groups, more pronounced differences and risk reductions emerge. Of all the medications analyzed reaching nominal statistical significance, risperidone LAI (HR, 0.58 [95% CI, 0.34-1.00]; $P = .049$) was associated with the lowest risk of psychiatric rehospitalization, followed by gabapentin (HR, 0.58 [95% CI, 0.44-0.77]), perphenazine LAI (HR, 0.60 [95% CI, 0.41-0.88]), and lithium (HR, 0.67 [95% CI, 0.60-0.73]). Owing to a relatively low

number of person-years, the result for risperidone LAI did not reach significance when correction for multiple comparisons was applied. The statistically significant results for gabapentin and sulpiride did not survive sensitivity analyses with time resets at outcome (hospitalization) (eTable 3 in the [Supplement](#)). In general, LAIs were associated with a significantly lower risk of psychiatric rehospitalizations than their oral counterparts (HR, 0.70 [95% CI, 0.55-0.90]), although the number of LAIs administered was low and the HRs for many individual LAI formulations did not reach statistical significance. In the sensitivity analysis with time reset at outcome, neither risperidone LAI nor perphenazine LAI remained statistically significant, but in the overall comparisons, LAIs were superior to identical oral formulations. The most frequently used antipsychotic treatment, quetiapine fumarate, showed only modest effectiveness (risk of psychiatric rehospitalization: HR, 0.92 [95% CI, 0.85-0.98]). Benzodiazepine use was associated with an increased risk of psychiatric rehospitalization (HR, 1.19 [95% CI, 1.12-1.26]).

Figure 2. Within-Individual Analysis of All-Cause Hospitalization



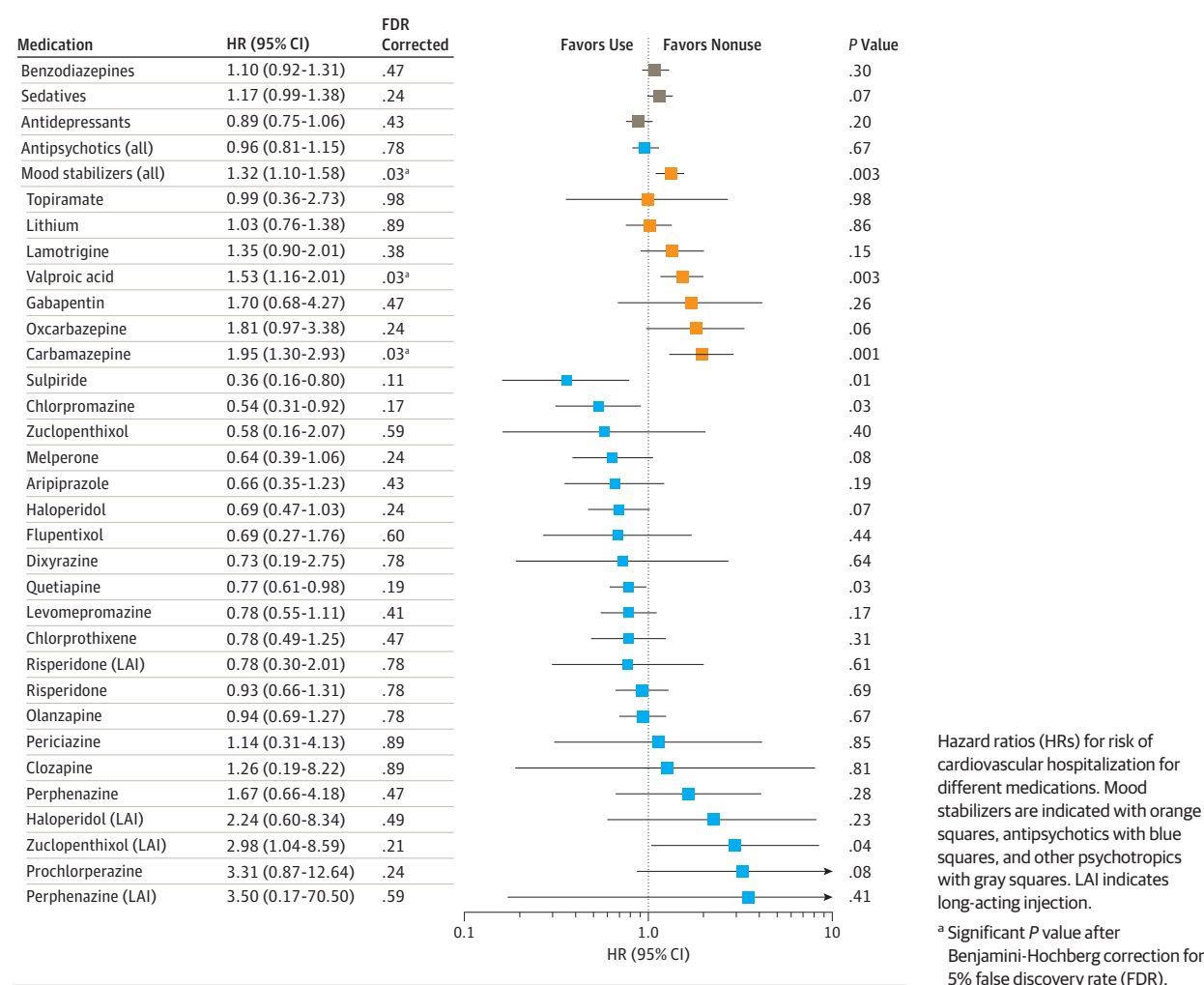
The results for all-cause hospitalizations are shown in Figure 2. Of all the medications studied, lithium (HR, 0.71 [95% CI, 0.66-0.76]) and sulpiride (HR, 0.73 [95% CI, 0.59-0.90]) were associated with the best outcomes. The lowered risk for sulpiride did not survive sensitivity analysis with time reset at outcome (hospitalization) (eTable 4 in the [Supplement](#)). Long-acting injections were associated with substantially better outcomes compared with identical oral antipsychotics (HR, 0.70 [95% CI, 0.57-0.86]). Quetiapine again showed only modest effectiveness (risk of all-cause hospitalization: HR, 0.93; 0.88-0.98). Benzodiazepine use was associated with an increased risk of hospitalization for any cause (HR, 1.15 [95% CI, 1.11-1.20]).

