Rates of Major Depressive Disorder and Clinical Outcomes Following Traumatic Brain Injury

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RAUMATIC BRAIN INJURY (TBI) IS a major cause of disability in the United States and a signature injury among wounded soldiers. Assessment and treatment of TBI typically focus on physical and cognitive impairments, yet psychological impairments represent significant causes of disability. Major depressive disorder (MDD) may be the most common and disabling psychiatric condition in individuals with TBI. Poorer cognitive functioning, aggression and anxiety, greater functional disability, poorer recovery, higher rates of suicide attempts, and greater health care costs are thought to be associated with MDD after TBI.

Despite considerable research, the rates, predictors, and outcomes of MDD after TBI remain uncertain. Depression prevalence rates have ranged from 10% to 77%. Small sample size, selection bias, retrospective reporting, use of measures without diagnostic validity, and failure to exclude patients who were depressed at the time of injury have limited studies of rates and correlates of TBI-related MDD. More definitive studies could galvanize efforts to improve recognition and treatment of this important secondary condition. Therefore, we sought to describe the rate of MDD during the first year after TBI, multivariate predictors of MDD, MDD-related comorbidities, and the relationship of MDD to 1-year quality-of-life outcomes in a large prospectively studied sample of consecutive patients hospitalized for complicated mild to severe TBI.

METHODS
This study was the recruitment phase of a clinical trial investigating the efficacy of sertraline for MDD after TBI. The trial is completed and the outcome analysis is in progress. Eligibility criteria for the cohort study were admission to Harborview Medical Center (a level I trauma center in Seattle, Washington) with TBI and radiological evidence of acute, traumatically induced brain abnormality or Glasgow Coma Scale (GCS) score lower than 13 (based on the lowest score within 24 hours after admission or the first af-
ter paralytic agents were withdrawn). Participants were residents of King, Pierce, Kitsap, Jefferson, Mason, Thurston, or Snohomish counties; at least 18 years old; and English speaking. We excluded those with uncomplicated mild TBI (GCS 13-15 and no radiological abnormality) because of diagnostic unreliability in this population. Other exclusion criteria were homelessness, no contact information, incarceration, and schizophrenia (Figure 1). Participants with GCS scores lower than 13 and no radiological evidence of TBI were excluded if their blood alcohol levels exceeded 199 mg/dL because alcohol intoxication can decrease GCS scores.

Enrollment occurred from June 2001 through March 2005 and follow-up assessments ended in February 2006. We obtained a waiver of consent to determine eligibility and retain selected demographic information about non-recruited patients. Otherwise, participation required written consent. Study procedures were approved by the University of Washington institutional review board and followed guidelines from the Health Insurance Portability and Accountability Act.

Procedures
Consecutively eligible inpatients with TBI were identified via daily automatic queries of electronic medical records and TBI consultation lists. Research staff obtained consent from eligible patients who were fully oriented prior to discharge. For patients disoriented at discharge, we obtained assent from legal next of kin to conduct follow-up. We recruited patients not approached by discharge via a letter from the attending neurosurgeon and telephone calls. Trained research personnel used structured telephone interviews to assess participants monthly from months 1 through 6 and at 8, 10, and 12 months following injury. Patients were required to pass a standardized orientation examination prior to consenting. We followed up disoriented patients for up to 1 year to determine whether they had become oriented and could be assessed.
MAJOR DEPRESSIVE DISORDER AFTER TRAUMATIC BRAIN INJURY

Measures
Demographic, medical, radiologic, and International Classification of Diseases, Ninth Revision (ICD-9), code data were obtained via participant interviews, medical record reviews, and the Harborview Trauma Registry. Race was obtained via self-report and record review because depression prevalence may vary by race. Other system injury severity was based on the Injury Severity Score excluding head injury. Serum blood alcohol level and toxicology screening results (cocaine and amphetamine) were available for 80% of the sample.

