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Population-based signals of antidepressant drug interactions associated with unintentional traumatic injury

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AUTHOR CONTRIBUTIONS

C.E.L. wrote the manuscript; C.E.L., W.B.B., and S.H. designed the research; C.E.L., C.M.B., E.K.A., T.A.M., G.K.D., J.R.H., S.C., W.B.B., S.D., S.E.S., T.P.P.N., M.M.M., D.W.O., D.J.W., and S.H. performed the research; C.M.B. and W.B.B. analyzed the data; and C.M.B. and W.B.B. contributed analytic tools.

Statement of Integrity

Dr. Leonard had full access to study data and directed the analyses. He is responsible for the study's integrity.

Prior Publication

An abstract summarizing this work was accepted for presentation at the American Society for Clinical Pharmacology & Therapeutics 2021 Annual Meeting.

SUPPLEMENTARY INFORMATION

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Abstract

Antidepressants are very widely used and associated with traumatic injury, yet little is known about their potential for harmful drug interactions. We aimed to identify potential drug interaction signals by assessing concomitant medications (precipitant drugs) taken with individual antidepressants (object drugs) that were associated with unintentional traumatic injury. We conducted pharmacoepidemiologic screening of 2000–2015 Optum Clinformatics data, identifying drug interaction signals by performing self-controlled case series studies for *antidepressant + precipitant* pairs and injury. We included persons aged 16–90 years co-dispensed an antidepressant and ≥1 precipitant drug(s), with an injury during antidepressant therapy. We classified antidepressant person-days as either precipitant-exposed or precipitant-unexposed. The outcome was an emergency department or inpatient discharge diagnosis for unintentional traumatic injury. We used conditional Poisson regression to calculate confounder adjusted rate ratios (RRs) and accounted for multiple estimation via semi-Bayes shrinkage. We identified 330,884 new users of antidepressants who experienced an injury. Among such persons, we studied concomitant use of 7,953 *antidepressant + precipitant* pairs. Two hundred fifty-six (3.2%) pairs were positively associated with injury and deemed potential drug interaction signals; twenty-two of these signals had adjusted RRs > 2.00. Adjusted RRs ranged from 1.06 (95% confidence interval: 1.00–1.12, p=0.04) for *citalopram + gabapentin* to 3.06 (1.42–6.60) for *nefazodone + levonorgestrel*. Sixty-five (25.4%) signals are currently reported in a seminal drug interaction knowledgebase. We identified numerous new population-based signals of antidepressant drug interactions associated with unintentional traumatic injury. Future studies, intended to test hypotheses, should confirm or refute these potential interactions.

Keywords

Antidepressive agents; drug interactions; injury; pharmacoepidemiology; population health; self-controlled case series

INTRODUCTION

Antidepressants are the most commonly used drug class among Americans aged 20–59 years,[1] and the second most common among persons of all ages.[2] Antidepressants have been consistently associated with many types of unintentional traumatic injuries,[3–6] which may be mediated through their known effects on central nervous system (CNS) sedation, hypotension, hypoglycemia, and other adverse effects. Unintentional injury is a major cause of morbidity and disability;[7,8] it is the leading and fourth leading cause of death in Americans <45 years of age and persons of all ages, respectively.[9] Among older adults, falls and motor vehicle crashes predominate,[10] leading to dramatic increases in mortality from injury beginning at 70 years of age.[9]

The majority of persons with depression have multiple chronic conditions, which greatly increases the likelihood of polypharmacy and therefore predisposes such individuals to potentially deleterious drug interactions. This may be of particular concern for the co-prescribing of antidepressants with other drugs having sedation potential.[4] Such a pharmacodynamic mechanism, in addition to interactions with pharmacokinetic underpinnings,[11] may contribute to antidepressant-attributed unintentional traumatic injuries. Reducing these events is of major public health importance, as such injuries often result in hospitalization and death, yet the precipitating drug interactions are potentially preventable. Therefore, it is understandable that numerous clinical practice guidelines[11–16] consider *drug interaction potential* as a factor to consider when selecting an antidepressant, especially in older adults. Relatedly, the United States (US) Senate Special Committee on Aging recently emphasized the potential role of interactions between CNS-active drugs on fall risk in older adults.[17] Further, the US National Highway Traffic Safety Administration considers the identification of antidepressant drug interactions as a critical countermeasure to prevent drug-impaired driving leading to injurious crashes.[18]

Prior population-based studies of antidepressant drug interactions and injury have been largely limited to concomitant use with alcohol,[19,20] benzodiazepines,[20–31] opioids,[27,29] and/or anticholinergic drugs.[23,29] While an initial focus on these CNS-active agents is intuitive, this leaves a critical knowledge gap. Antidepressants are co-prescribed with hundreds of other commonly used medications that may interact through known and unknown pharmacodynamic and/or pharmacokinetic mechanisms. The lack of evidence is especially worrisome given the high prevalence of polypharmacy among persons treated for depression.

Responding to the critical need to identify antidepressant drug interactions, we conducted high-throughput pharmacoepidemiologic screening of healthcare billing data to identify signals of potential clinically important interactions with antidepressants that might increase unintentional traumatic injury rates. We sought to provide researchers with an evidence-based list of signals, so that limited available resources could be directed to confirm or refute these potential interactions in future etiologic studies.

METHODS

Overview of pharmacoepidemiologic screening: Identifying antidepressant drug interaction signals

We conducted semi-automated, high-throughput pharmacoepidemiologic screening of US healthcare billing data to identify antidepressant drug interaction signals. We created new user cohorts of individuals who received antidepressants of interest (object drugs, the *affected* drugs of drug pairs[32]). Within these cohorts, we identified: exposure to candidate interacting precipitants (the *affecting drugs* of drug pairs[32]), operationalized as orally administered drugs frequently co-dispensed with antidepressants; and outcomes of interest. Of note, object-precipitant nomenclature is most intuitive for pharmacokinetic interactions.[32] We subsequently identified signals by performing thousands of confounder-adjusted self-controlled case series studies to examine associations between individual antidepressant + candidate precipitant pairs and unintentional traumatic injury (the primary outcome), typical hip fracture (a secondary outcome), and motor vehicle crash while the subject was driving (a secondary outcome).

For each antidepressant-precipitant pair, we conducted a bi-directional (defined in Supplemental Methods) self-controlled case series study to examine outcome rates in an antidepressant-treated individual during time exposed vs. unexposed to the precipitant. The self-controlled case series is a rigorous self-matched epidemiologic study design built on the framework of a cohort study, limited to persons experiencing an outcome of interest. The design is well-suited for drug interaction screening because: a) the causal contrast is made *within* an individual and thus inherently controls for confounding by static factors over an individual's observation period (e.g., genetics); b) the statistical model can (and does) control for dynamic factors; c) the approach is computationally-efficient, as it is limited to persons experiencing an outcome; and d) there is ample precedent for the use of high-throughput applications. Analogous screening studies have identified drugs associated with hypoglycemia in persons using insulin secretagogues,[33] rhabdomyolysis in persons using statins,[34] serious bleeding in persons using clopidogrel[35] and anticoagulants,[34,36,37] and injury in persons using opioids[38] as examples. Methods detailed below were adapted from our prior work on opioids.[38]

Data source

We used longitudinal enrollment and healthcare billing data within Optum Clinformatics Data Mart (May 1, 2000–September 30, 2015). The Data Mart includes >71 million commercially insured and Medicare Advantage beneficiaries from the largest US-based private health insurer by market share. See detail in Supplemental Methods.