The results for cardiovascular hospitalizations are shown in Figure 3. Mood stabilizers as a therapeutic group were associated with an increased risk of cardiovascular hospitalization (HR, 1.32 [95% CI, 1.10-1.58]). However, of the individual mood stabilizers, only valproic acid (HR, 1.53 [95% CI, 1.16-2.01]) and carbamazepine (HR, 1.95 [95% CI, 1.30-2.93]) were associated with a significantly increased risk of cardiovascu-

lar hospitalization. Apart from the mentioned mood stabilizers, no other medications were associated with a significantly altered risk of cardiovascular hospitalization when false discovery rate correction was applied, although sulpiride (HR, 0.36 [95% CI, 0.16-0.80]) and chlorpromazine (HR, 0.54 [95% CI, 0.31-0.92]) had 95% CIs suggesting an association with a lowered risk. In the comparison between the 3 most frequently used medications, lithium was associated with the lowest incidence of hospitalization owing to physical illness (6635 hospitalizations per 24 815 person-years [0.27 hospitalizations per person-year]), followed by valproate (9849 hospitalizations per 26 091 person-years [0.38 hospitalizations per person-year]) and quetiapine (8642 hospitalizations per 22 092 person-years [0.39 hospitalizations per person-year]).

Results from sensitivity analyses are shown in eTables 3 to 8 in the [Supplement](#) (showing also raw data on incidents and person-years). The main results on the comparative effectiveness of lithium and LAIs were in line with the previous analyses.

Figure 3. Within-Individual Analysis of Cardiovascular Hospitalization



Discussion

To our knowledge, this is the first study on the comparative real-world effectiveness of all widely used psychopharmacologic agents and routes of administration in bipolar disorder. The main results of our study indicate that lithium is superior to other mood stabilizers and that LAIs are markedly better than identical oral formulations of antipsychotics.

