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Treatment of Depression after Traumatic Brain Injury Reduces Risk of Neuropsychiatric Outcomes

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Abstract

The objectives of this study were to identify characteristics associated with receipt of antidepressants for treatment of incident depression diagnosed following traumatic brain injury (TBI) and to assess the impact of receipt of treatment for depression on risk of other neuropsychiatric outcomes associated with TBI. We conducted a retrospective cohort study of individuals with TBI who were subsequently diagnosed with incident depression between 2008 and 2014 using data from the OptumLabs® Data Warehouse. We identified factors associated with receipt of antidepressants and compared risk of new diagnosis of alcohol dependence disorder, anxiety, insomnia, and substance dependence disorder between those who received antidepressants and those who did not over a maximum 2-year follow-up, controlling for duration of use and clinical and demographic characteristics.

Of 9581 individuals newly diagnosed with depression following TBI, 4103 (43%) received at least one antidepressant. Moderate-severe TBI (odds ratio [OR] 1.44; 95% confidence interval [CI]: 1.39, 1.50), female sex (OR 1.21; 95% CI: 1.19, 1.24), diagnosis of Alzheimer's disease (OR 1.39; 95% CI: 1.35, 1.44), and anxiety (OR 1.35; 95% CI: 1.31, 1.38) were associated with receipt of antidepressants. Longer duration of antidepressant use was associated with decreased risk of newly diagnosed anxiety (hazard ratio [HR] 0.92; 95% CI: 0.89, 0.96), insomnia (HR 0.94; 95% CI: 0.91, 0.98), and substance dependence disorder (HR 0.92; 95% CI: 0.88, 0.97). These results provide evidence of a beneficial effect of antidepressant use on incidence of outcomes associated with poorer recovery from TBI.

Keywords: antidepressants; anxiety; depression; insomnia; substance dependence disorder; traumatic brain injury

Introduction

Individuals with traumatic brain injury (TBI) are at heightened risk for depression, with reported post-TBI prevalence ranging from 26 to 40%.[1–9] Depression post-TBI is associated with impaired cognitive and functional recovery, disability, and risk of suicide.[10–17] Apart from its impact on recovery from TBI, depression is also associated with poorer self-care, decreased adherence to medications, higher comorbid illness burden, and increased mortality.[18–20]

Evidence guiding treatment of pharmacological depression following TBI is scant, with many small observational studies and randomized controlled trials, as well as recent meta-analyses, reporting no or limited efficacy.[21–27] Research on whether treatment of depression following TBI impacts other outcomes is also limited, although improvements in cognitive functioning and quality of life have been reported.[21,26,28,29] As well, proactive treatment with antidepressants may reduce development of depression following TBI.[8,9]

A better understanding of who receives treatment for depression following TBI and how receipt of treatment impacts other outcomes associated with TBI would inform the current state of knowledge and help guide treatment decisions. We have previously used administrative claims data to conduct large-sample analyses of the risk of neuropsychiatric disorders following TBI and have provided evidence suggesting that incident depression and anxiety following TBI may be undertreated when compared with the pre-TBI period.[3,30–32] To inform treatment of depression following TBI, the objectives of this study were to: 1) identify characteristics associated with receipt of antidepressants for treatment of incident depression diagnosed following TBI, and 2) assess the impact of receipt of treatment for depression on risk of other neuropsychiatric outcomes associated with TBI.

Methods

Data source

Data for this study came from the OptumLabs® Data Warehouse (OLDW), which includes de-identified claims data for privately insured and Medicare Advantage (MA) enrollees.[33] The database

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has longitudinal health information on enrollees from different demographic and geographical regions across the United States and is representative of the general commercial/MA market in the geographic area where it operates.[33] Enrollees in the database have comprehensive, full insurance coverage for physician, hospital, and prescription drug services. In the OLDW, individuals ≥89 years are assigned an age of 89 years to minimize risk of re-identification in compliance with Health Insurance Portability and Accountability Act de-identification requirements. This study involved analysis of pre-existing, de-identified data and was determined exempt from the University of Maryland, Baltimore Institutional Review Board approval.

Study design

We conducted a retrospective cohort study to evaluate characteristics and outcomes associated with receipt of antidepressant treatment for incident depression following TBI. The follow-up period extended from the date of depression diagnosis post-TBI to the end of follow-up (maximum 24 months). Characteristics of individuals at the time of depression diagnosis were compared by receipt of treatment at any time during follow-up. Individuals diagnosed with depression for the first time were followed forward in time to determine whether they received treatment and to ascertain risk of studied outcomes.

