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Interventions for Mood-Related Issues Post Traumatic Brain Injury: Novel Treatments and Ongoing Limitations of Current Research

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Abstract Mood-related issues following traumatic brain injuries (TBI) are highly prevalent and negatively impact psychosocial functioning. Such symptoms are also frequently undertreated. The aim of this publication is to highlight work regarding interventions for the treatment of post-TBI mood issues. Twelve recently published articles were identified (two systematic reviews, one Cochrane protocol, and nine original research studies). Presented manuscripts support both traditional (e.g., psychotherapy) and novel (e.g., exercise) interventions. Despite these scholarly endeavors, definitive findings regarding effective treatments for post-TBI mood disorders remain sparse. Of particular concern was the lack of recent research regarding traditional pharmacological interventions. Further work is required to identify efficacious and effective interventions for members of this high risk population.

Keywords Traumatic brain injury · Mood · Intervention · Treatment

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Introduction

Mood-related issues are common neuropsychiatric complications following traumatic brain injury (TBI). In fact, major depression is the most frequent [1], and arguably the most disabling [2], psychiatric disorder post-TBI. Prevalence rates of up to 61 % have been reported [3, 4]. Although the risk for developing post-traumatic depression is greatest in the first year following injury (nearly 50 % among persons hospitalized for TBI) [5], the increased risk for depression persists over the entire lifespan. The risk for depression also spans the range of TBI severity (mild, moderate, and severe) [4]. Given the nearly 1.5 million TBIs that occur each year among United States civilians alone [6, 7], and the incidence of post-TBI depression, there are likely to be millions of new cases of depression among TBI survivors across the globe annually. Secondary mania may also complicate emotional health subsequent to TBI, adding to the burden of mood disorders experienced by this population. Mania after TBI is much less well-studied than post-traumatic depression, such that the incidence and prevalence remains relatively poorly characterized [3].

The frequency of post-traumatic mood disorders alone should mandate attention to such conditions among providers caring for persons with a history of TBI. The importance of maintaining such vigilance becomes all the more apparent when the consequences of post-traumatic mood disorders are considered. Post-traumatic depression

is a risk factor for both aggressive and suicidal behaviors, thereby adding to morbidity and mortality, and threatening the safety of patients, their families, and providers [8–11]. Depression also appears to adversely impact functional outcomes following TBI [12], and may contribute to both objective and subjective experiences of cognitive deficits. Post-traumatic mood disorders also add to the financial cost of caring for individuals with a history of TBI [13]. Hence, it is essential to monitor for, identify and aggressively treat mood disorders that emerge in the wake of TBI. The intent of this paper is to review current and interesting trends and/or developments in the treatment of post-traumatic mood disorders. Towards this end, 12 recently published articles were identified including: two systematic reviews [14••, 15]; one Cochrane protocol [16]; three studies regarding novel interventions where depression was the primary outcome [17•, 18, 19•]; two randomized controlled trials (RCTs) where depression was the secondary outcome [20, 21]; and four single group—pilot/feasibility trials in which depression was a secondary or exploratory outcome [22–25] (see Table 1). No recent publications were identified which explored the efficacy of traditional pharmacological interventions (e.g., antidepressant medications) and/or sufficiently addressed post-TBI hypo/manic symptoms.

Recently Published Systematic Reviews

Two recent systematic reviews/meta-analyses describe the general state of cognitive behavioral treatment (CBT) for mood following acquired brain injury (ABI). The first study [14••] used a systematic review and meta-analysis of published literature from 1990 through 2011 to examine the effectiveness of psychological interventions for depression following ABI in adults. Thirteen studies were included in the analysis, with eight data sets from seven of the studies used for the meta-analysis. There was a moderate overall effect size (ES) for the effectiveness of depression interventions provided at least a year post-injury. For pre-post treatment effectiveness of individual studies, four trials were reported to have large ES, and two others had medium effect sizes. Four of the significant studies used individual, group, or telephone CBT interventions, one used an education and counseling program, and one used mindfulness-based stress reduction (MBSR). This review is significant in that the authors reported that it was the first meta-analysis of depression interventions following ABI. According to the authors, the results stood in contrast with a prior systematic review that found no significant effect of psychological intervention following ABI [26]. The authors concluded that CBT appears to be an appropriate intervention for depression following ABI; however, their analysis included a limited number of studies, all of which used small samples [14••]. Additionally, the studies collapsed all levels of TBI severity with stroke, which limited the precision of their results.