Creating new user cohorts

We constructed a study cohort for new users, aged 16–90 years, of each antidepressant object drug. We required a 183-day baseline period that was devoid of a dispensed prescription for the given antidepressant. We utilized pharmacy claim dates and days' supply values to build object drug exposure episodes consisting of ≥1 dispensed prescription of the object antidepressant. We allowed a grace period—length calculated as days' supply × 0.20,

assuming 80% adherence—between contiguous antidepressant dispensings and at the end of the terminal dispensing.

Defining observation and baseline periods

For each antidepressant new user meeting inclusion criteria, we started the observation period upon antidepressant initiation and stopped it upon the earliest of: a) lapsed antidepressant exposure (permitting the grace period); b) a switch from a solid to non-solid formulation of the antidepressant; c) a switch from the antidepressant to an alternative antidepressive medication; d) health plan disenrollment (permitting a 45-day maximum enrollment gap); or e) the dataset end date. Given the case-only design, we required an outcome occurrence during each new use observation period. To ensure the validity of the self-controlled case series design, we did not censor the observation period upon outcome occurrence.

The baseline period was the 183 days immediately preceding yet excluding the observation period begin date. We required it to be devoid of: an interruption in insurance coverage; and a dispensing for the given antidepressant. To allow us to study second- and later-line antidepressant therapies, we did not exclude object episodes preceded by a baseline dispensing for an alternative antidepressant.

Identifying candidate interacting precipitant drugs during antidepressant use

We used pharmacy claim dates and days' supply values (including grace periods) to identify dispensed prescriptions for oral route solid formulation antidepressants, as object drugs. During periods of apparent antidepressant use, we used pharmacy claim dates and days' supply values (excluding grace periods, to minimize exposure misclassification) to identify dispensed prescriptions for any orally administered concomitant medication (precipitant drugs of interest). We utilized Facts & Comparisons eAnswers to categorize objects and precipitants by medication class. We lacked explicit data on clinical indications for objects and precipitants. See detail in Supplemental Methods.

Using precipitant drug exposure to categorize observation period time

We classified each observation day as precipitant-exposed or precipitant-unexposed. The former was defined by concomitant exposure to the object and candidate interacting precipitant drug and constituted focal windows, i.e., precipitant-exposed periods. The latter was all other observation days and constituted referent windows, i.e., precipitant-unexposed periods. We permitted referent windows before and after focal windows. Figure 1 provides a graphical representation of the design.

Several studies have found that the risk of an adverse event due to a drug interaction often peaks shortly after initiating concomitant therapy and declines thereafter.[39–41] Therefore, we examined a duration-response relationship for each object-precipitant pair by stratifying focal window time as follows: 0–15, 16–30, 31–60, 61–120, and 121–180 days from the point exposure.

Defining the exposure and covariates

Exposure was defined by candidate precipitant drug use. The self-controlled case series design implicitly controls for static, but not dynamic, covariates. To address the latter, we included in the regression model for each antidepressant the following covariates assessed during each observation day: a) antidepressant average daily dose based on the most recent prescription dispensing; and b) ever prior injury diagnosis on any claim type. Accounting for the latter is important since prior injury may predict subsequent injury, and the self-controlled case series design does not censor upon outcome occurrence.

Identifying outcomes

We defined unintentional traumatic injury, the primary outcome, as an emergency department or inpatient hospitalization for fracture, dislocation, sprain/strain, intracranial injury, internal injury of thorax, abdomen, or pelvis, open wound, injury to blood vessels, crushing injury, injury to nerves or spinal cord, or certain traumatic complications and unspecified injuries. Consistent with the American College of Surgeons' National Trauma Data Standard, this excluded: late effects of injuries, poisonings, toxic effects, and other external causes; superficial injuries; contusions with intact skin surface; and effects of a foreign body entering through orifice. Consistent with work by Sears et al,[42] we also excluded burns; such injuries seem unlikely due to antidepressant use.

Inpatient hospitalization for typical hip fracture was a secondary outcome; prior meta-analyses found antidepressants to be associated with hip fracture.[43,44] We excluded: pathologic hip fractures, since often due to a localized process (e.g., malignancy); and atypical hip fractures, since infrequently traumatic and commonly attributed to bisphosphonate and/or corticosteroid use. We also examined, as a secondary outcome, motor vehicle crash while the subject was driving; antidepressants have been associated with motor vehicle crash.[20,23,29,45,46] We defined this endpoint as an unintentional traumatic injury with an external cause of injury code for an unintentional traffic or nontraffic accident. Consistent with the Centers for Disease Control and Prevention's injury mortality framework, we excluded crashes of a self-inflicted, assault, or undetermined manner. Our study of motor vehicle crash resulted in our decision to study persons as young as 16 years, the minimum driving age for the vast majority of states. We provide operational outcome definitions, their operating characteristics, and other support for their use in Table S1.

Statistical analysis

For each antidepressant-outcome pair, we created an analytic file in which the unit of observation was the person-day during an active prescription for that antidepressant. The dichotomous dependent variable was whether an unintentional traumatic injury occurred on that day. Independent variables were: subject ID, whether a person-day was exposed or unexposed to the precipitant; and the dynamic covariates previously discussed. The parameter of interest was the outcome occurrence rate ratio during focal vs. referent windows, i.e., $rate_{object+precipitant}$ / $rate_{object}$. We separately examined, in a secondary analysis, rate ratios for the mutually exclusive focal window strata discussed above. We used conditional Poisson regression models (*xtpoisson* with *fe* option, Stata v.16) to estimate rate

ratios and 95% confidence intervals (CIs). We did not estimate rate ratios in settings of statistical instability. See detail in Supplemental Methods.

We used a semi-Bayes shrinkage method to address multiple estimation inherent in calculating numerous rate ratios. This increases effect estimate validity and minimizes false positive findings. See detail in Supplemental Methods.

To contextualize findings, we compared drug interaction signals generated by our screening approach to putative interactions documented in two drug interaction knowledgebases: Micromedex and Facts & Comparisons eAnswers.

Institutional review board approval and role of funding

The University of Pennsylvania's institutional review board approved this research as protocol #831486. The US National Institutes of Health had no input on the conduct or interpretation of this research.

RESULTS

Table S2 summarizes characteristics of persons constituting object drug cohorts for analyses of unintentional traumatic injury. Twelve of 26 antidepressants under study provided ≥1 million (M) person-days of observation (range: 1.3M for nortriptyline to 15.6M for sertraline); agents included five selective serotonin reuptake inhibitors (SSRIs: citalopram, escitalopram, fluoxetine, paroxetine, sertraline), two serotonin-norepinephrine reuptake inhibitors (SNRIs: duloxetine, venlafaxine), two tricyclics (amitriptyline, nortriptyline), one 5-hydroxytryptamine$_2$ receptor antagonist (trazodone), one dopamine reuptake blocker (bupropion), and one noradrenergic antagonist (mirtazapine). For these commonly used antidepressants, cohorts ranged from 5,442 new users of nortriptyline to 55,756 new users of sertraline, all of whom by design experienced an injury; the three most commonly occurring injuries were sprain/strain (47.7%), certain traumatic complications and unspecified injuries (24.2%), and dislocation (20.3%). Median durations of observation ranged from 92 days for trazodone to 185 days for venlafaxine. Users were predominantly female and Caucasian; the plurality were South Atlantic US residents. Median age upon initiation of new use ranged from 49.8 years for bupropion to 79.1 years for mirtazapine. In analyses of secondary outcomes, 10 and four antidepressants under study provided ≥100,000 person-days of observation for typical hip fracture and motor vehicle crash, respectively. Cohorts ranged from 468 new users of paroxetine with a motor vehicle crash to 3,267 new users of sertraline with a typical hip fracture. Table S3 and Table S4 summarize characteristics of persons constituting object drug cohorts for analyses of secondary outcomes.