At the initial assessment, we conducted a structured interview to assess preinjury history of psychiatric disorders and treatment. Participants were coded as depressed at injury if they reported any of the following within 6 months prior to TBI: diagnosis of depression, depression-related antidepressant use, depression-related counseling, or a suicide attempt. Preinjury history of depression was defined as ever receiving a diagnosis of or treatment for depression or making a suicide attempt. Lifetime history of depression was based on whether participants indicated they had ever been diagnosed with bipolar disorder or manic depression, generalized anxiety disorder, panic disorder, posttraumatic stress disorder (PTSD), obsessive-compulsive disorder, any phobia, schizophrenia, schizoaffective disorder, or any psychotic disorder. For descriptive purposes, we segregated lifetime history of depression or PTSD and collapsed the remainder of the diagnoses into “other mental health diagnoses.” Lifetime alcohol dependence was based on endorsing at least 2 items on the CAGE (cut down, of personal, anhedonia and a total of 5 or more symptoms of MDD at least several days during the prior 2-week period. Current panic disorder and other anxiety disorder were assessed on the same schedule using validated screening modules from the PHQ. At each contact, participants were asked about receiving antidepressants or counseling for depression. Patients were referred for further evaluation and treatment if they reported suicidal ideation with plan or intent.

Outcomes assessed at 12 months included health-related quality of life (1-item General Health Scale from the 36-item Short Form Health Survey), the European Quality of Life measure population-based weighted summary score, and 5 subcomponents of the European Quality of Life measure. We measured social role impairment attributed to depression symptoms as described by Kroenke and colleagues as well as current employment status and subjective percentage back to normal (preinjury functioning).

Data Analysis
Postinjury MDD rates are estimated as the proportion of cases ascertained with MDD for the first time after TBI at each assessment among the total sample of 559 patients. Point prevalence is the proportion of participants positive for MDD, regardless of whether it was new, persistent, or recurrent, among those interviewed at that assessment. Participants were classified as MDD+ if they qualified as depressed at any screening call and MDD− if they never qualified. Likewise, a person was considered to have a comorbid condition or treatment if he or she qualified at any interview. Both underestimate the true rates because participants may have had a condition only when they missed an interview. Binning regression with a log-linear link (Proc GENMOD, SAS version 9.2; SAS Institute, Cary, North Carolina) was used for comparing the risk of MDD and relating MDD to binary outcomes with or without adjustment for other factors. To assess independent predictors of MDD, a backward stepwise procedure was used starting with a model containing all predictors in Table 1. Separate multivariate models were built for all participants and for those who were not depressed at injury. The bivariate relationship between MDD and continuous outcomes was assessed with t tests. We adjusted for full-sample predictors of MDD, using linear or log-binomial regression, to see whether MDD independently predicted outcomes. Months depressed was calculated as the number of positive monthly screens plus twice the number of positive bimonthly screens. All probabilities are 2-tailed. Nominal P values are presented, but the Bonferroni-corrected significance level is given in footnotes.

RESULTS
We identified 1080 eligible patients, 559 of whom consented and underwent at least 1 interview. Those interviewed were significantly younger (mean [SD] age, 42.5 [17.9] vs 46.8 [21.5] years), more likely to have completed high school (89% vs 84%), and less likely to have Medicare insurance (16% vs 25%) compared with the nonrecruited group. The 2 groups were equivalent in terms of sex ratio, race, marital status, cause of injury, coma severity, other system injury severity, blood alcohol level, toxicology findings, and length of hospital stay. Participant interview rates among those eligible for interview at the 9 assessment points ranged from 79% to 90% (Figure 1). Fewer participants were interviewed at month 1 (n=289) vs subsequent months (n=338-432), primarily because more participants at month 1 were not eligible for interview, eg, pending consent (n=182) or not yet oriented (n=30).
**Rates of MDD**

During the first year after TBI, 297 of 559 patients (53.1%) met criteria for MDD at least once (FIGURE 2). The point prevalence of MDD was highest the first month after TBI. Point prevalence ranged from 21% to 31% with no trend (eFigure 1, available at http://www.jama.com). Among those screening positive for MDD in the first 3 months and interviewed at least twice, the median time depressed was 4 months; 27% screened positive only once, and 36% screened positive for 6 or more months (eFigure 2). Excluding those depressed at the time of injury, the rate of new (incident) MDD was 49% (233/471).