Traumatic brain injury

Enrollees aged ≥18 years and diagnosed with TBI of any severity between January 1, 2008 and June 30, 2014 with 12 months continuous insurance coverage (medical and pharmacy) prior to the date of TBI and 24 months continuous coverage post-TBI were included. TBI was defined using the Centers for Disease Control (CDC)'s surveillance definition using the *International Classification of Disease, 9th Revision Clinical Modification* (ICD-9-CM) codes 800.xx, 801.xx, 803.xx, 804.xx, 850.xx–854.1x, 950.1–950.3, and 959.01.[34,35] These ICD-9-CM codes have been previously shown to have high sensitivity and positive predictive value to detect TBI and identify TBI-related hospitalizations.[36,37] We searched for these ICD-9-CM codes in any position on an inpatient or outpatient claim.

Depression

We defined depression based on prior studies and clinical input using ICD-9-CM codes 296.20–296.25, 296.30–296.35, 300.4, or 311 on any inpatient, outpatient, skilled nursing facility, hospice, or home health claim.[38–40] We wanted to focus specifically on depression post-TBI; thus, we excluded those diagnosed with depression pre-TBI. Individuals received depression diagnoses at different times during the 24-month follow-up, resulting in differing amounts of follow-up per person. This descrepency is accomodated by our analytic technique.

Antidepressants

Antidepressants (Table 1) were identified from pharmacy claims with help from a pharmacist and a neuropsychiatrist (VR). Consistent with best practice in pharmacoepidemiological studies, we excluded prevalent antidepressant users (including those with a fill for an antidepressant during the 12 months pre-TBI and those with a fill for an antidepressant prior to post-TBI depression diagnosis) and implemented a new-user design.[41,42] We created indicators for evidence of a prescription fill in each month during the post-TBI study period. Fills for more than 30 days were pushed forward into the next period.

Antidepressant use varied by month over the course of the study period. To capture both the time-varying and cumulative aspects of antidepressant use after diagnosis of depression, we created three variables. First, we allowed antidepressant use (yes/no) to vary in each month following depression diagnosis. We also captured antidepressant use during the month before the month of interest. Finally, we summed the monthly antidepressant fills to create a duration of use variable.

Table 1. Antidepressants and Classes

Drug name	*Class*
Amitriptyline HCl	Tricyclic antidepressant (TCA)
Perphenazine/ Amitriptyline	Typical antipsychotic and TCA
Amitriptyline/ Chlordiazepoxide	TCA and benzodiazepine
Amoxapine	TCA
Bupropion	Miscellaneous antidepressant
Citalopram hydrobromide	Selective serotonin reuptake inhibitor (SSRI)
Clomipramine HCl	TCA
Desipramine HCl	TCA
Desvenlafaxine succinate	Serotonin-norepinephrine reuptake inhibitor (SNRI)
Doxepin HCl	TCA
Duloxetine HCl	SNRI
Escitalopram oxalate	SSRI
Fluoxetine HCl	SSRI
Fluvoxamine maleate	SSRI
Imipramine	TCA
Isocarboxazid	Monoamine oxidase inhibitor (MAOI)
Levomilnacipran	SNRI
Maprotiline	TCA
Mirtazapine	Miscellaneous antidepressant
Nortriptyline HCl	TCA
Olanzapine/Fluoxetine	Atypical antipsychotic and SSRI
Paroxetine	SSRI
Phenelzine	MAOI
Protriptyline HCl	TCA
Sertraline HCl	SSRI
Tranylcypromine	MAOI
Trazodone	Serotonin modulator
Trimipramine maleate	TCA
Venlafaxine HCl	SNRI
Vortioxetine	Serotonin modulator

Outcomes

We identified outcomes previously reported to be associated with poorer recovery from TBI.[5–7,43–48] These included anxiety (ICD-9-CM 300.0), alcohol dependence and abuse (ICD-9-CM 291, 303, 305.0, 571.0, 571.2, 571.3), insomnia (ICD-9-CM 307.4, 327.0, 780.5, V69.4), and substance dependence and abuse (ICD-9-CM 292, 304, 305.1–305.9). For each outcome, we excluded individuals who: 1) experienced the outcome prior to depression diagnosis, or 2) experienced the outcome within 30 days of depression diagnosis. This last exclusion was necessary given the monthly structure of the files and our desire to capture antidepressant use from the prior month. These exclusions resulted in a different denominator for each outcome analysis. Individuals could contribute to each outcome analysis and were not excluded based on experiencing outcomes other than the one studied.