The second review and meta-analysis focused on the use of CBT in treating a variety of psychological problems following ABI [15]. Relaxed inclusion criteria were used to allow for a greater number of studies from 1990 through 2012 to be included. Ultimately this resulted in 24 studies being included, half of which were single case studies. Although the authors explored a spectrum of psychological issues (e.g., anger, anxiety), results were extrapolated by the type of emotional issue. Four studies were identified for depression with a mean large ES. Notably, three of those studies examined CBT for depression following cerebral vascular accident (CVA) and one focused on depression following mild to moderate TBI. The authors concluded that although CBT is a viable option for treatment of psychological issues following ABI, it was not effective for all participants, and many studies showed no improvement. The studies reviewed widely varied on the CBT dose employed, and a dose effect was noted. Finally, CBT effects did not generalize, such that if one targeted CBT to address anger, depression symptoms did not necessarily improve.

CBT was the main treatment of focus in the studies included in these two reviews [14••, 15], and treatment modalities included individual, group, telephone, and internet deliveries. Other options for treating mood following ABI were used in two studies [14••], including the social-emotional module of an education counseling program [27] and MBSR [28]. Results from these two reviews/meta-analyses suggested that CBT treatments may be effective to addressing depression issues following ABI; however, CBT may not be effective treatment for every patient, particularly those with comorbid psychological conditions. Moreover, the effects may not generalize to a co-occurring symptom. Authors of both reviews [14••, 15] also suggested that additional, large-scale and well-controlled studies are needed. Finally, both reviews examined mood issues following ABI, but neither extrapolated type nor severity of injury. Thus, caution should be taken as to how the results apply to a specific population of interest (e.g., concussion versus severe TBI).

The Cochrane Library provides an open access database where review authors can submit proposed review protocols to allow for study tracking, a method which helps reduce biased reporting and informs stakeholders about future reviews to avoid duplication of work. A Cochrane protocol entitled *Pharmacological interventions for depression in people with traumatic brain injury* was recently published, providing details regarding methods for an upcoming review. In justifying this effort, Vattakatuchery et al. [16] noted the lack of previous research in this

Table 1 Original research regarding interventions with depression outcome after traumatic brain injury

