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Antidepressants for depression after concussion and traumatic brain injury are still best practice

Noah D. Silverberg[1,2*] and William J. Panenka[1,3,4]

Abstract

Background: Depression is a common complication of traumatic brain injury (TBI). New evidence suggests that antidepressant medication may be no more effective than placebo in this population.

Main body: Selective serotonin reuptake inhibitors are recommended as first-line treatment for depression in contemporary expert consensus clinical practice guidelines for management of TBI. This recommendation is based on multiple prior meta-analyses of clinical trials in depression after TBI as well as depression in the general population. The evidence is mixed. A recent clinical trial and new meta-analysis including that trial found no benefit of antidepressants for depression following TBI. We argue that this finding should not change practice, i.e., patients who present with depression after TBI should still be considered for antidepressant treatment, because they may (1) benefit from robust placebo effects, (2) benefit from an alternative or adjunctive medication if the agent prescribed first does not achieve a depression remission, and (3) make improvements that are not captured well by traditional depression outcome measures, which are confounded by TBI sequelae. Patients with mild TBI are especially appropriate for antidepressant therapy because they, on average, more closely resemble patients with no known TBI history enrolled in typical primary Major Depressive Disorder clinical trials than patients enrolled in TBI trials in placebo-controlled trials published to date.

Conclusion: TBI, and especially *mild* TBI, is not a contraindication for antidepressant therapy. Health providers should routinely screen and initiate treatment for depression after TBI.

Background

Depression is common after traumatic brain injury (TBI), with at least 1 in 5 patients meeting criteria for a Major Depressive Episode within the first six months [1–3]. This rate is similar across the spectrum of TBI severity. Depression may magnify the burden of physical and cognitive symptoms as well as functional disability after TBI [2, 4], making it an important treatment target.

Main text

Prior meta-analyses have concluded that antidepressant medications are effective for depression in a variety of neurological disorders [5], including TBI [6]. Correspondingly, selective serotonin reuptake inhibitors are recommended as first-line treatment for depression in recently published expert consensus clinical practice guidelines for management of TBI [7, 8]. However, a recently published systematic review [9] raised doubt about this evidence base. Kreitzer et al. [9] screened 1020 articles published before September 20, 2017 and found 11 eligible pharmacological intervention studies in TBI samples. Their meta-analysis of the five placebo-controlled trials revealed "no benefit of antidepressant over placebo in the treatment of [Major Depressive Disorder] following TBI" (standardized mean difference = − 0.3; 95% confidence interval = − 0.6 to 0.0; I [2] = 17%) [9]. This conclusion might lead some clinicians to not offer antidepressant therapy to their patients who present with depression after TBI, which in our view, would be unfortunate. Even if this meta-analytic finding is "real" (not a Type

* Correspondence: noah.silverberg@vch.ca
[1]Division of Physical Medicine and Rehabilitation, University of British Columbia, 4255 Laurel St, Vancouver, BC V5Z 2G9, Canada
[2]Rehabilitation Research Program, Vancouver Coastal Health Research Institute, GF Strong Rehab Centre, 4255 Laurel St, Vancouver, British Columbia V5Z 2G9, Canada
Full list of author information is available at the end of the article

II error), we argue here that proactive treatment should be considered, especially in *mild* TBI (concussion), for the following reasons.

First, when non-randomized and open-label studies were included in the Kreitzer et al. [9] study as well as prior meta-analyses on the same topic [6, 10], the treatment effect was significant. That is, patients who received antidepressant therapy got better. These gains may be attributable to placebo effects. Even so, placebos may be a powerfully effective treatment for various TBI-related problems [11]. For a patient who presents with depression after TBI, prescribers may have an opportunity to harness placebo effects with on-label use of an active medication.

Second, patients whose depression does not respond to an initial antidepressant trial often benefit from augmentation or switching to an alternative selective serotonin reuptake inhibitor or a selective serotonin-epinephrine reuptake inhibitor. This stepwise approach is recommended in guidelines for TBI management [7]. Placebo-controlled trials such as those synthesized in Kreitzer et al. [9] measure the change in depressive symptoms on the first attempted antidepressant agent in the "average" patient, not the potential for depression remission with stepwise medication trials, as in real-world clinical practice.

