Comparison of 29 monotherapies for psychiatric hospitalization risk in bipolar spectrum disorders

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Abstract

We present one of the largest reported retrospective observational study on drug-dependent risk of hospitalization in bipolar spectrum disorders, funded by the Patient-Centered Outcomes Research Institute (CER-1507-3160). The data were obtained from the Truven Health Analytics MarketScan® administrative claims database, transformed to the OMOP common data model v5.0.1. Competing risk regression was used to compare 29 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.

Background

- Hospitalization is an outcome of great clinical and socioeconomic importance, occurring in 17-40% patients with bipolar disorder (BD) in the first year following acute phase treatment [1].
- Evidence on drug-dependent risk of hospitalization in BD is incomplete and contradictory.
- Previous studies compared few drugs, had limited sample sizes (<28,000), mostly focused on outpatient visits only and BD type I.
- This study covers 29 drugs, has a sample size of 190,894 cases, includes both in- and outpatient adults with all BD types, as well as with schizoaffective disorder (SAD).

Methods

- Truven Health Analytics MarketScan® administrative claims database: 1.3M US patients with BD.
- Data transformed to the **OMOP common data model version 5.0.1.**
- **Inclusion criteria:** age 18-65 years, ≥2 diagnostic codes for BD or SAD during 2003-2015, newly prescribed one of 29 drugs of interest (Figure 1).
- **Exclusion criteria**: schizophrenia, chronic delusional disorders, intellectual disabilities, autism-spectrum disorders, organic mental disorders, Parkinson's disease, anti-dementia drugs occurring prior to and including the index prescription date.
- **Drugs of interest** (n≥250): *lithium, mood stabilizing anticonvulsants (MSAs), first- and second-generation antipsychotics (FGAs, SGAs), antidepressants (ADs).*
- **Competing risk regression** was used to compare 29 monotherapies with respect to the risk of the first event of interest after index prescription.
- **Covariates (forward stepwise selection):** age, sex, mode of prescription (inpatient or outpatient), 55 mental and somatic comorbidities, 35 classes of concomitant drugs in use.
- **Vocabularies:** loss of information from OMOP vocabulary mappings necessitated hand curation of CPT4, HCPCS, ICD9CM, ICD9Proc, ICD10CM, ICD10PCS terms, using source concept ids. Mapped SNOMED concept ids were used for comorbidities. MESHPA was used to select classes of RxNorm drug codes.
- **Injury covariate:** a pool of diagnostic and procedure codes was created manually. Three MD raters independently scored 10,000+ codes for probable injury. Discrepancies were resolved by consensus.
- **Data staging**: custom event oriented SQL pipeline. Atlas did not support a meta-visit concept.

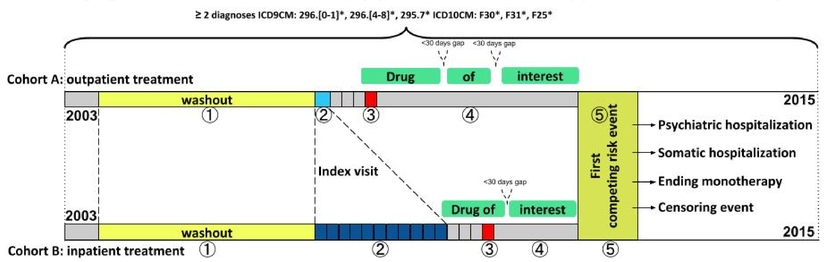

Figure 1: Sequence of events of interest

1) **12-month "washout" period:** no drugs of interest, no hospitalization/ER visit with primary psychiatric code;
2) **Index visit:** inpatient or outpatient mood episode meta-visit defined as a consecutive sequence of visits, at least one of which has a primary psychiatric diagnosis+code for BD, SAD or major depressive disorder (MDD);
3) **Index prescription:** prescription filled on or before the 4th day after outpatient visit/discharge;
4) **Competing risk outcomes:** (i) hospitalization/ER meta-visit with psychiatric code; (ii) hospitalization/ER meta-visit without psychiatric code ("somatic hospitalization"); (iii) ending monotherapy (changing schema/30-day non-refill); (iv) censoring event (death, end of data, occurrence of excluded conditions/drugs)

