Revealing unknown benefits of existing medications to aid the discovery of new treatments for post-traumatic stress disorder

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Background

Post-traumatic stress disorder (PTSD) affects approximately 7% of people in the United States at some point during their life (1,2). Cognitive behavioral therapy is the most common form of post-traumatic treatment designed to prevent the onset of PTSD and has been found to be only moderately effective (3). Recently, there has been an increased interest in the exploration of pharmacologic therapy for the prevention of PTSD (3,4). Currently, the only FDA approved treatments for PTSD are two selective serotonin reuptake inhibitors (SSRIs), sertraline and paroxetine (5). Explorations into new effective PTSD treatments have typically relied on a theory driven approach, which first hypothesizes how PTSD biologically manifests in trauma survivors and then identifies existing medications that may mediate that pathway (3). However, there is potential to look at a much broader landscape of medications. By leveraging retrospective observational data, it is possible to examine the association between all existing medications and the incidence of PTSD.

We utilized the Real-World Assessment and Research of Drug Performance (REWARD) framework, which utilizes hundreds of millions of patient records to study the association between all medications with thousands of outcomes (6–9).

Methods

Using a self-controlled study design, the association between 1399 medications and the incidence of PTSD across four US insurance claims databases covering commercially insured, Medicare eligible, and Medicaid patients was examined. A validated algorithm for identifying incident PTSD in claims data was used which required patients to have at least two claims containing a diagnosis for PTSD (ICD-9-CM code 309.81 or ICD-10-CM codes F43.10, F43.11, F43.12) on distinct service dates and occurring within 12 months of each other. Medications were identified by their RxNorm ingredient. Medications used to treat PTSD or its symptoms (e.g., antidepressants, antipsychotics) were excluded from the analysis. Medications associated with ≥30% reduction in risk of PTSD in ≥2 databases were identified. The incident rate ratios, 95% confidence intervals, and p-values were calibrated using negative controls to adjust for residual bias. Meta-analyses with random effects were used to pool results across databases.

Results

A total of 137,182,179 individuals were included in the analysis. Of the 15 medications identified, six were categorized as “primary signals” while the remaining nine were considered “potential signals”. The primary signals include medications that have been previously investigated or proposed as potential therapies for PTSD but are not commonly used for this purpose. The potential signals include medications that showed strong protective effects but may be due to off-label use or the treatment of PTSD symptoms. The primary signals include a beta blocker that has been previously studied for PTSD, and five medications used to treat attention-deficit/hyperactivity disorder. The potential signals include four medications used to treat substance use disorders and five medications used to treat sleep disorders. (**Figure 1**)

Conclusion

There is a large unmet need for medications that are effective at preventing or treating PTSD. The few

currently approved treatments are antidepressants that are limited in their efficacy for treating the totality of symptoms associated with PTSD and do not prevent incidence of the condition. This study leveraged a vast amount of observational data to perform large-scale analytics across multiple databases. The associations between nearly 1400 drugs and the outcome of incident PTSD were assessed, and a handful of signals were detected, which may be candidates for further investigation. Future research may aim to identify patients most at risk for the outcome of PTSD and those who have the highest probability of benefiting from an intervention related to those identified in this study. This approach provides tangible targets for more rigorous research that can aid in the discovery of new and effective treatments not only for PTSD but also other diseases for which the unmet medical need remains high.

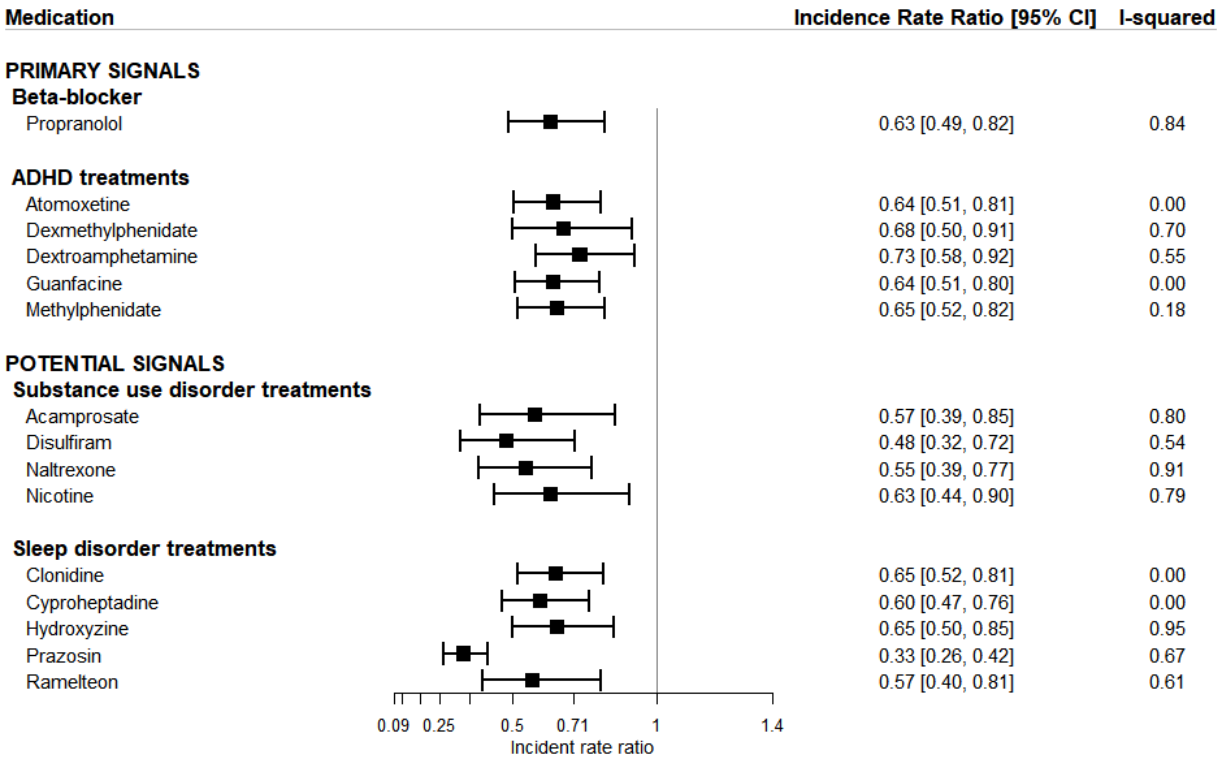

Figure 1. Forest plots of meta-analyses results for the medications found to have protective associations with PTSD

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