Study	Design	Sample	Size	Injury	Intervention	Depression outcome measure(s)/primary, secondary, or exploratory outcome	Results	Selected limitations
Bédard et al. [17•]	Before-after pilot	BI program at Canadian hospital or local chapter BA of Canada; age: mean (SD) 47.1 yrs (15.7); gender: 55 % male	$n = 23$ recruited; $n = 20$ completed	Type and severity NR	Combination of MBSR [41] and MBCT [42] 8 weekly individual sessions, 90 min each, 12 h total	PHQ-9, HADS-Dep, BDI-II Primary	Significant: PHQ-9: $p = 0.003$, $d = 0.96$; HADS-Dep: $p = 0.023$, $d = 0.64$; BDI-II: $p = 0.001$, $d = 0.71$	Pilot study with small sample size; no control group; TBI severity not reported or accounted for.
Hanks et al. [20]	RCT	Southeastern Michigan TBIMS; age: range, 17–86 yrs; gender: 89 % male	$n = 199$ total recruited; $n = 96$ with TBI completed $n = 62$ caregivers/ significant others completed	Complicated mTBI to severe; GCS median 9	Peer mentoring versus no mentoring Mentor–mentee contacts: mean (SD), 5.4 (0.4) (range, 1–66), majority telephone	BSI-18-dep Secondary	Not significant: $p = 0.24$; $d = 0.24$	TBI severity was not controlled for; participants determined treatment dose; participants did not report a statistically significant mean level of distress at start of study.
Harch et al. [22]	Before-after pilot	American active duty servicemen and Veterans with comorbid PTSD; age: mean 30 yrs (range, 21–45); gender: 100 % male	$n = 16$ recruited; $n = 15$ completed	Blast-induced mild to moderate TBI/PCS	40 sessions of 1.5 ATA/ 60 min HBOT sessions in 30 days, 40 h total	PHQ-9 Exploratory	Significant: $p < 0.001$	No control group; confounding polypharmacy
Hsieh et al. [21]	3-arm Pilot RCT	Australian hospital TBI rehabilitation program with co-morbid anxiety disorder; age: mean (SD) 38 yrs (13.2); gender: 88 % male	$n = 27$ recruited; n = 25 completed	Moderate or severe TBI	MI + CBT versus NDC + CBT versus TAU 12 weekly individual sessions, 50 min each, 10 h total	HADS-Dep, DASS-Dep Secondary	Both interventions not significant versus TAU	Small sample size
Nelson and Etsy [23]	Before-after pilot	American OEF/OIF Veterans with co-morbid PTSD; age: range, 23–42 yrs; gender: 60 % male	$n = 7$ recruited; $n = 5$ completed	At least mTBI	FNS variant of EEG biofeedback conducting EM 22–25 session protocol	NFI-Dep Secondary	Significant: $p = 0.02$, $d = 0.76$	Pilot study with small sample size; no control group; severity of TBI heterogeneous

Table 1 continued

Study	Design	Sample	Size	Injury	Intervention	Depression outcome measure(s)/primary, secondary, or exploratory outcome	Results	Selected limitations
Schwandt et al. [18]	Before-after pilot descriptive	Canadian outpatient clinic; age: range, 19–48 yrs; gender: 75 % male	$n = 5$ recruited; $n = 4$ completed	Moderate or severe TBI	Aerobic exercise (cycle, treadmill, step machine) Individual met with physiotherapist 3 times per week for 12 weeks, 30 min each session (plus warm-up & cool down), 18 h total	HAM-D Primary	Positive but descriptive only	Pilot study with small sample size
Wise et al. [19•]	Before-after (secondary analysis of the treatment arm of a RCT)	Community in Seattle, WA; age: mean 39.7 yrs; gender: 38 % male	$n = 42$ randomized to exercise arm recruited; $n = 40$ completed	Any TBI requiring medical evaluation immediately after injury	Aerobic exercise Exercise training, 1 time per week for 10 weeks with trainer, 30 min each session (plus warm-up & cool down), followed by independent sessions 4 times per week for 10 weeks, 30 min each session (plus warm-up & cool down), 25 h total + 12 maintenance phone calls (1 call every 2 weeks for 6 months)	BDI, SF-12-mental Primary	Significant: BDI: $p = 0.033$; SF-12-mental: $p = 0.040$	No control group; TBI severity based on self-report
Wolf et al. [24]	Before-after pilot	American OEF/OIF Veterans with comorbid PTSD; age: mean (SD) 33.1 (10.7); gender: 100 % male	$n = 10$ completed, drop out not reported	Mild to moderate TBI	Prolonged exposure, manualized individual treatment, 8–18 sessions	BDI-II Secondary	Significant: $p < 0.001$, $d = 1.82$	Pilot with small sample size; no control group; TBI severity not controlled for
Zollman et al. [25]	RCT pilot (within group analysis only presented)	Rehabilitation institute in Chicago, IL or community; age: mean (SD) 44.5 yrs (15.2); gender: 58 % male	$n = 14$ recruited from acupuncture arm $n = 12$ completed	Rancho Los Amigos cognitive scale score V or above	Acupuncture treatment Sessions 2 times per week for 5 weeks, 20 min each session, 3.33 h total	HAM-D Secondary	Pre-post acupuncture arm significant: $p < 0.01$	Pilot with small sample size