For the study of unintentional traumatic injury, we identified 713 candidate interacting precipitant drugs co-prescribed with one of the 26 antidepressants of interest. After application of inclusion criteria, we examined 617 precipitants in at least one confounder-adjusted self-controlled case series study. The number of precipitants studied ranged from two for trimipramine to 567 for sertraline. Table 1 provides summary data on rate ratios for unintentional traumatic injury, before and after confounder adjustment; Table S5 and Table S6 provide summary data for typical hip fracture and motor vehicle crash, respectively. Heat

maps in Figure S1, Figure S2, and Figure S3 graphically depict confounder-adjusted rate ratios for all outcomes using the primary variance parameter for semi-Bayes shrinkage, corresponding findings using the alternate variance parameter (which yielded similar results), and duration-response findings for the primary outcome, respectively. Fifty-four (87.1%) of 62 viable conditional Poisson models were able to accommodate the inclusion of antidepressant average daily dose as a time-varying covariate (Table S7).

Among 7,953 antidepressant + precipitant pairs included for study, 256 (3.2%, consisting of 158 unique precipitants) had statistically significantly elevated adjusted rate ratios for unintentional traumatic injury after semi-Bayes shrinkage. We therefore deemed these pairs as potential drug interaction signals (Table 2 and Figure 2). Signals for unintentional traumatic injury included precipitants in the following therapeutic classes: CNS agents (N = 81 of 256 signals, including 17 benzodiazepines, 10 muscle relaxants, and 9 opioids); anti-infective agents (N = 40); endocrine and metabolic agents (N = 31); renal and genitourinary agents (N = 28); cardiovascular agents (N = 27); gastrointestinal agents (N = 16); hematologic agents (N = 10); nutrients and nutritional agents (N = 10); respiratory agents (N = 6); biologic and immunologic agents (N = 4); and antineoplastic agents (N = 3). Semi-Bayes shrunk adjusted rate ratios for unintentional traumatic injury signals ranged from 1.06 (95% CI 1.00–1.12, p = 0.042) for citalopram + gabapentin to 3.06 (1.42–6.60) for nefazodone + levonorgestrel; among users of antidepressants with benzodiazepines, muscle relaxants, or opioids, signals were strongest for duloxetine + *flurazepam* (2.54, 1.35–4.79), desvenlafaxine + metaxalone (1.53, 1.07–2.18), and nefazodone + *meperidine* (2.94, 1.41–6.12), respectively. Sixty-five (25.4%), 39 (15.2%), and 31 (12.1%) of the 256 potential drug interaction signals are currently reported in Micromedex, Facts & Comparisons eAnswers, and both knowledgebases, respectively.

DISCUSSION

We conducted pharmacoepidemiologic screening of billing data to identify potential antidepressant drug interactions associated with unintentional traumatic injury, a clinical outcome of public health importance. Among nearly 8,000 antidepressant-precipitant pairs, 256 were associated with an increased rate of injury (22 with adjusted rate ratios > 2.00); the plurality of these drug interaction signals involved co-administered CNS drugs. We identified substantially fewer pairs (37 and 1) associated with increased rates of typical hip fracture and motor vehicle crash, respectively. Given our investigation's high-throughput nature, we consider our findings to be hypothesis generating. Our results may help researchers target limited available resources to assess etiology.

Despite the well-established associations between antidepressants and injury, few studies have examined the role of antidepressant drug interactions. A notable exception includes investigations of antidepressants with benzodiazepines,[20–29] although prior work has been limited to injuries of specific anatomical sites and specific causes, and ignored the potential for intraclass variation. Our study yielded many expected results for antidepressant-benzodiazepine combinations, although some had modestly elevated adjusted rate ratios. Concomitant use (vs. antidepressant use alone) was associated with statistically significantly increased injury rates for: short-acting benzodiazepines and related drugs[21] (sertraline

[adjusted RR = 1.1] and mirtazapine [1.3] with *alprazolam*; paroxetine with *eszopiclone* [1.2]; citalopram [1.1], paroxetine [1.1], amitriptyline [1.2], mirtazapine [1.2], and trazodone [1.2] with *lorazepam*; sertraline with *temazepam* [1.1]; and sertraline with *triazolam* [1.5]); and long-acting benzodiazepines[21] (sertraline [1.3] and venlafaxine [1.4] with *chlordiazepoxide*; citalopram [1.1] and escitalopram [1.2] with *clonazepam*; sertraline [1.1] and doxepin [1.6] with *diazepam*; and duloxetine with *flurazepam* [2.5]). For secondary outcomes, although no pairs signaled for motor vehicle crash, concomitant use of venlafaxine with *lorazepam* [2.1] and citalopram with *diazepam* [2.3] was associated with a statistically significantly increased rate of typical hip fracture. A case-control study of US long-term care residents reported an odds ratio [OR] = 6.9 for falls among users of antidepressants with a sedative-hypnotic-anxiolytic (vs. OR = 2.6 among users of antidepressants alone).[25] A cohort study of US Medicare beneficiaries reported hazard ratios [HRs] for hip fracture among female and male users of SSRI/SNRIs *with* (4.5 and 7.1) and *without* (2.3 and 3.0) benzodiazepines, respectively.[27] Other observational studies of falls,[24] hip fracture,[26,28] and motor vehicle crash[20] found no associations or did not examine benzodiazepine interaction effects separate from a heterogeneous group of psychoactive drugs.[21,30,31]

Interactions between antidepressants and benzodiazepines are biologically plausible given additive or synergistic pharmacodynamic (e.g., CNS depression) and/or pharmacokinetic (e.g., hepatic metabolism) effects. As an example of the former, prominent anticholinergic, sedative, and orthostatic effects of doxepin could be compounded by diazepam's long half-life and debated anticholinergic properties. Our identification of antidepressant-benzodiazepine signals, supported by mechanistic expectations and prior epidemiologic data, bolsters the validity of our drug interaction screening approach. The lack of signaling for some expected pairs (e.g., nefazodone with *clonazepam*, adjusted rate ratio$_{injury}$ = 1.3, 0.9–1.9) may be driven by limited statistical precision and suggests that assumptions employed during semi-Bayes shrinkage were appropriately conservative for use in this hypothesis-generating screening context.

Our study also yielded expected results for antidepressants with opioids, although some had modestly elevated adjusted rate ratios. Concomitant use was associated with statistically significantly increased injury rates for: opioid prodrugs (citalopram with *codeine* [1.1]; and citalopram [1.1], paroxetine [1.1], sertraline [1.1], venlafaxine [1.1], and mirtazapine [1.2] with *tramadol*); and active parent opioids (nefazodone with *meperidine* [2.9]; venlafaxine with *oxymorphone* [1.7]; and duloxetine with *tapentadol* [1.6]). For secondary outcomes, while no pairs signaled for motor vehicle crash, concomitant use of amitriptyline [1.4], citalopram [1.3], and maprotiline [5.3] with *hydrocodone*, duloxetine with *oxycodone* [1.8], and citalopram [1.4] and paroxetine [1.7] with *tramadol* were associated with a statistically significantly increased rate of typical hip fracture. Potential pharmacokinetic mechanisms (e.g., nefazodone's inhibition of cytochrome P450 [CYP] 3A4, an isozyme partly responsible for converting meperidine to a nonopioid metabolite) and pharmacodynamic effects (e.g., maprotiline's potentiation of hydrocodone's sedative effects) may support these associations. A cohort study of US Medicare beneficiaries reported HRs for hip fracture among female and male users of SSRI/SNRIs *with* (3.9 and 6.3) and *without* (2.3 and 3.0) opioids, respectively.[27]