Results

- Observation range: **1 day - 10 years** (scarce data after year 4).
- 50% of patients experienced one of the competing risks by day 32, mostly due to changing drug schema (25.5 - 57.1%) or non-refill (22.9-57.8%).
- 1-year rate of psychiatric hospitalization: 4.1-11.9%, of somatic hospitalization: 2.4-6.5%.
- Most commonly prescribed drug classes: **ADs > MSAs and lithium > SGAs > FGAs.**
- Compared to lithium MSAs performed better, many ADs, SGAs, and haloperidol – worse.
- There is a **heterogeneity** of risk of psychiatric hospitalization within a given drug class (Figure 2).
- **↓ risk of psychiatric hospitalization** (versus lithium): *valproate, aripiprazole, bupropion* (Table 1).
- **↑ risk of psychiatric hospitalization** (versus lithium): *haloperidol, clozapine, fluoxetine, sertraline, citalopram, duloxetine, venlafaxine, ziprasidone* (Table 1).
- **↓ risk of psychiatric hospitalization:** verified BD diagnostic subtype (I or II), antibacterial and non-steroidal anti-inflammatory drugs.
- **↑ risk of psychiatric hospitalization:** previous hospitalization due to mood episode, comorbid substance use disorder, index mood episode with depression or psychotic features, pulmonary and cardiovascular diseases, loop diuretics, non-mood stabilizing anticonvulsants, anxiolytics, sedatives, analgesics.

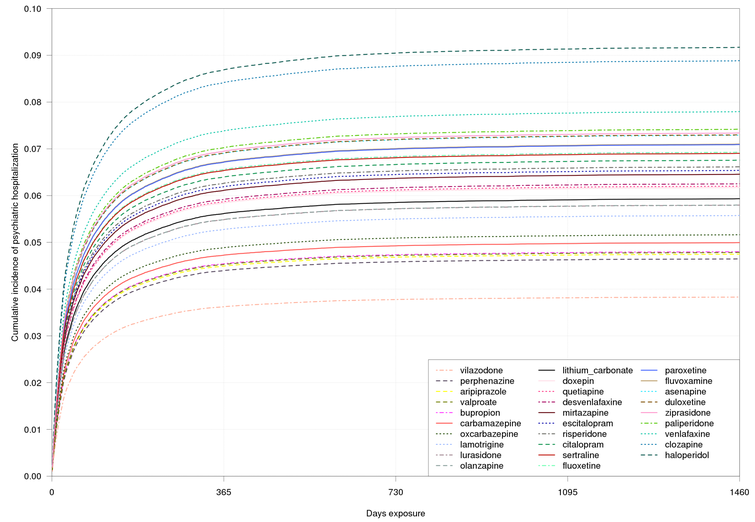

Figure 2. The cumulative incidence of psychiatric hospitalization for all 29 monotherapies based on the regression model at the average value of non-drug covariates. Drugs in the legend are sorted from lowest risk to highest.

Conclusions

1. Accounting for **competing risks** (particularly drug switching/ending) is an essential tool in survival-based comparative safety and effectiveness research.
2. With some exceptions, the drug-dependent risk of psychiatric hospitalization is **lowest for MSAs and lithium, and highest with antidepressants and antipsychotics.**
3. The data add to the evidence supporting the relative efficacy of **lithium and valproate** for reducing hospitalization risk in bipolar disorder.
4. Results highlight the potential **liabilities of antidepressant** use in BD.
5. Better performance of dopaminergic drugs aripiprazole and bupropion requires further investigation.

References

1. Woo YS, Bahk W-M, Jung Y-E, Jeong J-H, Lee H-B, Won S-H, et al. One-year rehospitalization rates of patients with first-episode bipolar mania receiving lithium or valproate and adjunctive atypical antipsychotics. Psychiatry Clin Neurosci. 2014 Jun;68(6):418–24.

Table 1. Competing risk regression model of psychiatric hospitalization risk in bipolar disorders. The model includes 29 drugs with lithium as a reference, as well as age, sex and other variables that were significant during the stepwise selection procedure. Wald test p-values show the combined significance for all drugs in a class relative to lithium. Statistically significant risk factors are shown in bold.