RCT randomized controlled trial, *TBI* traumatic brain injury, *mTBI* mild traumatic brain injury, *PCS* post-concussion syndrome, *PTSD* post-traumatic stress disorder, *Dep* depression, *Anx* anxiety, *BI* brain injury, *BA* brain association, *NR* not reported, *TBIMS* traumatic brain injury model systems, *MBCT* mindfulness-based cognitive therapy, *MBSR* mindfulness-based stress reduction, *CBT* cognitive behavior therapy, *NDC* non-directive counseling, *TAU* treatment as usual, *HBOT* hyperbaric oxygen therapy, *ATA* atmospheres absolute, *FNS* flexyx neurotherapy system, *EEG* electroencephalograph, *EM* electromagnetic energy, *PE* prolonged exposure therapy, *PHQ*-9 patient health questionnaire-9, *HADS* hospital anxiety & depression scale, *BDI* beck depression inventory, *DASS* depression, anxiety & stress scales, *NFI* neurobehavioral functioning inventory, *HAM-D* Hamilton rating scale for depression, *GCS* Glasgow coma scale, *BSI*-18 brief symptom inventory-18, *SF*-12 short form health survey-12, *Yrs* years, *SD* standard deviation, *OEF* operation enduring freedom, *OIF* operation Iraqi freedom

area, and referenced an earlier review conducted by Fann et al. [1] stating that the previous publication was "broad in its scope" in that it included all treatments for depression after TBI, did not focus on pharmacological interventions, and included "lower quality studies" (p. 2). In response to these limitations, the proposed review by Vattakatuchery et al. [16] will focus on evidence for the use of pharmacological agents among individuals with TBI and depression and will only include RCTs.

Novel Interventions: Depression Primary Outcome

Mindfulness-based cognitive therapy (MBCT) is comprised of two main components, mindfulness-based stress reduction (MBSR) and CBT. To evaluate the efficacy of MBCT to treat clinical depression among those with TBI, Bédard et al. [17•] conducted a single arm uncontrolled trial. Twenty-three participants enrolled in the trail. The intervention was 8 weeks in length and comprised of one 90 min group session per week. At baseline, participants were evaluated by the research team's physician who ensured that the participants had "clear signs of depression" (p. 16). The intervention was modified to address potential cognitive-related TBI impairments (e.g., shortened meditation sessions, memory aids, frequent reviews). Hypotheses included: (1) after the eight-week intervention participants would have lower depression scores; and (2) the proportion of those with depression will be significantly reduced. Post-treatment, significantly reduced scores were noted on measures of depression. Six out of nine participants whose baseline scores were 29 or greater on the Beck Depression Inventory II (BDI-II) [29] had post-treatment scores that were below that cutoff.

Wise et al. [19•] conducted a single group uncontrolled trial to examine the effect of an exercise intervention and maintenance program on depression. Forty participants with a history of TBI (6 months to 5 years post-injury) enrolled in the study. All had a Patient Health Questionnaire-9 (PHQ-9) [30] score of five or higher. The intervention consisted of a 10 week exercise program (60 min of supervised exercise plus homework to engage in 30 min of aerobic activity four times per week). For those randomized to the exercise group ($n = 42$ were initially randomized to the exercise group; see Hoffman et al. [31] for a description of the randomized clinical trial of the exercise program without maintenance), follow-up by telephone was conducted every 2 weeks for 6 months. From baseline to 10 weeks, the BDI-II test scores of those in the exercise group decreased from 21.7 to 16.5. For the 32 individuals who stayed in the exercise arm of the trial, lower BDI-II [29] scores were maintained and 48 % demonstrated increased physical activity at 6 months when compared to baseline. Moreover, at 6 months, 52 % of those randomized to the active arm were exercising more than 90 min or more per week. Individuals exercising 90 min or more per week had lower depression scores. Of note, although at 6 months depression continued to be lower, BDI-II scores continued to be in the mildly depressed range.