Covariates

Enrollee's demographic characteristics including insurance type and census region were obtained from OLDW files. Based on

distribution, we categorized age as <35, 35–49, 50–64, 65–79, and >79 years. We identified baseline (i.e., at the time of depression diagnosis) comorbidities using ICD-9-CM codes on inpatient or outpatient claims during the 12 months prior to TBI. We used ICD-9-CM codes to initially categorize TBI as unspecified head injury (959.01), concussion (850.x), and all other TBI (800.xx, 801.xx, 803.xx, 804.xx, 851.xx–854.1x, and 950.1–950.3). To create a moderate-severe TBI category, we required a diagnosis of ''other'' TBI in the inpatient setting, identified using point of service code 21 (inpatient hospital). All other TBIs were not moderate-severe TBI.

Statistical analysis

We assessed frequencies and distributions of all variables and made comparisons between those who received at least one antidepressant fill following depression diagnosis and those who did not. Comparisons were tested using chi square goodness of fit and Student's *t* test.

To identify independent predictors of receipt of antidepressant treatment for incident depression following TBI, we used logistic regression. We modeled receipt of treatment as a function of potential predictors identified in bivariate analysis using a *p*-value cutoff = 0.1 for initial inclusion. We retained variables whose *p*-value remained statistically significant at $p < 0.05$. Odds ratios (OR) and 95% confidence intervals (CI) are reported.

To assess the association between antidepressant use and each outcome (new diagnosis of a medical problem or non-depression-related neuropsychiatric problem as previously described), we first assessed the cumulative incidence of each outcome as a function of receipt of at least one antidepressant following depression diagnosis. Next, we implemented a discrete time approach using generalized estimating equations with a binary distribution and complementary log-log link.[49] Models were run separately for each outcome among individuals at risk for the outcome and individuals were censored after the outcome. First, we modeled the outcome as a function of antidepressant use in the 30-day period, use in the 30-day period before, and the duration of use variable. Next, we added covariates to the model, keeping those whose *p*-value remained <0.05. We report hazard ratios (HR) and 95% CI for any antidepressant in the period, any antidepressant in the period prior, and the duration of use variable. All analyses were performed with STATA/MP version 15 (StataCorp LLC).

Results

Of 207,354 individuals diagnosed with TBI between 2008 and 2014, 53,816 (26.0%) were diagnosed with depression following TBI. Of these, 26,889 (13.0% of 207,354) had previously been diagnosed with depression pre-TBI and an additional 12,503 (6.0% of 207,354) had a fill for an antidepressant pre-TBI. Of the remaining 14,424 with incident depression, 4843 (33.6%) had an antidepressant fill prior to their depression diagnosis. Following these exclusions, 9581 individuals diagnosed with TBI between 2008 and 2014 and subsequently diagnosed with incident depression remained in our study sample.

Less than half of individuals in our sample received at least one antidepressant ($n = 4103$ [42.8%]). Selective serotonin reuptake inhibitors (SSRIs) were the most commonly prescribed (73% of those on antidepressants), and among the SSRIs, citalopram (34% of SSRIs) and sertraline (30% of SSRIs) were the most common. Those who received at least one antidepressant differed from those who did not receive an antidepressant during follow-up ($n = 5478$ [57.2%]). They were younger (56.2 [standard deviation (SD) 22.3] years vs. 57.9 [SD 21.2] years, $p < 0.001$) and more likely to be female (60.3 vs. 57.3%, $p = 0.003$) and white (77.8 vs. 73.8%, $p < 0.001$; Table 2). They were slightly more likely to have

Table 2. Characteristics of Individuals Diagnosed with TBI between 2008 and 2014 and Subsequently Diagnosed with Incident Depression Who Met Study Criteria by Receipt of Antidepressants ($N = 9581$)

