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Comparison of 30 bipolar disorder monotherapies for risk of psychiatric hospitalization

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Abstract

We present the results of one of the most comprehensive large-scale retrospective observational studies on drug-dependent risk of hospitalization in bipolar disorder (BD), funded by the Patient-Centered Outcomes Research Institute (CER-1507-3160). The data were obtained from the Truven Health Analytics MarketScan® administrative claims database, containing information on 1.3 million US patients with BD, transformed to the OMOP common data model v5.0.1. Competing risk regression was used to compare 30 monotherapies with respect to the risk of first psychiatric hospitalization after treatment initiation, adjusting for multiple explanatory variables including age, sex, inpatient/outpatient status, comorbidities, and concomitant drugs.

Introduction

The evidence-based data on comparative effectiveness of bipolar disorder (BD) drugs is still incomplete and contradictory. Consistency of research findings is often compromised by methodological biases[1] and diversity of studied BD outcomes. Hospitalization is an outcome of great socioeconomic importance[2] with high incidence: hospital admission due to severe mood episode occurs in 17-40% of patients within the first year following BD acute phase treatment[3] in 50% of patients within 4 years[4] and in 79% of patients within 15 years[5]. Time to hospitalization can be analyzed as a function of pharmacotherapy, providing evidence on the comparative efficacy of drugs to inform providers' treatment choices.

The majority of published retrospective BD studies on drug dependent hospitalization risk compare a limited number of drugs, have sample sizes up to 28,000 cases, and are restricted to outpatient visits with BD type I diagnosis. This study on BD monotherapies covers 30 drugs from different pharmacological groups, has a sample size of 191,196 cases, includes both in- and outpatient adults with BD type I/II/NOS, as well as schizoaffective disorder (SAD) to account for lack of clinical distinction between the two diseases. Moreover, it uses competing risk regression to distinguish between psychiatric and non-psychiatric hospitalization outcomes as well as drug switching/ending (versus a problematic "intent-to-treat" model).

Methods

The data were obtained from the Truven Health Analytics MarketScan® administrative claims database, containing information on 1.3 million US patients with BD. Data have been transformed to the Observational Medical Outcomes Partnership (OMOP) common data model version 5.0.1[6], using the OHDSI ETL-CDMBuilder tool (https://github.com/OHDSI/ETL-CDMBuilder). We analyzed data on 191,196 inpatient and outpatient adults who had ≥2 diagnostic codes for BD or SAD during the observation period 2003-2015 and were newly prescribed one of 30 drugs of interest, including lithium, mood stabilizing anticonvulsants (MSA), first- and second-generation antipsychotics (FGA, SGA), and antidepressants. Each drug of interest had at least 250 observations that met the study design of Figure 1. The following sequence of events per patient was considered (Figure 1): 1) A 12-month "washout" period with no drugs of interest and no hospitalization/ER visit with primary psychiatric code; 2) inpatient or outpatient mood episode meta-visit ("index visit") defined as a consecutive sequence of visits, at least one of which has a primary psychiatric diagnosis and code for BD, SAD or major depressive disorder (MDD); 3) prescription of the drug of interest ("index prescription"); 4) hospitalization/ER meta-visit with psychiatric code or other competing risk event (somatic hospitalization/ER meta-visit, drug switching).

Competing risk regression was used to compare 30 monotherapies with respect to the risk of the first event of interest after index prescription, adjusting for multiple explanatory variables including age, sex, mode of prescription (inpatient or outpatient), 55 mental and somatic comorbidities, and 35 classes of concomitant drugs in use. A forward stepwise selection procedure was performed to select model covariates.

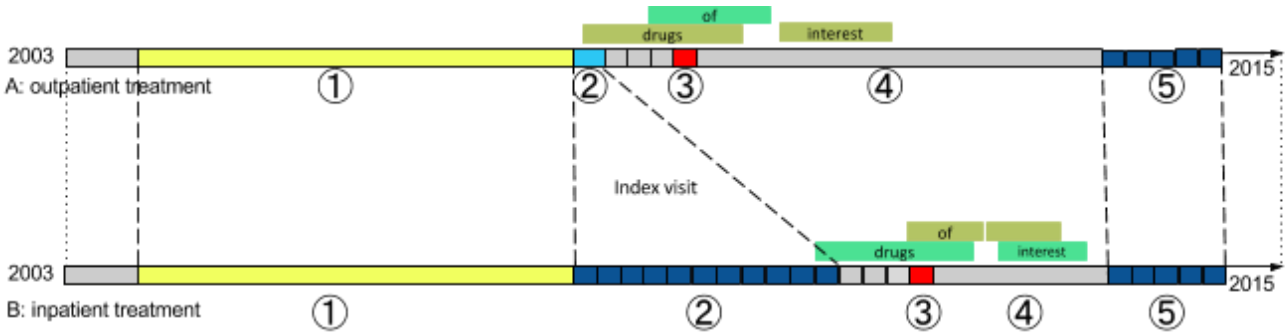

Figure 1. Sequence of events of interest in two cohorts (outpatient or inpatient prescription mode). (1) "Washout"; (2) Index visit: A) outpatient mood episode meta-visit B) mood episode hospitalization; (3) Index prescription: set of drugs active on the 4th day after A) outpatient visit B) discharge; (4) Time to psychiatric hospitalization/ER visit with competing risk of other events; (5) Outcome: first psychiatric hospitalization/ER visit or another competing risk event.

Results

The majority of patients were females (62.4%), with most (73.9%) of the population aged ≤45 years. Diagnosis of MDD constituted 44.7% of all index visits, SAD - only 2.2%. Mood episode polarity was recorded in 70.0% of all cases with 73.3% of them being depressive. Psychotic features were present in 7.5% of index meta-visits. Prescription of the drug of interest was predominantly made in the outpatient setting (89.8%). The most commonly prescribed drug class was antidepressants followed by MSA, SGA, lithium, FGA and clozapine. The duration of observation ranged from 1 day to 3683 days (10 years). We report results up to 4 years from the start of monotherapy due to the paucity of longer term observations.

Half of the patients experienced one of the competing risks by day 32, mostly due to either switching to another drug schema or failing to make a refill within 30 days. The drugs' risk profiles were different for psychiatric and somatic hospitalization/ER visits. For psychiatric hospitalization, MSAs performed comparably or better than lithium, with valproate having significantly lower risk. Among antipsychotics, clozapine and haloperidol had significantly higher risk than lithium, and aripiprazole had significantly lower risk. Among antidepressants, most SSRIs as well as two SNRIs had significantly higher risk than lithium, whereas the NDRI buproprion was significantly protective.

Conclusion

Statistically significant differences exist between classes and individual therapies in the risk of psychiatric and somatic hospitalization. Accounting for competing risks (particularly drug switching/ending) is an essential tool in survival-based comparative safety and effectiveness research.

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