We also identified signals for antidepressants with muscle relaxants—timely findings given substantial nationwide increases in chronic use of the latter.[47] Concomitant use was associated with statistically significantly increased injury rates for: escitalopram [1.2] and fluoxetine [1.2] with *carisoprodol*; citalopram [1.1], fluoxetine [1.1], and bupropion [1.2] with *cyclobenzaprine*; venlafaxine [1.2], citalopram [1.3], duloxetine [1.3], and desvenlafaxine [1.5] with *metaxalone*; and venlafaxine with *tizanidine* [1.3]. For secondary outcomes, although no pairs signaled for motor vehicle crash, concomitant use of escitalopram with *cyclobenzaprine* [1.9] was associated with a statistically significantly increased rate of typical hip fracture. Potential pharmacokinetic mechanisms (e.g., duloxetine's inhibition of CYP2D6, an isozyme that converts metaxalone to an inactive metabolite) and pharmacodynamic effects (e.g., cyclobenzaprine's augmentation of fluoxetine's serotonergic effects, potentially causing altered mental status and instability) may support these associations. A cohort study of US Medicare beneficiaries reported a HR for hip fracture among female users of SSRI/SNRIs *with* (2.9) and *without* (2.3) muscle relaxants.[27]

Of other potential drug interaction signals identified, many are biologically plausible. For example, inhibition of CYP3A4 by nefazodone and/or additive or synergistic sedative effects may precipitate the apparent 2.3-fold increase in injury rate when used with quetiapine. Sequelae of serotonin syndrome (e.g., mental status changes, autonomic instability) may explain the apparent 2.2-fold increase in injury rate during concomitant use of imipramine and ondansetron. Such associations, arising from concurrent use of two CNS drugs, may be viewed as unsurprising findings. Yet, we identified numerous plausible signals with concomitant use of non-CNS drugs. As a pharmacokinetic example, inhibition of CYP3A4 by ticagrelor may precipitate the apparent 2.3- increase in injury rate when used with citalopram. As a pharmacodynamic example, the hypotensive effects of tadalafil may precipitate the apparent 2.4-fold increase in injury rate when used with mirtazapine.

For signals that lack an obvious mechanism (e.g., sertraline with dipyridamole), it is especially unclear whether findings reflect unknown mechanisms that place patients at risk of injury, chance, reverse causality, or confounding by indication. Concerns about spurious findings may be especially relevant for precipitants used to treat injuries (e.g., nonsteroidal anti-inflammatory drugs, opioids, muscle relaxants) or their sequelae (e.g., anti-infectives). This should be a focus of future work.

Our study has strengths. First, we used a self-controlled case series design—well-suited to drug interaction screening[32]—to eliminate between-person and decrease within-person confounding. Second, we studied clinically meaningful outcomes identified by well-supported algorithms. Finally, we minimized type I error via semi-Bayes shrinkage.

Our study has limitations. First, drug dispensings may be imperfect markers for drug ingestion. This may be especially true for non-prescription drugs and those taken on an *as needed* basis. Second, we did not examine higher order drug interactions (e.g., triplets). Such findings may be of future interest given the prevalence of polypharmacy in persons with multiple chronic conditions. Third, we did not examine interactions among persons taking concurrent antidepressants. Fourth, the self-controlled case series design may be susceptible

to reverse causality/event dependent exposure. This may be of particular concern for precipitants prescribed to treat early symptoms or sequelae of an injury and may result in a spuriously elevated rate ratio for the precipitant even if concomitant antidepressant + precipitant use had no causal effect on injury. Fifth, our design precluded us from distinguishing a drug interaction from an inherent effect of a precipitant. Sixth, given the hypothesis generating intent of our work, we did not consider injury severity or within-patient changes in depression symptoms or severity; the latter two would be very challenging to directly capture or infer from billing data. Seventh, in addition to the potential for bias and confounding, one must consider the role of chance despite our use of semi-Bayes shrinkage. Finally, our findings may not be generalizable beyond commercially insured and Medicare Advantage ambulatory care populations.

Identifying potential drug interactions resulting in unintentional traumatic injury is a major unmet information need. We used healthcare billing data to screen for antidepressant interactions associated with unintentional traumatic injury, typical hip fracture, and/or motor vehicle crash. Our findings, intended to stimulate future work, provide an evidence-based list of antidepressant interaction signals, such that limited resources can be directed to confirm or refute these potential drug interactions in follow-on etiologic studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclosures

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STUDY HIGHLIGHTS

What is the current knowledge on the topic?

Antidepressant use has been associated with unintentional traumatic injuries. Population-based studies of injury (and sequelae) for drugs used concomitantly with antidepressants have been largely limited to alcohol and class effects of benzodiazepines, opioids, and select anticholinergics.

What question did this study address?

Among beneficiaries of a large United States health insurer, which drugs when used concomitantly with one of twenty-six different antidepressants were associated with an increased rate of unintentional traumatic injury?

What does this study add to our knowledge?

A small proportion (3%), yet large number (N = 256), of antidepressant-precipitant drug pairs were associated with unintentional traumatic injury. The majority of associations were with precipitant drugs outside of the central nervous system class (e.g., anti-infective, endocrine/metabolic, renal/genitourinary agents), most of which have not been previously described yet represent drug interaction signals of potential clinical concern.

How might this change clinical pharmacology or translational science?

Researchers should use our evidence-based list of drug interaction signals to direct limited available resources to confirm or refute these potential interactions in future etiologic studies.

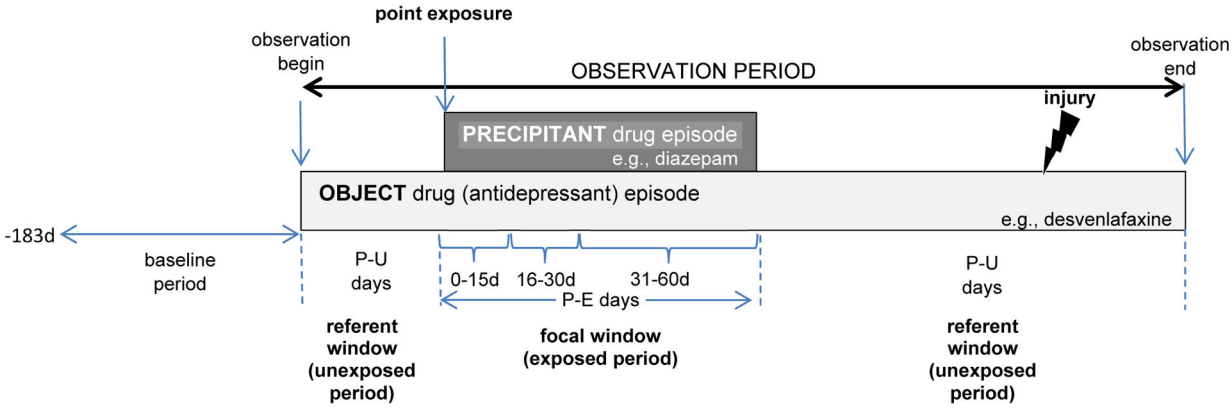

Figure 1. Example of antidepressant object drug episode eligible for inclusion.

The focal window is comprised of precipitant-exposed person-days. The referent windows are comprised of precipitant-unexposed person-days. The presence of a referent window before *and* after the focal window is indicative of a bi-directional implementation of the self-controlled case series design. P-E = precipitant-exposed; P-U = precipitant-unexposed.