	Antidepressant use post-TBI, n = *4103*	*No antidepressant use post-TBI,* n = *5478*	P-*value*
Age (years), mean (SD)	56.2 (22.3)	57.9 (21.2)	<0.001
Age categories, *n* (%)			
<35	931 (22.7)	1046 (19.1)	<0.001
35-49	652 (15.9)	853 (15.6)	
50-64	773 (18.8)	1162 (21.2)	
65-74	511 (12.5)	775 (14.2)	
75-84	1058 (25.8)	1370 (25.0)	
≥85	178 (4.3)	272 (5.0)	
Sex, *n* (%)			0.003
Male	1630 (39.7)	2340 (42.7)	
Female	2473 (60.3)	3138 (57.3)	
Race, *n* (%)			<0.001
White	3168 (77.8)	4005 (73.8)	
Black	395 (9.7)	625 (11.5)	
Hispanic	305 (7.5)	453 (8.3)	
Asian	79 (1.9)	120 (2.2)	
Other	127 (3.1)	226 (4.2)	
Education, *n* (%)			0.06
≤High school	1227 (30.2)	1553 (28.7)	
<Bachelor's degree	2228 (54.8)	2965 (54.8)	
≥Bachelor's degree	608 (15.0)	898 (16.6)	
Insurance type, *n* (%)			0.008
Commercial	2418 (58.9)	3081 (56.2)	
Medicare Advantage	1685 (41.1)	2397 (43.8)	
TBI severity, *n* (%)			<0.001
Mild TBI	3747 (91.3)	5118 (93.4)	
Moderate/Severe TBI	356 (8.7)	360 (6.6)	
Comorbid illness, *n* (%)			
Alcohol dependence and abuse	528 (12.8)	664 (12.1)	0.27
Alzheimer's and related dementias	674 (16.4)	774 (14.1)	0.002
Anemia	538 (13.1)	741 (13.5)	0.56
Anxiety	1130 (27.5)	1278 (23.3)	<0.001
Arthritis	1603 (39.1)	2235 (40.8)	0.09
Asthma	508 (12.4)	752 (13.7)	0.05
Atrial fibrillation	543 (13.2)	753 (13.8)	0.47
Bipolar	156 (3.8)	279 (5.1)	0.003
Chronic kidney disease	760 (18.5)	1090 (19.9)	0.09
Chronic liver disease	425 (10.4)	506 (9.2)	0.07
Chronic obstructive pulmonary disease	794 (19.4)	1127 (20.6)	0.14
Chronic pain	390 (9.5)	530 (9.7)	0.78
Diabetes	986 (24.0)	1361 (24.8)	0.36
Epilepsy	261 (6.4)	355 (6.5)	0.81
Heart failure	577 (14.1)	778 (14.2)	0.85
Hyperlipidemia	1967 (47.9)	2850 (52.0)	<0.001
Hypertension	2350 (57.3)	3306 (60.4)	0.002
Ischemic heart disease	977 (23.8)	1350 (24.6)	0.35
Parkinson's disease	102 (2.5)	144 (2.6)	0.66
Substance dependence and abuse	894 (21.8)	1097 (20.0)	0.04

SD, standard deviation; TBI, traumatic brain injury.

Table 3. Independent Factors Associated with Receipt of Antidepressant Treatment for Incident Depression after TBI between 2008 and 2014 ($N=9581$)

	Odds ratio (95% confidence interval)	P-*value*
Age	0.99 (0.99, 1.00)	<0.001
Sex		
Male	Reference	
Female	1.21 (1.195, 1.24)	<0.001
Race		
White	Reference	
Black	0.80 (0.78, 0.83)	<0.001
Hispanic	0.82 (0.79, 0.85)	<0.001
Asian	0.79 (0.73, 0.85)	<0.001
Other	0.70 (0.66, 0.74)	<0.001
TBI severity		
Mild	Reference	
Moderate-severe	1.44 (1.39, 1.50)	<0.001
Alzheimer's and related dementias	1.39 (1.35, 1.44)	<0.001
Anxiety	1.35 (1.31, 1.38)	<0.001
Asthma	0.96 (0.93, 0.99)	0.009
Bipolar	0.64 (0.61, 0.67)	<0.001
Hyperlipidemia	0.96 (0.94, 0.98)	0.001
Substance abuse/ dependence	1.14 (1.11, 1.17)	<0.001

TBI, traumatic brain injury.

moderate-severe TBI (8.7 vs. 6.6%, $p<0.001$). Individuals who received at least one antidepressant were more likely to have a diagnosis of Alzheimer's disease and related dementias (16.4 vs. 14.1%, $p=0.002$) and anxiety (27.5 vs. 23.3%, $p<0.001$).

Our final logistic regression model contained 10 independent predictors of receiving antidepressant treatment for incident depression following TBI (Table 3). The strongest predictors were moderate-severe TBI (OR 1.44; 95% CI: 1.39, 1.50) and diagnosis of Alzheimer's disease and related dementias (OR 1.39; 95% CI: 1.35, 1.44) and anxiety (OR 1.35; 95% CI: 1.31, 1.38) at the time of depression diagnosis.

