

# Treatment of depression following a traumatic brain injury

## Abstract

Depression following a brain injury constitutes a threat to an optimal recovery. Depressed individuals who have suffered a brain injury are likely to experience poorer outcomes; have lower level of psychosocial functioning; and potentially decline or stagnate in their recovery. In addition, they may be at higher risk for suicide than their non-depressed peers. Timely, effective treatment is essential to maintain functional gains. This article aims to provide an overview of clinical issues that can allow for an early identification of depression and lead to more effective interventions. Moreover, the available treatment strategies which have already garnered a degree of empirical support are discussed. There is some evidence for effective depression treatment utilizing sertraline and other antidepressants. Also there is growing empirical support for many non-medication therapeutic options, such as Cognitive Behavioral Therapies, and mindfulness-based protocols. The importance of an integrated, systematic framework to serve as a guide to the treating mental health professionals is highlighted.

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### Brief overview of Depression Associated with Brain Injury

Brain injury can and often does carry heavy cost for its survivors in terms of physical impairments, cognitive difficulties, and psychosocial dysfunction.<sup>1</sup> One of the most common psychiatric complications hindering functional recovery and contributing to disability in brain injury patients is depression.<sup>2-5</sup> Depressive symptoms, whether reaching the clinical threshold of DSM 5 Depressive Disorders or presenting at a subclinical level, can translate into poorer outcomes and greater disability for brain injury patients.<sup>2,6-8</sup> Moreover, depression has been shown to increase the risk of suicidal ideation and behavior in this population.<sup>9</sup>

More specifically, Jorge et al.,<sup>2</sup> found that traumatic brain injury (TBI) patients who were depressed evidenced greater impairment in their executive functions than their non-depressed counterparts. The study also reported a relationship between depressive symptoms and difficulty in psychosocial functioning.<sup>2</sup> In addition, research has highlighted a link between depression in TBI patients and more severe cognitive deficits, as well as a decreased ability to perform activities of daily living (ADLs).<sup>7-11</sup> Similarly, severe depressive symptoms may exacerbate impairment or cause regression into disability following a period of good recovery.<sup>8</sup> In terms of behavioral changes, individuals who experience depression after a brain injury have manifested heightened aggressive and violent behavioral tendencies.<sup>12</sup> These changes might be connected to injury-related cognitive issues which may cause a person to be more impulsive, have less ability to cope, and thus be more inclined to act on suicidal thoughts. In fact, depression appears to increase suicide rates for all TBI patients regardless of the severity of their brain injury.<sup>9</sup> Finally, post-TBI depression is also related to higher comorbidity rates with other psychiatric disorders such as anxiety disorders and alcohol use disorders.<sup>2,3,12,13</sup>

### Prevalence

As evidenced by numerous studies, onset of depressive symptoms following brain injury constitutes a threat to optimal recovery for TBI

survivors. Thus, it is essential that clinicians and health care providers are aware of risk factors, diagnose symptoms quickly, and are able to implement effective interventions. However, the last two decades of post-TBI depression research have painted an increasingly complex picture of its etiology and correlates. Thus, it may be difficult for the treating mental health professional to make research-informed recommendations for care. Specifically, the prevalence rates of post-TBI depression reported in the literature cover a wide range from as low as 6% to as high as 77%.<sup>14,15</sup> While some of the inconsistency of findings has been attributed to diverse methodologies and/or weaknesses in research design,<sup>7,16,17</sup> investigators have equally stressed the number of different variables that can contribute to depression in TBI patients,<sup>12,14,18</sup> as well as the overlap in symptomatology related to the patients' cognitive difficulties and depression.<sup>19,20</sup>

Although the theoretical models of the etiology and pathophysiology of depression following brain injury are not well-integrated in the literature,<sup>4,16</sup> many researchers categorize important risk factors into three general areas: pre-injury, injury, and post-injury factors.<sup>4,18-21</sup> With regard to the pre-injury variables, research has consistently identified prior history of depression or other mood disorder as one of the predictors of depressive symptoms following TBI.<sup>2,22</sup> The injury characteristics that appear to play a significant role focus on the location and/or type of damage to the central nervous system. Specifically, some studies have identified relationship between bilateral dorsomedial and dorsolateral lesions in the prefrontal cortex and high level of depressive symptoms.<sup>23</sup> Additionally, studies have found a link between a reduction of volume of left lateral frontal cortex and post-TBI depression, although it remains unclear whether this reduction is the result of the injury, consequence of the depression, or pre-existing vulnerability toward mood disorders.<sup>2</sup> Further, in another study depressed TBI patients evidenced significantly more pronounced volume difference in their frontal lobes (i.e. right frontal lobe larger than left) and significantly less pronounced differences in parietal lobes (i.e. right parietal lobe larger than left) than non-depressed controls.<sup>21</sup> Finally, in terms of investigated post-injury risk factors, level of perceived stress,<sup>16</sup> family dysfunction,<sup>24</sup> and unemployment<sup>25</sup> have been shown to be associated with depressive symptoms after a brain injury. Another important consideration is that for many individuals the risk of depression following a TBI can increase with time when

