Comparing 102 psychotropic drug regimens for diabetes mellitus risk

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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.1-3 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.4-6 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://github.com/PCORIUNMPUBLIC/diabetes_public.
• 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 ≥25 cases of DM following exposure.
• Using the coverage 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.).

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 (SSRIs) 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.

References

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