Comparing drug-dependent risk of self-harm in bipolar disorder using machine learning imputed outcomes

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Background

Bipolar disorder (BD) has one of the **highest suicide risks among all psychiatric disorders.**
One of the strongest predictors of suicide attempts is **self-harm (intentional or not).**
Problem: **self-harm is undercoded in US billing records**. Most outcomes uncoded →biased and low-power comparison of treatments to prevent self-harm in BD.
Goal: **compare ALL commonly used BD drug regimens and psychotherapy** for risk of self-harm in a large population of commercially insured individuals, **using self-harm imputation** to overcome undercoding.
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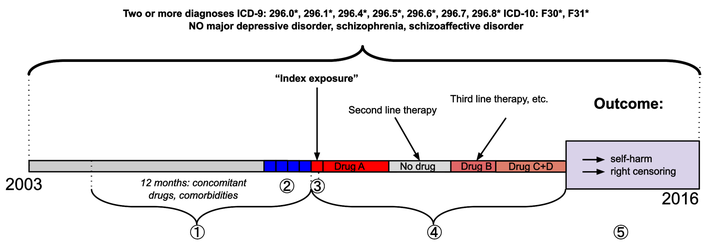
Methods

Data source: CCAE and Medicare → transformed to the **OMOP CDM 5.0.1**.
Sequence of events extracted: 1) One year before the index exposure; 2) **Index visit:** any meta-visit with BD diagnosis; 3) **Index exposure**: first day of exposure on the last day of index visit; 4) **Time-varying drug exposure period:** series of time intervals in which distinct regimens were prescribed; 5) **Outcome**: the first meta-visit with coded and/OR imputed self-harm or a censoring event.



We used previously developed **machine learning (ML)** approach [1] **to impute probable but uncoded self-harm** (p>0.5) + other probability thresholds were examined in a sensitivity analysis.
11M individuals with any major mental illness (MMI) (635M meta-visits) → ML on 26M eligible meta-visits (5-fold cross-validation) → categorization used to classify 529,359 patients with ≥2 BD and no other MMI.
Comparators: lithium, mood-stabilizing anticonvulsants (MSAs), second-generation antipsychotics (SGAs), first-generation antipsychotics, antidepressants (Ad) (SSRI and SNRI classes), and "No drug" periods.
The start and stop time was recorded for each treatment exposure period.
Cox regression models were built, comparing self-harm risk in:
i) 67 individual drug regimens (including "No drug") vs. lithium (Li)
ii) Any drug regimen (all drugs combined) with or without psychotherapy vs. "NO treatment" (neither drug or psychosocial intervention).
Benjamini-Yekutieli procedure was used to correct for multiple comparisons.
Resolution IV fractional factorial design: 78 pre-treatment covariates →29 of them were associated with drug risk estimates - chosen as "**time-fixed" covariates**: sex, age, concomitant drugs received, comorbidities.
Three **"time-varying" covariates** (number of previously used unique BD drugs; current regimen used; psychotherapy code presence during current treatment regimen).

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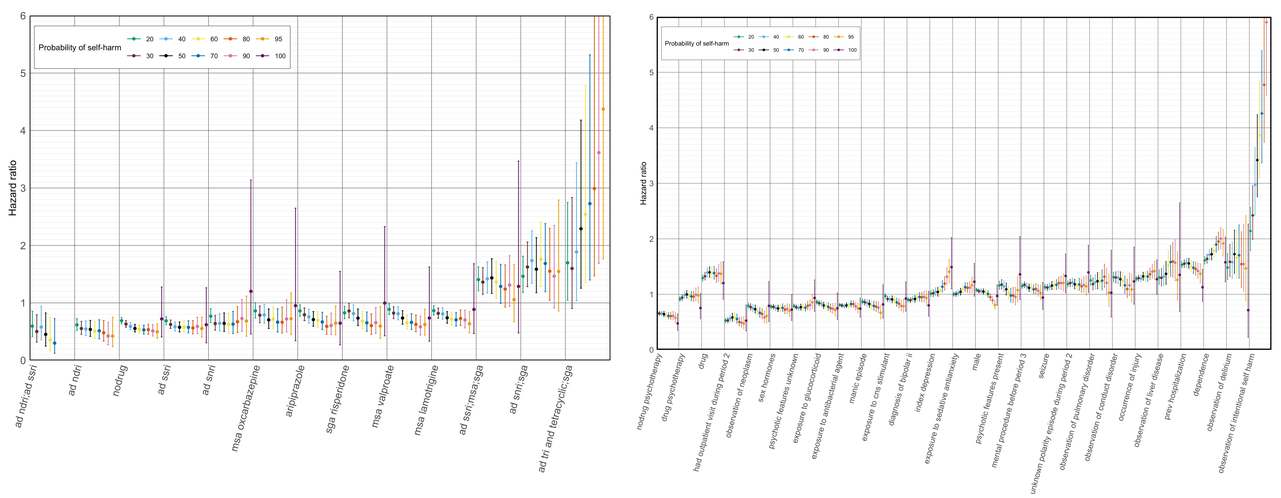
Results

Machine learning allowed us to add extra 8,028 meta-visits with imputed self-harm to our analytical pipeline, in addition to the 481 meta-visits with coded self-harm (8,509 individuals with self-harm).
Out of 529,359 exposed patients, **1.6% had imputed and/or coded self-harm**.
3 regimens were of higher risk of self-harm than Li: 1) tri/tetracyclic antidepressant +SGA, 2) SNRI antidepressant +SGA, 3) SSRI antidepressant +MSA+SGA **[HRs ranged 1.44-2.29, p<0.01]**
10 regimens were of lower risk than Li: lamotrigine, valproate, risperidone, aripiprazole, oxcarbazepine, SNRI class, SSRI class, "No drug", bupropion, and bupropion+SSRI **[HRs ranged 0.45-0.74, p<0.01].**
Psychotherapy alone had a lower self-harm risk than no treatment at all (HR=0.64, 95%CI=0.60-0.69, $p=7.05\times10^{-33}$).
Sensitivity analysis: NO change in direction of drug-outcome associations as a function of self-harm **probability** threshold.



Sensitivity analyses for the "low risk" and "high risk" covariates in two regression models comparing individual regimens (on the left) and combined pharmacotherapy+/-psychotherapy with non-drug covariates (on the right) for self-harm. Ad - antidepressant; ndri - norepinephrine-dopamine reuptake inhibitor Ad class.

Conclusions

Our data support the evidence on the effectiveness of antidepressants, MSAs, and psychotherapy for self-harm prevention in BD. Machine learning imputation of self-harm can enhance power for comparative effectiveness studies of BD treatments.

References

1. Kumar P et al. Imputation and characterization of uncoded self-harm in major mental illness using machine learning, J Am Med Inform Assoc. 2020 Jan 1;27(1):136-146.