**Predictors of MDD**

Table 1 shows the composition of the 559 participants interviewed as well as the percentage depressed during the study period in various subgroups based on demographics and injury characteristics and the univariate risk ratio (RR) for depression. Participants were mostly men injured in vehicular crashes who sustained complicated mild injuries. Factors closely related to MDD when considered individually include age; sex; cocaine intoxication; lifetime alcohol dependence; and preinjury history of depression, PTSD, or other mental health diagnosis. Independent predictors of MDD in the multivariate models (TABLE 2) were age and preinjury depression for both the full sample and the sample that excluded those depressed at injury. Lifetime alcohol dependence was independently associated with MDD only in the full sample model, and sex was associated with MDD only in the sample not depressed at injury. Figure 3 and eFigures 3 through 5 display the cumulative rate of MDD depending on history of depression, PTSD, alcohol dependence, and other mental health diagnosis. The group with preinjury history of depression comprised those with a history of depression diagnosis (n=61, 41%); a history of suicide attempt (n=41, 28%); or treatment for depression, including antidepressants (n=121, 81%), inpatient treatment (n=17, 11%),

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or outpatient counseling (n=52, 35%). Patients with TBI with or without these comorbid conditions appeared to be at risk of MDD throughout the 12 months.

**Comorbid Anxiety**

Major depressive disorder was associated with increased risk of meeting criteria for post-TBI panic disorder (27% vs 1%; RR=23.82; 95% confidence interval [CI], 7.62-74.50) and other anxiety disorder (54% vs 6%; RR=8.82; 95% CI, 5.42-14.35) (eTable 1). Those with MDD were more likely to report any comorbid anxiety disorders after TBI than those without MDD (60% vs 7%; RR, 8.77; 95% CI, 5.56-13.83).

### Table 1. Demographic and Injury Characteristics of Participants (N = 559) According to Depression Status* (continued)

<table>
<thead>
<tr>
<th>Variable</th>
<th>MDD−</th>
<th>MDD+</th>
<th>MDD−/ MDD+ RR (95% CI)</th>
<th>P Value</th>
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<td>&gt;79</td>
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<td>116</td>
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<td>Preinjury history of depression,</td>
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<tr>
<td>No</td>
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<td>181</td>
<td>52.2</td>
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<tr>
<td>Yes</td>
<td>29</td>
<td>55</td>
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</table>

Abbreviations: CAGE, cut down, annoyed, guilty, eye opener—a screening questionnaire for potential alcoholism; CI, confidence interval; MDD−/+, negative or positive for major depressive disorder; PTSD, posttraumatic stress disorder; RR, risk ratio; TBI, traumatic brain injury.

*Percentage with MDD within each variable category.

All results in this table are from univariate analyses. The P value in the row for the reference level reflects an overall difference among the levels of the variable. The P value for each nonreference level refers to the RR comparing that level with the reference level. P values ≤.001 are significant after adjusting for the 45 comparisons within the table using the Bonferroni correction.

Other mental health diagnoses included bipolar disorder or manic depression, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, any phobia, schizophrenia, schizoaffective disorder, or any psychotic disorder.

**Figure 2. Rate and Cumulative Rate of Major Depression Depending on Time Since Traumatic Brain Injury (N=559)**

Postinjury rate is the proportion of cases ascertained with major depressive disorder for the first time after traumatic brain injury at each assessment. The values underestimate the true rates because not all participants were assessed at each time. Error bars indicate 95% confidence intervals.