their progress fails to meet their expectations.<sup>4,17</sup> Moreover, the stress of living with a chronic disability and the possibility of diminished psychosocial support can contribute to the onset of depression.<sup>4</sup>

## Treatment

Whether treating someone with or without a brain injury, it is likely clinically prudent to combine medications with other types of non-medication based treatments. Additionally, when trialing an antidepressant medication, it is important to understand the limitations of any one agent. Approximately one-third of people with depression that are treated with medication fail to report a complete remission. Sixty to 70% of people get clear benefit from the first agent tried.<sup>26</sup> These numbers suggest that many individuals with Major Depressive Disorder (MDD) continue to suffer residual symptoms while on antidepressants.

Various studies, including the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) study,<sup>27</sup> have found that the likelihood of achieving remission significantly decreases if an individual's depression did not remit after two treatment strategies. Since partial response to antidepressant treatment is common, many augmentation strategies have evolved. Randomized-controlled studies (RCTs) and meta-analyses lend support for a stepwise, evidenced-based approach to augmentation. For example The Texas Medical Algorithm Project Manual provides a clear and explicit stepwise approach to treating MDD.<sup>28</sup> Specifically, most treatment algorithms and the one described in the aforementioned manual suggest starting with a selective serotonin reuptake inhibitor (SSRI), selective norepinephrine reuptake inhibitor (SNRI), or dopamine-norepinephrine reuptake inhibitor (DNRI). If there is no response then switching to another agent with a different mechanism of action is the next step. If a partial response occurs then augmentation with another agent that is suspected to have efficacy for the residual symptoms is appropriate. For example, augmentation with a stimulant may improve fatigue and attention and augmentation with a second generation antipsychotic may help alleviate the depression and perhaps decrease mood lability.<sup>28,29</sup> Most algorithms discourage SSRI augmentation with SNRIs and vice-versa because of the risk of serotonin toxicity.

Similar to the literature focused on prevalence rates and correlates of depression among TBI patients, the research available on effectiveness of psychopharmacological treatments is limited and varies in methodology and soundness of design.<sup>4,30</sup> Thus far, investigators have found some support for the efficacy of SSRIs. Specifically, Ashman et al.,<sup>12</sup> saw higher rates of responders in their experimental group with a sertraline regimen than in the placebo group; however, the differences between the groups were not statistically significant. In another study, sertraline was associated with cognitive improvements along with reduction in depressive symptoms.<sup>19</sup> Nonetheless, the researchers pointed out that the cognitive gains may have been part of the natural recovery process rather than product of the treatment. Lee et al.,<sup>31</sup> reported that sertraline had significantly alleviated depressive symptoms of their participants. The study also provided support for the use of stimulants to attenuate post TBI depression: in their second experimental group, methylphenidate significantly improved depressed mood as well as cognitive performance and alertness of the participants.<sup>31</sup> In addition to sertraline, limited evidence has been established for the use of citalopram<sup>32</sup> and fluoxetine.<sup>33</sup>

Conversely, investigators' attempts to assess the efficacy of tricyclic antidepressants (TCAs) have produced mixed results. While some support for the use of desipramine with the TBI population exists,<sup>34</sup> other studies have called attention to the higher potential for adverse side-effects, especially seizures.<sup>35</sup> As sertraline appears to be

well tolerated with minimal reports of negative side effects<sup>22</sup> and has, thus far, received the most research backing, it is recommended as the first-line treatment option for depression in the TBI population by the Neurobehavioral Guidelines Working Group.<sup>36</sup>