Our most important finding is that when a patient with bipolar disorder uses an LAI, the patient's risk of relapse leading to psychiatric hospitalization as well as all-cause hospitalization owing to mental or somatic illness is about 30% lower than during time periods when the same patient uses an identical oral antipsychotic. It is questionable if this result can be generalized with certainty to patients who have never used LAIs. However, in the traditional between-individual analysis including all patients, all LAIs were associated with a substantially lower risk of rehospitalizations than their identical oral formulations. This result is similar to results from a Swedish nationwide cohort of patients with schizophrenia, which indicate that insufficient treatment adherence is a similar prob-

lem in bipolar disorder and schizophrenia.²² Most treatment guidelines¹⁰ do not encourage the use of LAIs instead of oral formulations, which is owing to lack of any studies on head-to-head comparison between LAIs and oral formulations.

Our results indicate that, as a therapeutic group, mood stabilizers are associated with the lowest risk of psychiatric hospitalization in bipolar patients. Of the specific medications studied in order of risk reduction, risperidone LAI, gabapentin, perphenazine LAI, lithium, sulpiride, carbamazepine, lamotrigine, risperidone, valproic acid, levomepromazine maleate, and quetiapine were associated with a lowered risk of psychiatric hospitalization. However, from the medications listed, the results with gabapentin and sulpiride did not survive sensitivity analyses with time reset at outcome rather than treatment initiation (eFigure in the Supplement). In addition, the result for risperidone LAI did not remain statistically significant when corrected for multiple comparisons. Therefore, the results for these medications should be interpreted with caution. The Finnish national treatment guidelines recommend avoiding ("Do not do") the use of gabapentin as monotherapy for either bipolar mania or bipolar depression in ("Käypä hoito" [current care guidelines]). Gabapentin is thus

rarely used as a first-line medication for bipolar disorder. However, some studies have suggested that gabapentin might be effective, especially as an adjunct treatment to prevent relapses in bipolar disorder.²³

As previous studies have reported,¹³⁻¹⁷ we also observed a marked association for reduced risk of psychiatric hospitalization with lithium. Surprisingly, lithium use was also associated with the lowest risk of hospitalization for any cause of all the compounds studied. The incidence of hospitalization owing to any physical illness was substantially lower during lithium treatment when compared with 2 of the other most frequently used medications, valproate and quetiapine. Mood stabilizers as a group were associated with an increased risk of cardiovascular hospitalization, and, of the individual mood stabilizers, only valproic acid and carbamazepine were associated with a significant increase in risk. High serum carbamazepine levels have been associated with coma, seizures, respiratory failure, sinus tachycardia, and cardiac conduction defects in previous studies,^{24,25} and valproic acid use has been associated with increased weight gain,²⁶ although studies that have not found such associations exist as well.²⁷ The observed potential risk with these medications should, however, be considered when prescribing these medications in clinical practice.

Benzodiazepine use was associated with an increased risk for both psychiatric hospitalization and hospitalization for any cause, as reported previously.²⁸⁻³⁰ Although the within-individual model does control for confounding related to anxiety, we cannot rule out that some of the observed association with an increased risk for hospitalization with benzodiazepines comes from patients with an acutely worsened state of comorbid anxiety or a substance abuse disorder. As data on the harmful effects of long-term benzodiazepine use are becoming more prominent, care should be taken when prescribing these medications to ensure they remain in use for only as long as necessary.