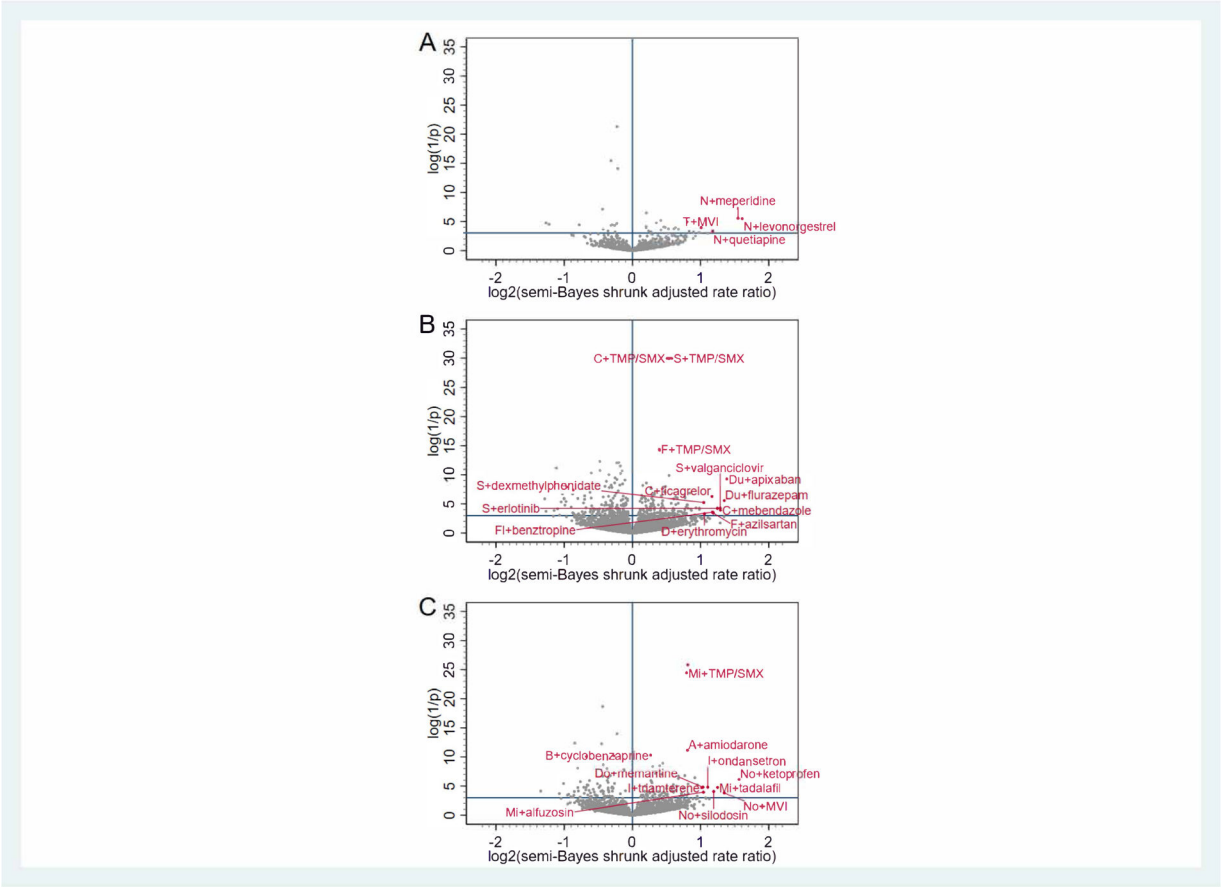

Figure 2. Antidepressant + precipitant drug associations with unintentional traumatic injury.

Panel A depicts associations for antidepressants with 5-hydroxytryptamine receptor antagonist properties (nefazodone [N], trazodone [T], vortioxetine [V]). Panel B depicts associations for selective serotonin reuptake inhibitors (citalopram [C], escitalopram [E], fluoxetine [F], fluvoxamine [Fl], paroxetine [P], sertraline [S], vilazodone [Vi]) and serotonin-norepinephrine reuptake inhibitors (desvenlafaxine [D], duloxetine [Du], levomilnacipran [L], venlafaxine [Ve]). Panel C depicts associations for other antidepressants (amitriptyline [A], amoxapine [Am], bupropion [B], clomipramine [Cl], desipramine [De], doxepin [Do], imipramine [I], maprotiline [M], mirtazapine [Mi], nortriptyline [No], protriptyline [Pr], trimipramine [Tr]). The x-axis represents the log base 2 semi-Bayes shrunk adjusted rate ratio for antidepressant + precipitant vs. antidepressant. The y-axis represents the log (1 / p-value) for the semi-Bayes shrunk adjusted rate ratio. Data points in the upper right quadrant represent statistically significant elevated semi-Bayes shrunk adjusted rate ratios for the association between antidepressant + precipitant (vs. antidepressant) and unintentional traumatic injury (i.e., putative drug interaction signals). For ease of reading, we limited labeling to upper right quadrant data points with log base 2 semi-Bayes shrunk adjusted rate ratio ≥1 or log (1 / p-value) for the semi-Bayes shrunk adjusted rate ratio ≥10. MVI = multivitamin with iron, SMX = sulfamethoxazole, TMP = trimethoprim.

Table 1.

Summary data on candidate interacting precipitants and semi-Bayes shrunk rate ratios for unintentional traumatic injury, by antidepressant object drug

	Object drug								
	Amitriptyline	**Amoxapine**	**Bupropion**	**Citalopram**	**Clomipramine**	**Desipramine**	**Desvenlafaxine**	**Doxepin**	**Duloxetine**
Unadjusted analyses									
Candidate interacting precipitants examined, count	495	21	483	549	121	175	303	341	485
DDI signals, count (%)	33 (6.7)	0 (0.0)	37 (7.7)	50 (9.1)	1 (0.8)	0 (0.0)	9 (3.0)	13 (3.8)	30 (6.2)
Increased rate *	11 (2.2)	0 (0.0)	13 (2.7)	19 (3.5)	0 (0.0)	0 (0.0)	4 (1.3)	4 (1.2)	13 (2.7)
Decreased rate **	22 (4.4)	0 (0.0)	24 (5.0)	31 (5.6)	1 (0.8)	0 (0.0)	5 (1.7)	9 (2.6)	17 (3.5)
RR range, min to max	0.40 – 1.92	0.69 – 1.27	0.55 – 2.15	0.41 – 2.52	0.45 – 1.85	0.63 – 2.08	0.50 – 2.09	0.54 – 1.89	0.58 – 2.60
Confounder-adjusted analyses									
Candidate interacting precipitants examined, count	495	21	483	549	121	174	303	341	484
DDI signals, count (%)	40 (8.1)	0 (0.0)	38 (7.9)	55 (10.0)	1 (0.8)	2 (1.1)	10 (3.3)	11 (3.2)	32 (6.6)
Increased rate *	16 (3.2)	0 (0.0)	16 (3.3)	27 (4.9)	0 (0.0)	2 (1.1)	5 (1.7)	5 (1.5)	16 (3.3)
Decreased rate **	24 (4.8)	0 (0.0)	22 (4.6)	28 (5.1)	1 (0.8)	0 (0.0)	5 (1.7)	6 (1.8)	16 (3.3)
RR range, min to max	0.39 – 1.94	0.60 – 1.26	0.55 – 2.19	0.42 – 2.45	0.52 – 1.98	0.59 – 2.10	0.50 – 2.08	0.50 – 2.05	0.55 – 2.62
	Escitalopram	**Fluoxetine**	**Fluvoxamine**	**Imipramine**	**Levomilna.**	**Maprotiline**	**Mirtazapine**	**Nefazodone**	**Nortriptyline**
Unadjusted analyses									
Candidate interacting precipitants examined, count	560	546	181	296	11	13	449	206	384
DDI signals, count (%)	39 (7.0)	39 (7.1)	6 (3.3)	3 (1.0)	0 (0.0)	0 (0.0)	30 (6.7)	4 (1.9)	17 (4.4)
Increased rate *	18 (3.2)	16 (2.9)	5 (2.8)	2 (0.7)	0 (0.0)	0 (0.0)	25 (5.6)	3 (1.5)	9 (2.3)
Decreased rate **	21 (3.8)	23 (4.2)	1 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	5 (1.1)	1 (0.5)	8 (2.1)
RR range, min to max	0.43 – 1.95	0.59 – 2.18	0.43 – 2.24	0.55 – 2.10	1.23 – 2.31	0.91 – 2.06	0.55 – 2.22	0.59 – 3.05	0.57 – 2.44
Confounder-adjusted analyses									
Candidate interacting precipitants examined, count	560	545	181	294	11	13	449	206	383
DDI signals, count (%)	39 (7.0)	41 (7.5)	7 (3.9)	5 (1.7)	0 (0.0)	0 (0.0)	34 (7.6)	5 (2.4)	16 (4.2)