Third, traditional depression outcome measures may lose responsiveness when applied in TBI studies, resulting in underestimation of treatment benefit. For example, 3 out of the 5 placebo-controlled trials pooled by Kreitzer et al. [9] measured depressive symptoms with the Hamilton Depression Rating Scale (HAM-D). The authors acknowledge that "instead of demonstrating antidepressants do not work over time, it could be possible that this outcome measure may not change sufficiently with time due to factors related to the underlying TBI [9]. The HAM-D, like most depression measures, includes non-specific symptoms that could reflect structural brain injury. There is external evidence from non-pharmacological treatment trials that the HAM-D and its subscales are suboptimally responsive to improvements in depression after TBI [12].

The rationale for using antidepressants after mild TBI is most compelling. Patients with mild TBI patients may more closely resemble patients with no known TBI history enrolled in typical primary Major Depressive Disorder clinical trials than patients enrolled in TBI trials in placebo-controlled trials published to date. Consider for example the "only study to influence the results of the RCT meta-analysis" in Kreitzer et al's sensitivity analyses (that is, the only study that, if excluded, would have resulted in a statistically significant meta-analytic finding favoring antidepressants): the recent trial by Fann et al. [13]. These authors only enrolled patients with mild TBI if they had radiological evidence of brain injury and were admitted to a Level 1 trauma center. Many patients with mild TBI do not present to an acute care hospital. Of those who do, a minority will have a trauma-related intracranial abnormality on computed tomography and/or be admitted to hospital. Therefore, the mild TBI patients in Fann et al's study are not representative of the mild TBI population, but rather reflect a subset at the "severe" end of mild TBI spectrum.

Conclusions

We argue that TBI, and especially *mild* TBI, is not a contraindication for antidepressant therapy. Proactive detection and treatment of psychiatric problems following TBI of any severity has the potential to improve not only mental health outcomes [14, 15] but also cognition [16–18], somatic symptoms [19, 20], and daily functioning [2, 4, 21]. We recognize that a systematic review of randomized placebo-controlled trials is the highest level of evidence, but caution clinicians against changing their practice on the basis of the Kreitzer et al. [9] study. Clinicians who continue to prescribe will be compliant with practice guidelines [7, 8] and the best available evidence [6, 9, 10]. Selective serotonin reuptake inhibitors (e.g., sertraline or citalopram) are generally recommended as first-line [7, 18, 22, 23]. Efficacy and tolerability of selective serotonin-epinephrine reuptake inhibitors are less well-established [23], but expert consensus guidelines endorse their use [7]. Tricyclic antidepressants are thought to have a less favorable benefit-risk profile, with lowering of the seizure threshold in patients with moderate-severe TBI being a potential concern [8, 23, 24].

Psychotherapy should be offered as an alternative or adjunctive treatment, where accessible [7]. The majority of patients with TBI prefer psychotherapy to pharmacotherapy treatment options [25]. There is insufficient evidence to recommend one modality of psychotherapy over another, but cognitive-behavioural therapies have been most well-studied [23, 26]. Remote delivery, such as by telephone, appears feasible and as effective as in-person therapy [27]. The minimum effective "dose" of psychotherapy is unknown.

Routine screening by rehabilitation and primary care providers can facilitate timely detection of depression after TBI. For example, the Personal Health Questionnaire-9 is a brief self-report depression case-finding tool with strong psychometric properties [12] and diagnostic accuracy in TBI [28]. A positive screening result should trigger a diagnostic clinical assessment with a qualified provider [7, 8].

Abbreviations

RCT: Randomized controlled trial; TBI: Traumatic brain injury

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Author details
[1]Division of Physical Medicine and Rehabilitation, University of British Columbia, 4255 Laurel St, Vancouver, BC V5Z 2G9, Canada. [2]Rehabilitation Research Program, Vancouver Coastal Health Research Institute, GF Strong Rehab Centre, 4255 Laurel St, Vancouver, British Columbia V5Z 2G9, Canada. [3]Department of Psychiatry, British Columbia Neuropsychiatry Program, University of British Columbia, Vancouver, Canada; 2255 Wesbrook Mall, Vancouver, BC V6T 2A1, Canada. [4]Department of Psychiatry, British Columbia Mental Health and Addictions Research Institute, University of British Columbia, Vancouver, Canada; 2255 Wesbrook Mall, Vancouver, BC V6T 2A1, Canada.

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