Overall, the research of psychopharmacological treatments for depression in TBI patients has been plagued by small sample sizes and methodological shortcomings.<sup>4,30</sup> Additionally, researchers have cautioned prescribing physicians and psychiatrists that slow titration of dosage and close monitoring is advised, as the potential for atypical effects is higher in neurologically compromised patients.<sup>30</sup> Additionally, the increased risk for seizures after brain injury causes many prescribers to be cautious. Thus exploring psychotherapeutic interventions in conjunction with or in lieu of pharmacotherapy is desirable. Among the therapeutic modalities that have been explored in treating post-TBI depression, Cognitive Behavioral Therapy (CBT) has received a degree of empirical support. For example, Bradbury et. al.,<sup>37</sup> found group CBT or individual telephone CBT more effective at diminishing depressive symptoms than the control treatment—an educational group. Individual CBT combined with cognitive remediation was found significantly more effective in alleviating depressive and anxiety symptoms compared with controls.<sup>38</sup> In addition, participants in a small, no control group study experienced improvement in their depressive and cognitive symptoms implementing an internet-based CBT program.<sup>39</sup>

Moreover, researchers are beginning to investigate emerging therapeutic modalities belonging to the so-called “third wave of cognitive-behavioral therapies”<sup>40</sup> as interventions for depression following a brain injury. In a pilot study utilizing a manualized protocol for mindfulness-based stress reduction, Bédard et al.,<sup>41</sup> reported overall improvement in quality of life and decrease in depressive symptoms, which was approaching significance. These improvements were generally retained at a one-year follow up.<sup>42</sup> Even more recently, Bédard et. al.,<sup>43</sup> executed another trial with depressed TBI patients utilizing mindfulness-based cognitive therapy and reported large effect sizes for depressive symptom reduction in addition to diminishment of pain intensity and increased energy levels. Mindfulness-based treatment strategies have also been successfully utilized to alleviate mental fatigue,<sup>44</sup> a chronic cognitive symptom frequently associated with TBI, as well as to reduce symptoms of post-concussive syndrome.<sup>45</sup> While, to our knowledge, no research with TBI patients have been conducted using Acceptance and Commitment Therapy (ACT), two recent review articles appear to encourage such undertaking.<sup>46,47</sup>

In addition to psychotherapeutic interventions, the literature evidences a modest degree of support for certain biological interventions, such as low-intensity magnetic field exposure<sup>48</sup> and biofeedback.<sup>49</sup> While interventions such as transcranial magnetic stimulation, electroconvulsive therapy, and neuro feedback have growing data supporting treatment of depression, these modalities still have limited data supporting the effective treatment of depression after acquired brain injury. These treatments may be appropriate options for some individuals. Mixed evidence can also be found in support of physical exercise programs. For example, swimming appeared to reduce depression more than vocational therapy.<sup>50</sup> Conversely, aerobic exercise produced mixed results,<sup>51-55</sup> with some concerns noted about the ability of the participants to adhere to the rigors of the programs.

## Summary and discussion

Although a considerable amount of research has targeted depression associated with brain injury, the results are hardly systematic and exceedingly difficult to integrate into a theoretical framework. While

some therapies are emerging as being more consistently supported empirically (e.g., sertraline and CBT interventions), others have been neglected by clinical researchers, and all require more extensive and rigorous investigation in order to build confidence in their efficacy.

Because of the risk that post brain injury depression may negatively impact the rehabilitation process and also the discharge disposition and subsequent functioning, it is important to effectively address this condition. Currently, there is no gold standard algorithm for the treatment of depression after brain injury, and the numerous inconsistent findings and small sample studies complicate the efforts to establish one. For example, some research studies recommend starting treatment with an SSRI because it may not only improve the depression, but also possibly contribute to improved recovery of cognitive functioning.<sup>12,19,31</sup> Though there is some limited empirical support for this position, there is also research which suggests that individuals with brain injury may be at risk for more frequent medication side effects.<sup>30</sup> That body of research is consistent with the position that non-medication based treatments should be the initial step in the therapeutic process. Presently, when medications are tried, it seems that an evidenced based algorithm is likely the best guide and when considering an SSRI, sertraline appears an evidenced based first choice. Given the chronic nature of brain injury symptoms and their potential to increase the risk of relapse of depression, it is recommended by many clinicians that psychotherapies be an aspect of the treatment.

## Conclusion

Emerging empirical evidence supports the efficacy of many variants of CBT. Yet, there continues to be a great need for large, well controlled studies evaluating the aforementioned treatments of depression following brain injury.

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## Conflicts of interest

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