### Mental Health Treatment

Individuals with MDD were more likely to receive antidepressants (41% vs 18%; RR=2.26; 95% CI, 1.67-3.05) and counseling (20% vs 5%; RR=3.92; 95% CI, 2.20-7.00) during the year after TBI compared with those without MDD (excluding participants in the treatment trial) (eTable 1). Only 44% of those with MDD received antidepressants or counseling.

### Health-Related Quality of Life and Role Impairment at 12 Months

Major depressive disorder within the first year after TBI was associated with greater problems with mobility, usual activities, and pain/discomfort and greater difficulty with role functioning at 12 months after TBI, after controlling for MDD-related risk factors (eTable 2).

### COMMENT

The 1-year cumulative rate of MDD in this study sample is 7.9-times greater than would be expected in the general population (33.1% in our cohort vs 6.7% in the general population). Previous high-quality studies may have underestimated the rates of MDD during the first year after TBI by reporting rates in the 12% to 42.3% range. Our rate estimate may be higher because we conducted frequent assessments and were able to capture the cases with transient (1-month) major depressive episodes. In addition, the sample was characterized by high rates of depression-related risk factors such as alcohol dependence and other preinjury mental health diagnoses. Nevertheless, because of incomplete data at each assessment time point, the rate and depression duration estimates are likely conservative.
Our data indicate that 15.7% of the sample were depressed at the time of injury and that 26.8% had a preinjury history of depression but were not depressed when injured. Of the total sample, 11.4% had a major depressive episode both at injury and after the injury, 18.4% experienced a recurrence of major depression after the injury, and 23.3% experienced MDD for the first time after the injury. Only 46.9% did not experience MDD in the year after injury. Preinjury depression and depression at the time of injury heralded higher post-TBI rates of MDD compared with those with no depression history. Nevertheless, by 12 months, 41% of those without depression history also had an episode of MDD. High rates of preinjury depression in this and other samples compared with the lifetime prevalence of MDD in the general population (16.2%) is consistent with the notion that depression is a risk factor for TBI. Our estimate of preinjury depression may be higher than other studies because we included prior antidepressant treatment, prior psychotherapy for depression, and history of suicide attempt as indicators of depression history.

Several features of MDD after TBI are pertinent to future detection and treatment efforts. About half of the patients who became depressed were identified by 3 months. These data contradict the theory that poor awareness of impairment precludes depressive reactions during the first 6 months after injury and suggest a window of opportunity for early identification and treatment or prevention efforts. Nevertheless, TBI survivors remained at risk of MDD throughout the first year regardless of preinjury depression history. Risk of post-TBI MDD probably persists beyond 1 year since the curves (Figures 3, eFigures 3 through 5) do not seem to level off by 12 months. In 27% of cases, MDD lasted only 1 month and may not have required treatment. Depression after TBI was complicated by a history of substance abuse disorders and PTSD as well as co-occurring anxiety, conditions that can limit the efficacy of antidepressants.

Multivariate risk factors for MDD following TBI were similar to those for primary MDD in the general population. History of depression around the time of injury and history of depression prior to that time were the strongest predictors of post-TBI depression. These data contradict theories that history of psychiatric disorder is either unrelated to or inversely related to MDD following TBI. The relationship of alcohol dependence to both TBI and depression merits particular attention as a potentially modifiable risk factor. We did not find a relationship between injury characteristics and rate of MDD. Severity of TBI as a predictor of MDD has been controversial. Other biological markers, such as the apolipoprotein E ε4 allele, neurotransmitter...
Major Depressive Disorder after Traumatic Brain Injury

Depression after TBI was associated with comorbid anxiety and poorer functional outcomes in multiple domains 1 year after injury. After we controlled for all variables associated with depression after TBI, MDD remained a significant predictor of poorer self-reported health and lower quality of life. These results are correlational; therefore, causality cannot be inferred. Prior research has linked post-TBI depression with a host of poorer subjective and objective outcomes. Effective depression treatment may reduce disability, and this hypothesis deserves further research.