Schwandt et al. [18] conducted a smaller feasibility trial in which they explored the effectiveness of aerobic exercise on post-TBI related depressive symptoms among those with moderate to severe TBI. Although 28 participants were identified to participate, four completed the program. The intervention was a 12-week aerobic exercise program in which the individuals worked with a physical therapist three times a week at the rehabilitation hospital physiotherapy gym. Findings from the study suggested that post-TBI depressive symptoms can be reduced in a clinically meaningful way by engaging in aerobic exercise for 30 min/three times per week for 12 weeks.

Potentially Promising Interventions: Depression Secondary Outcome

Two randomized controlled trials were identified in which depression was a secondary outcome. Hanks et al. [20] enrolled a total of 199 participants (96 individuals with TBI and 62 significant others/caregivers completed the study) who were randomly assigned to treatment (peer mentoring) or no treatment conditions prior to discharge from the rehabilitation inpatient program. Mentors who were matched with mentees based on sex and role (individual with TBI or caregiver) were instructed to: (1) arrange a meeting within 2 weeks of the initial contact; (2) meet and/or talk by phone at least once weekly for the first month, biweekly for the next two to three months; and monthly for the reminder of the year. Areas of focus for the mentorship sessions included: "(1) emotional well-being; (2) post-TBI quality of life; and (3) community integration," (p. 1301). The control group received treatment per usual. Although the primary outcome measure was the peer mentoring questionnaire [32], the Brief Symptom Inventory-18 (BSI-18) [33] was also administered with no difference between mentored and control groups identified on the depression subtest.

In a second trial, 27 participants with moderate to severe TBI were recruited and randomized to receive one of three interventions: (1) motivational interviewing (MI) + cognitive behavioral therapy (CBT) ($n = 9$); (2) non-directive counseling (NDC) + CBT ($n = 10$); or (3) treatment as usual (TAU) ($n = 8$) [21]. In this single center, parallel-group trial, evaluations were conducted at baseline, post-NCD or MI, post-CBT, and 9 weeks post-CBT. Although the primary aim of the study was to address post-TBI related anxiety, measures of depression (Hospital Anxiety

Depression Scale [HADS] depression subscale [34], Depression, Anxiety, and Stress Scales [DASS]—depression [35]) were also administered. Post-treatment, no between group differences were found on depression scales.

Single Group—Pilot/Feasibility Trials: Depression Secondary or Exploratory Outcome

Harch et al. [22] conducted a "pilot proof-of-concept" (p. 169) study among individuals with mild to moderate TBI secondary to a blast which occurred at least 1 year prior but post September 11, 2001. All service members had to have a prior diagnosis of "chronic TBI/PCS [post concussive symptoms] or TBI/PCS/PTSD [post traumatic stress disorder]" (p. 169). Data from 16 of the service members in the trial was provided. These individuals received a "29-day treatment course of 1.5 atmospheres absolute (ATA) of hyperbaric oxygen therapy (HBOT)" (p. 172). Harch et al. [22] reported a "biphasic response, with transient worsening of symptoms in 4 of the 16 subjects," (p. 169). A number of outcomes were obtained including depression using the PHQ-9 [30]. Significant differences were observed pre- and post-treatment. Of note, several Letters to the Editor were written in response to these findings including: Armistead and Lee [36], and Wortzel et al. [37]. In these letters concerns regarding the methodologies employed were articulated, as well as questions regarding Harch et al.'s conclusions about the efficacy of HBOT.

In another publication, Nelson and Esty [23] employed a variant of electroencephalograph (EEG) biofeedback (Flexyx Neurotherapy System; FNS) to address neurobehavioral and PTSD symptoms among seven "treatment refractory" (p. 237) Operation Iraqi Freedom/Operation Enduring Freedom Veterans. TBI injury severity was described as being at least mild, though three participants were reported as having had losses of consciousness which lasted up to 45 min. Using the Neurobehavioral Functioning Inventory (NFI) [38], the authors found that scores on the Depression subscale decreased significantly following intervention (pre-treatment, $M = 52.8$, SD = 9.0; post-treatment, $M = 39.2$, SD = 5.9). The authors suggested that although findings were promising, further rigorous study of this novel intervention was indicated.