Increased rate *	20 (3.6)	20 (3.7)	5 (2.8)	3 (1.0)	0 (0.0)	0 (0.0)	24 (5.3)	5 (2.4)	10 (2.6)
Decreased rate **	19 (3.4)	21 (3.9)	2 (1.1)	2 (0.7)	0 (0.0)	0 (0.0)	10 (2.2)	0 (0.0)	6 (1.6)
RR range, min to max	0.41 – 2.06	0.48 – 2.28	0.45 – 2.26	0.48 – 2.15	1.36 – 2.54	0.91 – 2.06	0.52 – 2.38	0.61 – 3.06	0.53 – 2.96
	Paroxetine	**Protriptyline**	**Sertraline**	**Trazodone**	**Trimipramine**	**Venlafaxine**	**Vilazodone**	**Vortioxetine**	
Unadjusted analyses									
Candidate interacting precipitants examined, count	529	36	567	490	2	510	164	44	
DDI signals, count (%)	35 (6.6)	0 (0.0)	62 (10.9)	30 (6.1)	0 (0.0)	45 (8.8)	0 (0.0)	0 (0.0)	
Increased rate *	13 (2.5)	0 (0.0)	23 (4.1)	13 (2.7)	0 (0.0)	18 (3.5)	0 (0.0)	0 (0.0)	
Decreased rate **	22 (4.2)	0 (0.0)	39 (6.9)	17 (3.5)	0 (0.0)	27 (5.3)	0 (0.0)	0 (0.0)	
RR range, min to max	0.50 – 2.01	0.78 – 1.87	0.48 – 2.44	0.40 – 1.99	0.81 – 0.86	0.51 – 1.79	0.57 – 2.05	0.73 – 1.72	
Confounder-adjusted analyses									
Candidate interacting precipitants examined, count	528	36	567	490	2	510	164	43	
DDI signals, count (%)	35 (6.6)	0 (0.0)	60 (10.6)	30 (6.1)	0 (0.0)	46 (9.0)	0 (0.0)	0 (0.0)	
Increased rate *	17 (3.2)	0 (0.0)	28 (4.9)	16 (3.3)	0 (0.0)	21 (4.1)	0 (0.0)	0 (0.0)	
Decreased rate **	18 (3.4)	0 (0.0)	32 (5.6)	14 (2.9)	0 (0.0)	25 (4.9)	0 (0.0)	0 (0.0)	
RR range, min to max	0.48 – 1.98	0.80 – 1.88	0.47 – 2.44	0.42 – 2.02	1.20 – 1.26	0.46 – 1.81	0.57 – 2.02	0.67 – 1.63	

DDI = drug-drug interaction; levomilna. = levomilnacipran; max = maximum; min = minimum; RR = rate ratio

* lower bound of the 95% confidence interval for the RR of interest excluded the null value

** upper bound of the 95% confidence interval for the RR of interest excluded the null value

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Table 2.

Antidepressant drug interaction signals, given statistically significantly increased rates of unintentional traumatic injury, by pharmacologic class of antidepressant, by therapeutic category of precipitant drug, by magnitude of association

Object drug (ASO rating)	Precipitant drug	Precipitant drug therapeutic category	RR, semi-Bayes shrunk	Lower bound of 95% CI	Upper bound of 95% CI
5-hydroxytryptamine$_2$ receptor antagonist					
Nefazodone (4)	meperidine[*,**,***]	CNS	**2.94**	1.41	6.12
	quetiapine[†,‡]		**2.26**	1.06	4.83
	levonorgestrel	Endocrine and metabolic	**3.06**	1.42	6.60
	finasteride	Renal and genitourinary	1.86	1.03	3.38
	cetirizine	Respiratory	1.55	1.07	2.25
Trazodone (3)	cefaclor[***]	Anti-infective	1.96	1.01	3.81
	hydroxychloroquine[*]	Biologic and immunologic	1.38	1.06	1.80
	hydralazine	CV	1.40	1.06	1.85
	indomethacin[†,***]	CNS	1.45	1.05	2.00
	nabumetone[†,***]		1.34	1.03	1.75
	donepezil[*]		1.18	1.01	1.38
	lorazepam[*]		1.15	1.03	1.29
	desogestrel	Endocrine and metabolic	1.75	1.16	2.64
	liothyronine		1.53	1.06	2.21
	risedronate		1.28	1.07	1.54
	levothyroxine		1.15	1.06	1.26
	sodium biphosphate[*]	GI	1.78	1.04	3.06
	metoclopramide		1.34	1.09	1.65
	multivitamin with iron	Nutrients and nutritional	**2.02**	1.12	3.64
	spironolactone	Renal and genitourinary	1.21	1.01	1.45
	homatropine	Respiratory	1.60	1.05	2.44
Dopamine reuptake blocking compound					
Bupropion (1)	nebivolol[†,‡]	CV	1.41	1.03	1.92
	valsartan		1.23	1.05	1.43
	atorvastatin		1.10	1.01	1.19
	rizatriptan	CNS	1.26	1.03	1.54
	buspirone		1.23	1.04	1.45
	pregabalin		1.23	1.01	1.49
	cyclobenzaprine[***]		1.21	1.10	1.32
	glimepiride	Endocrine and metabolic	1.37	1.05	1.79
	glipizide		1.31	1.02	1.69

Object drug (ASO rating)	Precipitant drug	Precipitant drug therapeutic category	RR, semi-Bayes shrunk	Lower bound of 95% CI	Upper bound of 95% CI
	allopurinol		1.27	1.00	1.60
	lubiprostone	GI	1.70	1.24	2.34
	metolazone	Renal and genitourinary	1.76	1.08	2.89
	silodosin		1.70	1.05	2.74
	furosemide		1.21	1.07	1.36
	sildenafil		1.17	1.00	1.36
	cetirizine	Respiratory	1.15	1.01	1.32
Noradrenergic antagonist					
Mirtazapine (3)	clarithromycin***	Anti-infective	1.94	1.21	3.09
	trimethoprim***		1.76	1.50	2.06
	sulfamethoxazole***		1.74	1.48	2.05
	metronidazole		1.37	1.02	1.86
	levofloxacin***		1.34	1.13	1.60
	rosuvastatin	CV	1.57	1.13	2.16
	amiodarone		1.32	1.00	1.74
	caffeine	CNS	1.89	1.27	2.80
	butalbital***		1.76	1.19	2.61
	primidone		1.62	1.02	2.57
	lamotrigine		1.60	1.19	2.14
	pregabalin		1.60	1.20	2.12
	alprazolam*		1.32	1.14	1.54
	tramadol*,**,***		1.23	1.10	1.38
	lorazepam*		1.22	1.07	1.40
	megestrol	Endocrine and metabolic	1.24	1.04	1.49
	rabeprazole	GI	1.74	1.05	2.89
	clopidogrel	Hematological	1.37	1.16	1.60
	tadalafil	Renal and genitourinary	**2.38**	1.25	4.53
	alfuzosin		**2.06**	1.12	3.77
	solifenacin		1.43	1.01	2.03
	spironolactone		1.35	1.04	1.76
	hydrochlorothiazide		1.21	1.07	1.38
	furosemide		1.12	1.01	1.23
Serotonin-norepinephrine reuptake inhibitors					
Desvenlafaxine (0)	erythromycin***	Anti-infective	**2.08**	1.04	4.14
	fenofibrate	CV	1.48	1.01	2.17
	lisinopril		1.23	1.00	1.50
	metaxalone*,***	CNS	1.53	1.07	2.18