Following depression diagnosis, cumulative incidence of each outcome was elevated in the group that received at least one antidepressant compared with the group that received no antidepressants (Table 4). Incidence was highest for anxiety (19.0% in the antidepressant group and 8.2% in the no-antidepressant group) and lowest for alcohol dependence and abuse (3.2% in the antidepressant group and 1.4% in the no-antidepressant group).

Results from our adjusted discrete time models are presented in Table 5. The HR and 95% CI for antidepressant use ''in month'' reflects the association between antidepressant use and the outcome in the month of the outcome. Antidepressant use the ''month before'' captures the association between use in the month before the outcome and the outcome. Duration of antidepressant use is interpreted per month of use.

Increased duration of antidepressant use was associated with decreased risk of anxiety (HR 0.92; 95% CI: 0.89, 0.96), insomnia (HR 0.94; 95% CI: 0.91, 0.98), and substance dependence and abuse (HR 0.92; 95% CI: 0.88, 0.97) per month of use (Table 5). Antidepressant use during the month of the outcome (month of new diagnosis of a medical problem or non-depression-related neuropsychiatric problem) was associated with diagnosis of all outcomes except alcohol dependence and abuse.

Discussion

To our knowledge, this is the first study to evaluate the association between receipt of pharmacological treatment of depression following TBI and incidence of health outcomes associated with poorer recovery. Less than 50% of individuals diagnosed with incident depression following TBI received antidepressants. Among those who used antidepressants, longer duration of use was associated with decreased risk of anxiety, insomnia, and substance dependence disorder diagnoses. These results provide evidence of a beneficial effect of antidepressant use on incidence of outcomes associated with poorer recovery from TBI and add to the evidence base on treatment of depression following TBI.

In this cohort of individuals with incident depression following TBI, those who received antidepressant treatment were younger and more likely to have moderate-severe TBI, to be female, and to be diagnosed with Alzheimer's disease and related dementias or anxiety at the time of depression diagnosis. Female sex has been associated with antidepressant initiation and use in general populations of depressed individuals and most studies suggest that older age, especially age 65 years and older, is associated with decreased antidepressant use.[50–52] Comorbid anxiety has also been associated with antidepressant use.[50] Together, these results suggest that factors associated with receipt of antidepressants following TBI mirror those among depressed individuals generally. On the other hand, individuals with TBI and newly diagnosed depression who received at least one antidepressant had higher rates of studied outcomes (new diagnosis of a medical problem or non-depression-related neuropsychiatric problem) compared with those who did not receive treatment. This suggests that medically complex patients are likelier to receive treatment. Whether this effect is caused by receiving a subsequent diagnosis that alerts physicians to the underlying depression is unclear.

Yet, this is the first time that TBI severity has been associated with receipt of treatment for incident depression. Injury severity

Table 4. Cumulative Incidence of Newly Diagnosed Outcomes Over Up to 24 Months Follow-Up among Individuals Diagnosed with TBI between 2008 and 2014 and Subsequently Diagnosed with Incident Depression by Receipt of Antidepressants at Any Time after Depression Diagnosis

	Antidepressant use post-TBI		*No antidepressant use post-TBI*	
	Frequency	*Cumulative incidence*	*Frequency*	*Cumulative incidence*
Alcohol dependence and abuse	115	3.2%	69	1.4%
Anxiety	409	19.0%	256	8.2%
Insomnia	338	9.8%	217	4.6%
Substance dependence and abuse	238	7.5%	180	4.1%

TBI, traumatic brain injury.

Table 5. Adjusted Association between Receipt of Antidepressants for Incident Depression and Outcomes among Individuals Diagnosed with TBI between 2008 and 2014 ($N=9581$)

Outcome	*Hazard ratio (95% confidence interval)*	P-*value*[a]
Alcohol dependence and abuse[b]		
Antidepressant use in month	2.09 (0.94, 4.65)	0.07
Antidepressant use month before	1.09 (0.52, 2.32)	0.82
Duration of antidepressant use	0.98 (0.93, 1.04)	0.56
Anxiety[c]		
Antidepressant use in month	5.83 (4.24, 8.00)	<0.001
Antidepressant use month before	0.74 (0.82, 1.06)	0.10
Duration of antidepressant use	0.92 (0.89, 0.96)	<0.001
Insomnia[d]		
Antidepressant use in month	4.84 (3.31, 7.08)	<0.001
Antidepressant use month before	0.66 (0.43, 1.01)	0.06
Duration of antidepressant use	0.94 (0.91, 0.98)	0.001
Substance dependence and abuse[e]		
Antidepressant use in month	2.97 (1.97, 4.48)	<0.001
Antidepressant use month before	0.95 (0.63, 1.43)	0.81
Duration of antidepressant use	0.92 (0.88, 0.97)	0.001