In a similar population of ten veterans with a history of mild to moderate TBI and PTSD, Wolf et al. [24] conducted a "preliminary examination" (p. 26) of prolonged exposure (PE). Although primary outcomes were PTSD-related, the BDI-II [29] was also administered. Clinically meaningful pre- ($M = 34.4$, SD = 9.7) to post-treatment ($M = 17.7$, SD = 8.6) were noted. The authors highlight that aside from the inclusion of "memory-enhancing strategies," "increased structure," and "additional session time [30 min per session]," few "modifications" were required to obtain desired outcomes (p. 28).

Finally, in a study of 24 adults with a history of TBI (Rancho Cognitive Scale of V or above) and complaints of insomnia were randomized to acupuncture ($n = 12$) or control ($n = 8$) [25]. Although insomnia related hypotheses were not supported, within group improvements in depression scores were noted among those in the acupuncture group. However, based on the manner in which scores were reported, it is difficult to determine whether or not changes on the Hamilton Depression Rating Scale [39] (HAM-D) were clinically meaningful.

Conclusions

Depressive symptoms are prevalent among those with a history of TBI, and findings suggest that less than half of those with such injuries and major depression receive antidepressants or counseling [5]. Studies presented above highlight the importance of examining the benefits of using more holistic approaches to treat post-traumatic depressive-related symptoms. In addition to encouraging those with a history of TBI to engage in traditional evidence-based interventions (i.e., CBT), publications reviewed suggested that other modalities (e.g., exercise, acupuncture, mindfulness) may prove to be effective. Recognizing that TBI can have an impact on numerous areas of functioning, holistic or biopsychosocial approaches that emphasizes wellness and healing of the entire person may be particularly suitable to treating post-TBI mood disturbances. Despite promising findings, larger scale controlled trials are needed to investigate the effectiveness of these and other complementary and alternative practices to prevent and treat depression following TBI. Given that those with TBI represent a diverse population, more research is needed to examine potential moderators of treatment response. For example, improved understanding regarding characteristics of individuals whom are more likely to benefit from holistic approaches, such as exercise and mindfulness-based interventions will enhance our ability to tailor interventions and more effectively and efficiently treat depression among those with TBI.

Research examining how combined pharmacological and/or behavioral interventions can be used to optimize treatment response for post-TBI depression is another area that warrants greater attention. In their review of RCTs for those post-TBI, Lu et al. [40] suggest that in an "effort to overcome the treatment research challenges faced by clinicians working with this heterogeneous population, multiple institutions are recommending development of more effective combined treatments for TBI" (p. 1543).

Exploration of combination treatments of mood-related symptoms may help to address the reality that findings from most studies do not show complete remission of depressive symptoms [15]. Further study will be required to empirically answer this question. Certainly pharmacological interventions will continue to play an important role in treatment of depression among those with a history of TBI. As such, findings from Vattakatuchery et al. [16] are expected to provide further guidance in terms of areas for future research regarding single and combination therapies. Moreover, study regarding interventions aimed at addressing post-TBI hypo/mania continued to be absent.

Although this review highlights a number of pathways for future research, advancing the field will remain a significant challenge if fundamental issues with respect to sample and measurement selection are not adequately addressed. Many of the studies presented continue to suffer from limitations frequently discussed with respect to interventional trials for those with a history of TBI. This includes small and heterogeneous samples. Perhaps most concerning is the continued practice of including those with mild versus moderate to severe injuries in the same trial. Tools used to measure depression-related outcomes also vary, which contributes to challenges associated with comparing findings across studies or combining samples. To meet the needs of those with post-TBI mood-related issues further patient-centered research is required which focuses on symptoms, depressive and hypo/manic, which are most distressing to TBI survivors and their family members/caregivers.

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