Object drug (ASO rating)	Precipitant drug	Precipitant drug therapeutic category	RR, semi-Bayes shrunk	Lower bound of 95% CI	Upper bound of 95% CI
	methylprednisolone	Endocrine and metabolic	1.44	1.02	2.03
Duloxetine (0)	famciclovir	Anti-infective	1.75	1.16	2.65
	trimethoprim***		1.25	1.09	1.43
	sulfamethoxazole***		1.24	1.07	1.43
	levofloxacin***		1.19	1.03	1.37
	methotrexate	Antineoplastic	1.35	1.09	1.68
	hydroxychloroquine	Biologic and immunologic	1.34	1.12	1.61
	flurazepam	CNS	**2.54**	1.35	4.79
	valproic acid		1.82	1.10	3.03
	tapentadol*,***		1.64	1.06	2.54
	metaxalone*,‡,***		1.25	1.04	1.51
	gabapentin		1.07	1.00	1.15
	liothyronine	Endocrine and metabolic	1.58	1.18	2.12
	apixaban†	Hematological	**2.62**	1.62	4.26
	multivitamin with minerals	Nutrients and nutritional	1.91	1.14	3.19
	multivitamin prenatal		1.59	1.06	2.39
	levocetirizine	Respiratory	1.38	1.07	1.79
Venlafaxine (0)	proguanil	Anti-infective	1.81	1.11	2.95
	atovaquone		1.69	1.03	2.79
	isosorbide dinitrate	CV	1.58	1.02	2.44
	ramipril		1.34	1.11	1.62
	atorvastatin		1.09	1.01	1.17
	oxymorphone*,***	CNS	1.67	1.04	2.66
	valdecoxib†,***		1.55	1.18	2.06
	chlordiazepoxide		1.41	1.02	1.93
	etodolac†,‡,***		1.36	1.08	1.71
	tizanidine***		1.25	1.10	1.43
	rizatriptan*,**		1.23	1.00	1.50
	metaxalone*,**,***		1.22	1.01	1.46
	tramadol*,**,***		1.11	1.02	1.22
	ethynodiol	Endocrine and metabolic	1.76	1.12	2.77
	liothyronine		1.33	1.04	1.70
	methylprednisolone		1.18	1.00	1.38
	clidinium	GI	1.51	1.04	2.19
	methscopolamine		1.36	1.00	1.85
	cholecalciferol	Nutrients and nutritional	1.71	1.21	2.41

Object drug (ASO rating)	Precipitant drug	Precipitant drug therapeutic category	RR, semi-Bayes shrunk	Lower bound of 95% CI	Upper bound of 95% CI
	bumetanide	Renal and genitourinary	1.59	1.14	2.22
	metolazone		1.44	1.03	2.02
Selective serotonin reuptake inhibitors					
Citalopram (0)	mebendazole	Anti-infective	**2.45**	1.15	5.20
	ampicillin***		1.61	1.06	2.43
	amantadine		1.55	1.12	2.15
	sulfamethoxazole***		1.45	1.33	1.57
	trimethoprim***		1.43	1.32	1.55
	losartan	CV	1.09	1.00	1.18
	valproic acid	CNS	1.51	1.01	2.25
	pramipexole		1.37	1.15	1.63
	haloperidol*,**		1.34	1.06	1.69
	modafinil		1.33	1.02	1.73
	metaxalone*,‡,***		1.25	1.04	1.49
	lamotrigine		1.20	1.04	1.38
	sumatriptan*,**		1.16	1.01	1.33
	tramadol*,**,***		1.11	1.05	1.18
	codeine*,***		1.11	1.01	1.23
	cyclobenzaprine*,‡,***		1.08	1.01	1.15
	clonazepam		1.08	1.01	1.16
	lorazepam		1.08	1.01	1.15
	gabapentin		1.06	1.00	1.12
	norgestrel	Endocrine and metabolic	1.52	1.16	2.00
	mesalamine	GI	1.29	1.02	1.62
	ticagrelor†	Hematological	**2.25**	1.35	3.74
	prasugrel†		1.50	1.02	2.20
	multivitamin	Nutrients and nutritional	1.36	1.02	1.80
	omega-3 polyunsaturated fatty acid		1.25	1.01	1.54
	metolazone	Renal and genitourinary	1.45	1.21	1.74
	bumetanide		1.36	1.11	1.68
Escitalopram (0)	amantadine	Anti-infective	1.70	1.22	2.37
	sulfamethoxazole***		1.21	1.09	1.34
	trimethoprim***		1.21	1.09	1.34
	cyclosporine	Biologic and immunologic	1.88	1.02	3.49
	aliskiren	CV	1.46	1.02	2.09

Object drug (ASO rating)	Precipitant drug	Precipitant drug therapeutic category	RR, semi-Bayes shrunk	Lower bound of 95% CI	Upper bound of 95% CI
	ranolazine *		1.41	1.00	1.99
	terazosin		1.33	1.00	1.77
	losartan		1.15	1.03	1.27
	pramipexole	CNS	1.30	1.07	1.58
	aripiprazole *		1.24	1.07	1.43
	carisoprodol ***		1.20	1.05	1.38
	clonazepam		1.15	1.07	1.24
	thyroid desiccated	Endocrine and metabolic	1.20	1.01	1.43
	glimepiride		1.19	1.01	1.40
	rabeprazole	GI	1.16	1.02	1.32
	omeprazole *,**		1.07	1.01	1.14
	dabigatran †	Hematological	1.56	1.01	2.39
	fesoterodine	Renal and genitourinary	1.46	1.02	2.09
	tolterodine *		1.20	1.03	1.40
	theophylline	Respiratory	1.49	1.03	2.16
Fluoxetine (1)	ampicillin ***	Anti-infective	1.69	1.05	2.72
	sulfamethoxazole *,***		1.32	1.18	1.48
	trimethoprim *,***		1.32	1.18	1.47
	nitrofurantoin		1.22	1.06	1.41
	azilsartan	CV	**2.28**	1.07	4.83
	carvedilol		1.13	1.00	1.29
	nabumetone †,‡,***	CNS	1.25	1.05	1.50
	divalproex sodium ‡		1.24	1.06	1.45
	carisoprodol ***		1.16	1.02	1.32
	cyclobenzaprine *,**,***		1.10	1.03	1.19
	budesonide	Endocrine and metabolic	1.73	1.04	2.89
	desogestrel		1.25	1.02	1.53
	levothyroxine		1.10	1.04	1.16
	esomeprazole	GI	1.14	1.04	1.25
	cilostazol †,‡	Hematological	1.70	1.09	2.65
	clopidogrel †,‡		1.17	1.05	1.31
	acetazolamide	Renal and genitourinary	1.74	1.16	2.62
	solifenacin *		1.20	1.00	1.44
	Furosemide		1.08	1.01	1.16
	Pseudoephedrine	Respiratory	1.11	1.00	1.23