Variable	Coef	RR	se(coef)	p-value
First generation antipsychotics: (Wald test)	-	-	-	**2.32E-03**
haloperidol	**4.53E-01**	**1.57**	**1.37E-01**	**9.40E-04**
perphenazine	-2.51E-01	0.78	2.82E-01	3.70E-01
Second generation antipsychotics: (Wald test)	-	-	-	**7.99E-08**
clozapine	**4.19E-01**	**1.52**	**1.76E-01**	**1.70E-02**
paliperidone	2.31E-01	1.26	1.87E-01	2.20E-01
ziprasidone	**2.20E-01**	**1.25**	**8.04E-02**	**6.20E-03**
asenapine	2.13E-01	1.24	2.41E-01	3.80E-01
risperidone	1.12E-01	1.12	6.48E-02	8.30E-02
quetiapine	4.59E-02	1.05	5.54E-02	4.10E-01
olanzapine	-2.36E-02	0.98	7.32E-02	7.50E-01
lurasidone	-2.41E-02	0.98	1.75E-01	8.90E-01
aripiprazole	**-2.29E-01**	**0.80**	**6.41E-02**	**3.50E-04**
Antidepressants: (Wald test)	-	-	-	**1.31E-18**
venlafaxine	**2.83E-01**	**1.33**	**5.78E-02**	**1.00E-06**
duloxetine	**2.14E-01**	**1.24**	**6.17E-02**	**5.10E-04**
paroxetine	1.84E-01	1.20	1.66E-01	2.70E-01
fluvoxamine	1.86E-01	1.20	1.84E-01	3.10E-01
sertraline	**1.57E-01**	**1.17**	**5.32E-02**	**3.20E-03**
fluoxetine	**1.60E-01**	**1.17**	**5.52E-02**	**3.70E-03**
citalopram	**1.34E-01**	**1.14**	**5.43E-02**	**1.30E-02**
escitalopram	1.00E-01	1.11	5.38E-02	6.20E-02
mirtazapine	8.72E-02	1.09	8.12E-02	2.80E-01
desvenlafaxine	5.41E-02	1.06	1.09E-01	6.20E-01
doxepin	4.09E-02	1.04	1.94E-01	8.30E-01
bupropion	**-2.18E-01**	**0.80**	**5.99E-02**	**2.80E-04**
vilazodone	-4.49E-01	0.64	2.67E-01	9.30E-02
Mood stabilizing anticonvulsants: (Wald test)	-	-	-	**3.85E-03**
lamotrigine	-6.43E-02	0.94	5.32E-02	2.30E-01
oxcarbazepine	-1.43E-01	0.87	8.60E-02	9.60E-02
carbamazepine	-1.77E-01	0.84	1.17E-01	1.30E-01
valproate	**-2.21E-01**	**0.80**	**6.15E-02**	**3.20E-04**
Other variables not related to drugs:				
inpatient prescription mode	**5.21E-01**	**1.68**	**3.00E-02**	**<2.23E-308**
drug abuse/dependence	**3.21E-01**	**1.38**	**2.73E-02**	**<2.23E-308**
loop diuretics	**3.02E-01**	**1.35**	**7.13E-02**	**2.30E-05**
other drugs acting on central nervous system	**2.73E-01**	**1.31**	**2.09E-02**	**<2.23E-308**
baseline depressive mood episode	**2.17E-01**	**1.24**	**2.23E-02**	**<2.23E-308**
baseline psychotic features	**1.98E-01**	**1.22**	**3.41E-02**	**5.80E-09**
pulmonary diseases	**2.02E-01**	**1.22**	**4.69E-02**	**1.70E-05**
cardiovascular diseases	**1.00E-01**	**1.11**	**2.32E-02**	**1.60E-05**
male sex	2.48E-02	1.03	1.92E-02	2.00E-01
age at index prescription	**-5.81E-03**	**0.99**	**8.04E-04**	**4.90E-13**
antibacterial agents	**-7.86E-02**	**0.92**	**2.07E-02**	**1.50E-04**
non-steroid anti-inflammatory drugs	**-1.28E-01**	**0.88**	**2.57E-02**	**6.10E-07**
bipolar type I at index visit	**-2.99E-01**	**0.74**	**2.23E-02**	**<2.23E-308**
bipolar type II at index visit	**-3.03E-01**	**0.74**	**3.57E-02**	**<2.23E-308**