[a]Two-tailed test of null hypothesis of coefficient = 0, controlling for other variables in the model; [b]adjusted for time, age, sex, Medicare Advantage, and substance dependence and abuse; [c]adjusted for time, age, sex, race, education, chronic kidney disease, hypertension, hyperlipidemia, heart failure, substance dependence and abuse, bipolar disorder, chronic pain, and Parkinson's disease; [d]adjusted for time, age, sex, Alzheimer's disease, diabetes, anxiety, post-traumatic stress disorder, and chronic pain; [e]adjusted for time, age, sex, Medicare Advantage, alcohol dependence and abuse, education, chronic pain, Alzheimer's disease, and chronic obstructive pulmonary disease.

TBI, traumatic brain injury.

has not been consistently associated with risk or severity of depression following TBI.[2,16,21,53–57] However, increased interaction with health care providers following more severe TBI may result in higher likelihood of receiving antidepressant treatment for diagnosed depression. This suggests that the majority of individuals with less severe TBI may be undertreated for depression. We have previously reported that older adults who were hospitalized with TBI and subsequently diagnosed with depression were less likely to receive antidepressants compared with similar individuals without TBI, but as of yet this study has not been replicated in younger populations or across different TBI diagnosis locations.[31]

Longer duration of antidepressant use was associated with reduced risk of anxiety, insomnia, and substance dependence disorder. It is not surprising that treatment of depression can help improve symptoms of anxiety and insomnia and decrease substance abuse, but this study is the first to demonstrate this effect in a large and heterogenous population of individuals with TBI and diagnosed with depression.[8,58] Recent studies conducted among individuals with TBI provided evidence that preemptive treatment with antidepressants reduces risk of depression.[8,9] Whether risk of new anxiety, insomnia, or substance dependence disorders following TBI could be reduced with preemptive treatment should be investigated in future studies.

We observed strong associations between antidepressant use and anxiety, insomnia, and substance dependence disorder in the month of diagnosis. These associations are likely not causal but related to capture of antidepressant use and outcomes within a 30-day period without knowing which event occurred first. Given that no significant associations were observed for the lagged antidepressant variable, we can conclude that diagnosis of these outcomes in a person with comorbid depression prompted treatment, either for the previously diagnosed but untreated depression or possibly for newly diagnosed anxiety or insomnia, for which we observed the largest effect sizes.

Strengths of this study include a large national sample of individuals diagnosed with TBI across multiple points of service, the new-user study design, and the clinically meaningful research question. However, limitations of the study should be considered when interpreting results. First, we required continuous enrollment in medical and prescription coverage for the duration of the study period but have no information on diagnoses or prescriptions received outside that period. Second, we relied on diagnosis codes for identification of TBI, depression, and all outcomes. Although the diagnosis codes for TBI are those recommended by the CDC for TBI surveillance, underdiagnosis of mental health disorders and insomnia in claims data is well established.[59–63] Among a cohort of individuals diagnosed with depression, this would likely result in bias toward the null, suggesting our results may be an underestimate of the true effect of antidepressants on incidence of studied outcomes.

Third, our administrative data lack information on severity of depression or our outcome measures. We also lacked clinical TBI severity measures. We used ICD-9-CM codes in combination with diagnosis of TBI in the inpatient setting to identify moderate-severe TBI, but hospitalization could have been due to other injuries rather than the TBI and this could not be discerned. Fourth, our data were limited to individuals with commercial or MA coverage provided through a single provider. Consequently, individuals receiving insurance coverage through Medicare fee-for-service or Medicaid are not represented. Finally, this analysis was restricted to individuals without a depression diagnosis or antidepressant use prior to TBI. Although this is methodologically correct, it resulted in exclusion of many individuals.[41,42] Thus, generalizability of these results to those excluded should be examined in future studies.

In conclusion, results from this study suggest that antidepressant treatment of incident depression following TBI may reduce risk of anxiety, insomnia, and substance dependence disorder. Future studies should evaluate this potential benefit of treating depression following TBI.

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Author Disclosure Statement

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