Comparing 102 psychotropic drug regimens for diabetes mellitus risk

Anastasiya Nestsiarovich, M.D., Ph.D.[1], Berit Kerner, M.D.[2], Aurélien J. Mazurie, Ph.D.[3], Daniel C. Cannon[4], Yiliang Zhu, Ph.D.[5], Stuart J. Nelson, M.D.[6,7], Tudor I. Oprea, M.D., Ph.D.[7], Annette S. Crisanti, Ph.D.[8], Mauricio Tohen, M.D., Dr.PH., MBA[8], Douglas J. Perkins, Ph.D.[1], Christophe G. Lambert, Ph.D.[1,7]

[1] Center for Global Health, Department of Internal Medicine, University of New Mexico Health Sciences Center, Albuquerque, New Mexico, USA
[2] Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine, University of California, Los Angeles, California, USA
[3] TwoFoldChange Consulting, Bozeman, Montana, USA.
[4] Iterative Consulting, Albuquerque, New Mexico, USA
[5] Division of Epidemiology, Biostatistics, and Preventive Medicine, Department of Internal Medicine, University of New Mexico Health Sciences Center, Albuquerque, New Mexico, USA
[6] University of New Mexico Health Sciences Library and Informatics Center, Albuquerque, New Mexico, USA.
[7] Translational Informatics Division, Department of Internal Medicine, University of New Mexico Health Sciences Center, Albuquerque, New Mexico, USA.
[8] Department of Psychiatry & Behavioral Sciences, University of New Mexico Health Sciences Center, Albuquerque, New Mexico, USA.

Abstract

The risk of diabetes mellitus (DM) was compared among 102 bipolar disorder (BD) drug regimens with "No drug" as a reference. The IBM MarketScan® administrative claims database was used to retrospectively analyze data on 565,253 adults with BD without prior glucose metabolism-related diagnoses. The pharmacotherapies compared were lithium, mood-stabilizing anticonvulsants, antipsychotics, and antidepressants (monotherapy and multi-class polypharmacy). Cox regression modeling included fixed pre-treatment covariates and time-varying drug exposure covariates to estimate the hazard ratio of each treatment versus "No drug". The findings show an increased DM risk associated with antipsychotic use and multi-drug treatments. The evidence of a lower-than-baseline risk of DM with lamotrigine, oxcarbazepine, lithium, and bupropion monotherapy should be further investigated.

Background

Patients with BD have 1.7-3.2 times higher risk of diabetes mellitus (DM) compared with age- and gender-matched controls.[1,2] While biological factors and lifestyle play major roles in metabolic alterations, recent studies provide evidence on the diabetogenic properties of psychotropic drugs, in particular, antipsychotics and antidepressants.[3,4] There is a knowledge gap on DM risk in mood stabilizers, first generation antipsychotics, as well as psychotropic polypharmacy, which is used by 36-85% of patients with BD in the US.[5] No guidelines are currently available to inform DM-prevention strategies for choosing: a) one BD drug over another, b) monotherapy versus polypharmacy, or c) one multi-drug regimen versus the other. This study aimed to compare the risk of DM in the largest set of BD pharmacotherapies investigated to date (102 drugs and drug combinations).

Methods

- Retrospective observational study.
- **IBM MarketScan® administrative claims data (2003-2015).**
- 932,815 commercially insured US in-and outpatients with BD.
- Data transformed to the **OMOP common data model.**
- PostgreSQL queries and Python data transformations are available online: https://gitlab.com/PCORIUNMPUBLIC/diabetes_public.

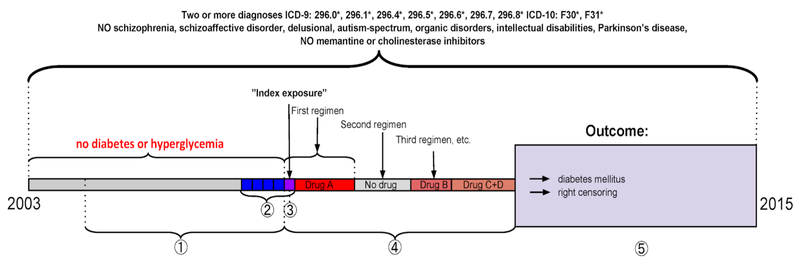

Figure 1. Study schema. (1) minimum of one year of observation, (2) Index visit: meta-visit with a diagnosis of bipolar disorder, (3) Index exposure: first day of exposure observable on the last day of the index visit, (4) Time-varying drug exposure period: series of time intervals with exposures [drug(s) of interest or "NO drug"] used in time-varying covariates regression model, (5) Outcomes of interest.