Depression was undertreated in the study sample. Moreover, based on research in primary care settings, we suspect that an even smaller proportion received guideline-level depression treatment. The dearth of rigorous pharmacotherapy and psychotherapy trials likely contributes to the inadequate treatment of MDD after TBI. Only 1 negative but underpowered class I antidepressant (sertraline) treatment trial has been published. A randomized placebo-controlled depression prevention trial found that 50 mg of sertraline daily for 3 months after TBI resulted in significantly lower depression severity in the treated group vs controls at the end of the trial but not beyond.

Psychotherapy was especially underused in our sample, possibly due to poor access to counseling. A trial of proactive telephone counseling has demonstrated that patients receiving treatment reported less depressive symptomatology 1 year after TBI compared with controls receiving usual care. Additionally, survey research indicates that individuals with TBI favor counseling and physical exercise over other depression treatment modalities. In-person or telephone counseling was preferred over Internet-delivered depression treatment.

Characteristics and comorbidities of TBI-related depression may influence treatment efficacy. For example, executive dysfunction, which is common following TBI, predicts poor response to selective serotonin reuptake inhibitors in non-TBI samples. Cognitive impairments may affect the feasibility and efficacy of standard psychotherapeutic interventions. Integrated medical and psychosocial interventions, including substance abuse interventions, might be required to produce satisfactory outcomes.

Systematic integration of mental health services into standard care of patients with TBI may be needed to improve long-term outcomes after TBI. Within inpatient rehabilitation, integrated clinical pathways can be used to organize early identification, risk assessment, diagnosis, and guideline-driven treatment of MDD. Systematic depression screening and stepped-care treatment protocols should be integrated into routine outpatient care. For those without or beyond routine follow-up, novel case-finding programs may be useful, possibly via scheduled telephone contacts, Internet-based screening or other technology-assisted methods. The manner in which substance abuse treatment has been integrated into trauma care and depression treatment integrated into primary care may provide models of how to incorporate depression treatment into TBI care.

Several study limitations should be highlighted. First, the presence or absence of MDD was based on structured telephone interviews using the PHQ-9, not more traditional diagnostic interviews such as the SCID. Nevertheless, we have reported excellent interrater reliability and good diagnostic sensitivity and specificity when comparing the PHQ-9 with the SCID in individuals with TBI. Caution should be exercised comparing these results with studies that have used other diagnostic approaches.

Next, the study was conducted at a single level I trauma center serving the northwestern United States. The patient population was characterized by high rates of Medicaid recipients and somewhat limited ethnic/racial diversity. The results of this study may not be generalizable to other regions or populations with different socioeconomic or ethnic/racial characteristics.

1. REFERENCES

2. Additional Contributions: Erika Pellet, BS, University of Kentucky. Psychosomatic Medicine; provided expert assistance and oversight in data collection efforts. She was compensated for her contributions.

3. DISCLOSURE: Pfizer supplied masked sertraline and HD39415 to Drs Bombardier and Fann (co–principal investigators). Pfizer supplied masked sertraline and HD39415 to Drs Bombardier and Fann (co–principal investigators). Pfizer supplied masked sertraline and HD39415 to Drs Bombardier and Fann (co–principal investigators). Pfizer supplied masked sertraline and HD39415 to Drs Bombardier and Fann (co–principal investigators).

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9. Previous Presentations: Parts of the manuscript were presented at the annual national meetings of the American Psychiatric Association, Rehabilitation Psychology Division; Charlotte, North Carolina; March 2007; and the Academy of Psychosomatic Medicine; Amelia Island, Florida; November 2007.


11. CONCLUSIONS: The present study is the first to report risk factors for major depressive disorder following traumatic brain injury in a large longitudinal sample of soldiers with mild traumatic brain injury. The findings provide evidence for the need of future work to better understand the relationship between traumatic brain injury and major depressive disorder in military populations. The findings are relevant to the health care of military personnel and veterans, as well as to the public health community.