Limitations

Although our study was comprehensive, any results should be interpreted with caution. The study population included only Finns, and as such, all patients were diagnosed with Finnish *International Classification of Diseases, Ninth Revision* and *ICD-10* criteria according to Finnish practice. Although Finnish registries are comprehensive and of high quality,³¹ they still do not contain all the information that would be needed to per-

form optimal observational studies. Sources of bias are thus unavoidable. The most prominent of these biases is confounding by indication, which rises from the fact that treatments for individual patients are (it is hoped) not selected at random but are rather products of comprehensive clinical decision making, the reasons for which are often not stored in basic registries. However, the within-individual approach used here eliminates bias from permanent individual characteristics since the individual is used as his or her own control. In between-individual analysis, the order of comparative effectiveness was in line with the results from the within-individual analysis, but the HRs were higher than in the primary within-individual analysis, indicating residual confounding due to selection bias (ie, the most mildly ill patients did not use any medication during the follow-up). The results of the study also must be framed in the context of the primary outcome (hospitalization). Although this is a measurable, reliable, and clinically relevant outcome, bipolar disorder morbidity is not limited to full episodes or suicidality requiring hospitalization. Hence, the findings on drug effectiveness do not necessarily apply to alleviating other symptoms that do not often lead to hospitalization, such as subthreshold depressive symptoms,³² which have a strong effect on psychosocial functioning.³³ Moreover, since mania is a more common cause of hospitalization than is depression, the results may be favoring compounds with a high polarity index³⁴ (more antimanic than antidepressant preventive efficacy) or with antisuicidal properties,³⁵ as suicidal patients are more often hospitalized.

Conclusions

According to our data, lithium is associated with substantially reduced risks of psychiatric and all-cause hospitalization and should remain as the first line of treatment for bipolar disorder, after decades of underprescription.³⁵ The most widely used agent, quetiapine, showed only modest effectiveness (8% risk reduction), which does not support its use for this indication. Long-acting injectable formulations of antipsychotic medications were associated with approximately a 30% lower risk than identical oral formulations of the same medication. Although more research is needed to support the notion, LAIs might offer a safe and effective option for relapse prevention in bipolar disorder for patients for whom lithium is not suitable.

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Conflict of Interest Disclosures: Dr Lähteenvuori reported being a major shareholder and board member at Genomi Solutions Ltd, a Finnish based bioinformatics company; receiving research grants or awards from Boehringer-Ingelheim; receiving travel grants from Sunovion Ltd; and working as a coordinator for a research project funded by the Stanley Foundation. Dr Tanskanen reported participating in research projects funded by Janssen Cilag and Eli Lilly with grants paid to the Karolinska Institutet and serving as a member of the advisory board for Janssen-Cilag. Dr Taipale reported participating in research projects funded by Janssen-Cilag and Eli Lilly, with grants paid to the Karolinska Institutet. Dr Hoti and Ms Vattulainen are employed by EPID Research, which is a contract research organization that performs commissioned pharmacoepidemiologic studies; thus, its employees have been and currently are working in collaboration with several pharmaceutical companies. Dr Vieta reported receiving grants and serving as consultant, advisor, or continuing medical education speaker for AB-Biotics, Aequus, Adamed, Alexza, Allergan, Almirall, AstraZeneca, Bial, Bristol-Myers Squibb, Daiichi Sankyo, Forest Research Institute, Gedeon Richter, GlaxoSmithKline, Janssen-Cilag, Jazz, Johnson & Johnson, Lundbeck, Merck, Novartis, Organon, Otsuka, Pfizer, Pierre-Fabre, Rovi, Qualigen, Roche, Sanofi, Servier, Schering-Plough, Shire, Solvay, Sunovion, Takeda, Telefónica, Teva, the Spanish Ministry of Science and Innovation, the Seventh European Framework Programme, the Stanley Medical Research Institute, United Biosource Corporation, and Wyeth. Dr Tiihonen reported serving as a consultant to AstraZeneca, Bristol-Myers Squibb, Eli Lilly, F. Hoffman-La Roche, Janssen-Cilag, Lundbeck, Organon, and Finnish Medicines Agency; receiving fees for giving expert testimony to AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Otsuka, and Pfizer; receiving lecture fees from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Novartis, Otsuka, and Pfizer; receiving grants from Stanley Foundation and Sigrid Jusélius Foundation; serving as a member of advisory boards for AstraZeneca, Eli Lilly, Janssen-Cilag, and Otsuka; and having research collaboration with Lilly and Janssen-Cilag.

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