- **Inclusion criteria:** 18-64 years old, ≥2 diagnoses of BD in 2003-2015 (ICD 9CM/ICD 10CM), received BD drug(s) at least once.
- **Exclusion criteria:** insulin filled, any glucose-related diagnoses prior to index exposure, schizophrenia, schizoaffective disorder, chronic delusional disorders, intellectual disabilities, autism spectrum disorders, mental illness of organic origin, and Parkinson's disease.
- **"Meta-visits"**: consecutive inpatient, ER visit, outpatient visit(s) with no gap of >1 day.
- **Start and stop time was recorded** for each treatment exposure period (including "No drug") (Figure 1).
- Observation ended if patient had a DM-unrelated hospitalization/ER meta-visit (no data were available on pharmacotherapy for these visits).
- **Cox regression model** compared DM risk in 102 pharmacotherapies versus the "No drug" regimen.
- **"Time-varying covariates"** modeled the series of different time intervals of drug exposures from index exposure until outcome.
- Each regimen was required to have ≥1,000 exposure periods and ≥5 cases of DM following exposure.
- Using the covariance structure of the regression model, we also performed comparisons of **2-drug combinations vs. monotherapies, 3-drug combinations vs. 2-drug combinations, and 4-drug combinations versus 3-drug combinations (Figure 2).**
- Resolution IV fractional factorial design of experiments was used to select **85 pre-treatment covariates** (mood polarity, severity, psychotic features, comorbidities, medications, etc.).

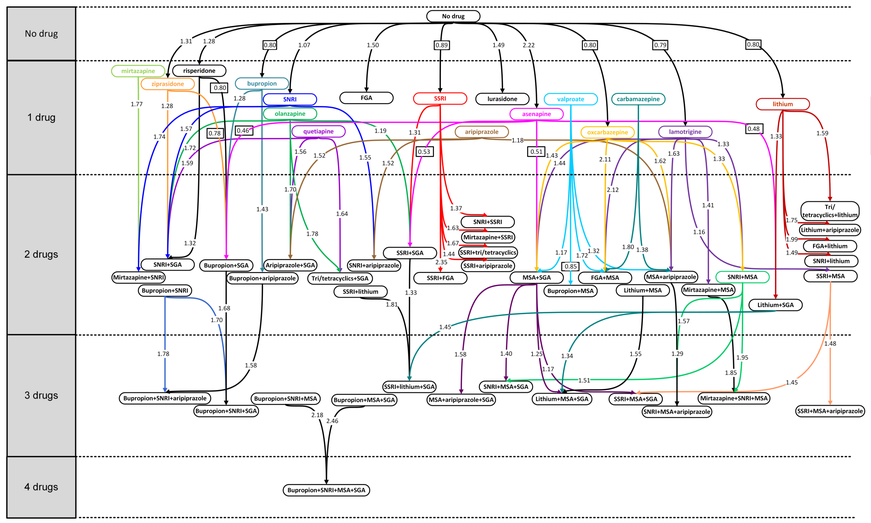

Figure 2. Polypharmacy risk hierarchy

Results

- **565,253 adults** met the inclusion criteria
- 95.9% of patients had right censoring.
- **4.1% of patients (22,951) had newly observed DM.**
- Among those censored, 48.5% were admitted to a hospital/ER for DM-unrelated conditions.
- The **annual incidence of new-onset diabetes during the exposure period was 3.09%** (22,951 patients).
- The 659 observed treatment regimens collapsed to **19 monotherapies and 83 drug combinations** fitting selection criteria.
- **The hazard ratios (HRs) of drug-dependent DM ranged 0.79 -2.37.**
- One-third of the studied pharmacotherapies, including **multi-drug combinations and most of the antipsychotic-containing regimens, had a significantly higher risk of DM** compared to "No drug".
- A significantly **lower DM risk was associated with lithium, lamotrigine, oxcarbazepine, bupropion, selective serotonin reuptake inhibitors (SSRI) mono-class therapy, and several drug combinations containing bupropion and an SSRI.**
- As additional drugs were combined in more complex polypharmacy, higher HRs were consistently observed.

Conclusions

- DM risk on pharmacotherapy versus "No drug" varied 3-fold among different regimens (HR = 0.79-2.37, p<0.05).
- Pharmacotherapies associated with significantly lower risk of DM compared to "No drug" were newly identified.
- The high risk of DM associated with psychotropic polypharmacy requires increased awareness from researchers and clinicians.

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