Opioid Drug-Drug-Drug Interactions and Unintentional Traumatic Injury: Screening to Detect Three-Way Drug Interaction Signals

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Background

- Growing evidence suggests that drug interactions represent major, potentially addressable contributors to the known association between prescription opioid use and unintentional traumatic injury
- However, prior research has exclusively focused on the role of pairwise interactions, with the importance of higher-order (i.e., drug-drug-drug) interactions (3DIs) remaining unexamined

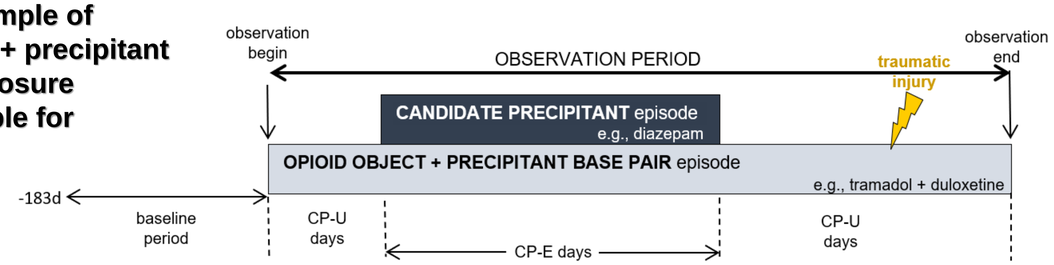
Objective

- To identify signals of opioid 3DIs with commonly co-dispensed medications leading to unintentional traumatic injury using semi-automated, high-throughput screening of US commercial health insurance data

Methods

- We conducted bi-directional, self-controlled case series studies using 2000-2015 Optum Clinformatics data
- Rates of unintentional traumatic injury were examined in individuals dispensed opioid-precipitant base pairs during time exposed vs unexposed to a candidate interacting precipitant
- Cohorts consisted of 16-90 year-old new users of opioid-precipitant base pairs, with ≥1 outcome during observation
- To estimate rate ratios (RRs), we used conditional Poisson regression adjusted for opioid dose and prior traumatic injury as time-varying covariates assessed during each day of observation time
- Semi-Bayes shrinkage was applied to address multiple estimation

Figure 1. Example of opioid object + precipitant base pair exposure episode eligible for inclusion



CP-E = candidate precipitant-exposed; CP-U = candidate precipitant unexposed

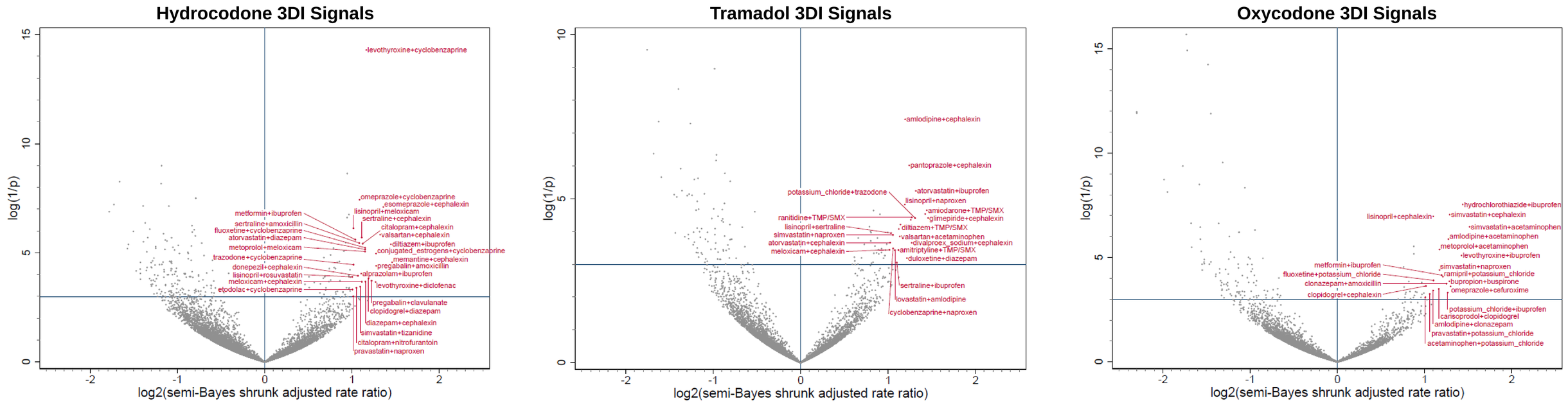
Results

- For hydrocodone, tramadol, and oxycodone (most commonly used opioids), we examined 16024, 8185, and 9330 base pairs ± candidate precipitants, respectively
- Among these, 75 (0.5%; hydrocodone), 57 (0.7%; tramadol), and 42 (0.5%; oxycodone) were significantly positively associated with traumatic injury (50 unique base precipitants, 34 unique candidate precipitants) and were therefore deemed potential 3DI signals
- Statistically significantly elevated adjusted RRs ranged from 1.38 (95% CI 1.03–1.83) for hydrocodone+hydrochlorothiazide with cyclobenzaprine to 2.86 (1.49–5.49) for oxycodone+simvastatin with acetaminophen

Conclusions

- We present a novel approach for 3DI signal detection using pharmacoepidemiologic screening, which could have broad applicability across drug classes and healthcare databases
- The signals found in this study provide valuable foundations for the advancement of future research into opioid 3DIs, promoting hypothesis generation and serving as a basis for crucially needed 3DI etiologic studies

Figure 2. Commonly prescribed opioid + precipitant base pair with candidate interacting precipitant associations with unintentional traumatic injury



The x-axis represents the log base 2 (semi-Bayes shrunk adjusted RR) for opioid + precipitant base pair with candidate interacting precipitant vs. opioid + precipitant base pair. The y-axis represents the log (1 / p-value) for the semi-Bayes shrunk adjusted RR. Data points in the upper right quadrant represent statistically significant elevated RR for the association between opioid + precipitant base pair with candidate interacting precipitant and injury.