Object drug (ASO rating)	Precipitant drug	Precipitant drug therapeutic category	RR, semi-Bayes shrunk	Lower bound of 95% CI	Upper bound of 95% CI
Fluvoxamine (1)	Lisinopril	CV	1.71	1.04	2.81
	Ezetimibe		1.62	1.06	2.48
	Benztropine	CNS	**2.26**	1.09	4.67
	buspirone**		1.52	1.08	2.14
	esomeprazole‡	GI	1.79	1.26	2.54
Paroxetine (3)	quinine*	Anti-infective	1.47	1.02	2.11
	terbinafine**		1.33	1.04	1.69
	sulfamethoxazole***		1.22	1.07	1.38
	trimethoprim***		1.22	1.08	1.38
	ciprofloxacin***		1.16	1.03	1.30
	Methotrexate	Antineoplastic	1.33	1.02	1.72
	propafenone*	CV	1.98	1.15	3.40
	Primidone	CNS	1.41	1.05	1.88
	prochlorperazine		1.38	1.02	1.87
	Eszopiclone		1.24	1.00	1.53
	Lorazepam		1.14	1.05	1.25
	tramadol*,**,***		1.09	1.00	1.19
	Gabapentin		1.09	1.00	1.18
	Hydrocortisone	Endocrine and metabolic	1.73	1.13	2.64
	Sitagliptin		1.25	1.01	1.54
	Omeprazole	GI	1.11	1.04	1.19
	multivitamin with iron	Nutrients and nutritional	1.61	1.01	2.58
Sertraline (0)	Valganciclovir	Anti-infective	**2.44**	1.20	4.98
	sulfamethoxazole***		1.50	1.38	1.63
	trimethoprim***		1.46	1.35	1.59
	levofloxacin*,***		1.12	1.02	1.23
	Erlotinib	Antineoplastic	**2.37**	1.19	4.74
	mycophenolate mofetil	Biologic and immunologic	1.50	1.06	2.12
	nebivolol†	CV	1.39	1.14	1.68
	Midodrine		1.33	1.02	1.74
	dexmethylphenidate‡	CNS	**2.07**	1.24	3.44
	pyridostigmine		1.98	1.13	3.47
	triazolam†		1.51	1.09	2.11
	chlordiazepoxide		1.32	1.00	1.74
	haloperidol†,‡		1.29	1.02	1.63

Object drug (ASO rating)	Precipitant drug	Precipitant drug therapeutic category	RR, semi-Bayes shrunk	Lower bound of 95% CI	Upper bound of 95% CI
	butalbital ***		1.23	1.06	1.43
	Caffeine		1.22	1.05	1.42
	Diazepam		1.13	1.01	1.26
	Temazepam		1.13	1.00	1.28
	tramadol †, **, ***		1.10	1.03	1.16
	alprazolam *		1.08	1.02	1.14
	thyroid desiccated ‡	Endocrine and metabolic	1.21	1.03	1.41
	Progesterone		1.20	1.03	1.40
	Megestrol		1.18	1.01	1.39
	dipyridamole †	Hematological	1.33	1.03	1.70
	clopidogrel †		1.13	1.05	1.22
	omega-3 polyunsaturated fatty acid	Nutrients and nutritional	1.40	1.16	1.68
	Indapamide	Renal and genitourinary	1.54	1.03	2.29
	Mirabegron		1.48	1.12	1.97
	Metolazone		1.39	1.15	1.69
Tricyclic and related antidepressants					
Amitriptyline (9)	sulfamethoxazole *, **, ***	Anti-infective	1.28	1.11	1.47
	trimethoprim *, **, ***		1.27	1.10	1.45
	amiodarone **	CV	1.76	1.36	2.27
	Ramipril		1.52	1.13	2.03
	isosorbide mononitrate		1.30	1.05	1.62
	risperidone *	CNS	1.52	1.07	2.16
	Lamotrigine		1.49	1.11	2.00
	Lorazepam		1.17	1.01	1.34
	Pregabalin		1.17	1.03	1.34
	Prednisone	Endocrine and metabolic	1.13	1.02	1.26
	levothyroxine **		1.09	1.00	1.18
	Esomeprazole	GI	1.12	1.00	1.26
	Clopidogrel	Hematological	1.15	1.02	1.31
	potassium chloride	Nutrients and nutritional	1.14	1.04	1.26
	Darifenacin	Renal and genitourinary	1.68	1.13	2.48
	Metolazone		1.48	1.08	2.04
Desipramine (4)	Atorvastatin	CV	1.50	1.00	2.25
	Methylprednisolone	Endocrine and metabolic	1.93	1.04	3.60
Doxepin (9)	sulfamethoxazole *, **, ***	Anti-infective	1.43	1.04	1.96

Object drug (ASO rating)	Precipitant drug	Precipitant drug therapeutic category	RR, semi-Bayes shrunk	Lower bound of 95% CI	Upper bound of 95% CI
	trimethoprim *,**,***		1.38	1.01	1.88
	Memantine	CNS	**2.05**	1.20	3.49
	Diazepam		1.56	1.09	2.21
	Pantoprazole	GI	1.41	1.09	1.84
Imipramine (6)	ondansetron *,**	CNS	**2.15**	1.22	3.80
	Omeprazole	GI	1.39	1.05	1.85
	Triamterene	Renal and genitourinary	**2.02**	1.19	3.43
Nortriptyline (3)	sulfamethoxazole *,**,***	Anti-infective	1.33	1.03	1.73
	trimethoprim *,**,***		1.33	1.03	1.73
	ketoprofen †,***	CNS	**2.96**	1.48	5.91
	oxaprozin †,***		1.67	1.02	2.74
	Glipizide	Endocrine and metabolic	1.65	1.05	2.60
	pioglitazone		1.65	1.07	2.53
	estradiol *,**		1.50	1.08	2.07
	omeprazole	GI	1.19	1.03	1.39
	multivitamin with iron	Nutrients and nutritional	**2.55**	1.14	5.67
	silodosin	Renal and genitourinary	**2.28**	1.16	4.51

ASO = anticholinergic activity, sedation, and orthostasis; CV = cardiovascular; CNS = central nervous system; GI = gastrointestinal; RR = rate ratio

Rate ratios > 2.00 are bolded to highlight N = 22 potential signals that may warrant particular attention in future etiologic work.

Categorization of object drugs by severity of anticholinergic activity, sedation, and orthostasis: Within the Facts & Comparisons eAnswers central nervous system agents therapeutic category, we used the antidepressants monograph to categorize object drugs by severity of anticholinergic activity, sedation, and orthostasis. Our rationale for focusing on these adverse effects was their potential relationships with the unintentional traumatic injury outcomes being examined. For each antidepressant, we calculated a composite score by summing numeric severity ratings (0 = none or very low, 1 = low, 2 = moderate, 3 = high) for each of the three adverse effects. Therefore, each antidepressant was assigned a score of zero through nine, with a nine indicating a drug with high severity for anticholinergic activity, sedation, and orthostasis.

*drug interaction with impact on object documented in Micromedex

**drug interaction with impact on object documented in Facts & Comparisons eAnswers

***finding may be particularly affected by protopathic bias

†drug interaction with impact on precipitant documented in Micromedex

‡drug interaction with impact on precipitant documented in Facts & Comparisons eAnswers