Technical Report #2

Treatment for Depression Following Traumatic Brain Injury: A Systematic Review

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Background: Depression following TBI is associated with worse global outcomes (Federoff et al., 1992), worse social functioning during the first year post injury (Jorge et al., 1993b; Schoenhuber et al., 1988), and lower health-related quality of life (Christensen et al., 1994; Rutherford, 1977), even after controlling for medical, demographic and neuropsychologic factors.

Purpose: This report outlines the methodology used to systematically review the published literature on pharmacologic, other biological (e.g., electroconvulsive therapy), and psychotherapeutic or rehabilitation treatments for depression after TBI. (see Fann, J., Hart, T. & Schomer, K., *Treatment for Depression Following Traumatic Brain Injury: A Systematic Review*, Journal of Neurotrauma (in press).

Process for Topic Selection: This topic was nominated by members of the Traumatic Brain Injury Model Systems and approved by the directors of the Traumatic Brain Injury Model Systems during the directors' meeting in December, 2007. Authors for this review were nominated by members of the MSKTC Research Advisory Board.

Criteria for Considering Studies for Review: The following criteria were used to select studies of depression interventions in the TBI population in the published literature for this systematic review (see Appendix A: Project Development Plan):

a) a study of depression in persons with TBI;

b) published since 1980;

c) written in English;

d) conducted in adults over 18 years;

e) a study population that includes adults with TBI and depression. In populations of adults with TBI and acquired brain injury (traumatic + other such as stroke, anoxia, etc.), the focus was on traumatic brain injury.

f) Is peer-reviewed. Study designs, including randomized controlled, case control, cohort, case series, review papers, meta-analyses and correlational/surveys.

Search Methods for the Identification of Studies: Separate searches of the published literature were conducted in Pubmed, Medline, Psychinfo, Proquest, CINAHL, Google Scholar and Web of Science. Specific search terms used for each database included: (a) major depression, (b) major depressive disorder, (c) TBI, (d) head injury and (e) brain injury. See table 1 for a comprehensive list of search terms and measures by database.

Table 1: *Search Terms and Measures*[1] *by Database*

Database	Search Terms
PubMed	traumatic brain injury and (Beck Depression Inventory or Zung Self-Rating Depression Scale or Center for Epidemiologic Studies or Patient Health Questionnaire or Structured Clinical Interview for DSM or Hamilton or Hospital Anxiety and Depression Scale or Minnesota Multiphasic Personality Inventory or Diagnostic Interview Schedule or Brief Symptom Inventory or Short Form -36 Health Survey or Neurobehavioral Functioning Inventory or Composite International Diagnostic Interview or present-state exam or major depression or depressive disorder) In PubMed, terms are searched as both keywords and subject headings simultaneously and abbreviations are used for the scale names when appropriate. The term *Older Adult Mood and Health* did not add results and was omitted from the final search.
CINAHL	brain injuries and (Center for Epidemiological Studies Depression Scale or Beck Depression Inventory or Self-Rating Scale or Minnesota Multiphasic Personality Inventory or Hamilton Rating Scale for Depression or Hospital Anxiety and Depression Scale* or Brief Symptom Inventory or Short Form-36 Health Survey (SF-36) or Neurobehavioral Functioning Inventory* or present-state exam* or Depression) Terms with an asterisk did not have associated CINAHL subject headings and were searched as keywords; other terms were searched as CINAHL subject headings. Scale abbreviations were used when appropriate. The abbreviated terms *DIS, CIDI, SCID,* and *PHQ-9* did not add results and were omitted from the final search.
PsycINFO	traumatic brain injury and (Beck Depression Inventory or Zung Self-Rating Depression Scale or Minnesota Multiphasic Personality Inventory or Hamilton* or Hospital Rating Scale for Depression* or Brief Symptom Inventory* or Short form-36 health survey* or Neurobehavioral Functioning Inventory* or Composite International Diagnostic Interview* or present-state exam* or Major Depression) Terms with an asterisk did not have associated PsycINFO subject headings and were searched as keywords; other terms were searched as PsycINFO subject headings. Scale abbreviations were used when appropriate. The abbreviated terms *DIS, SCID, CESD,* and *PHQ-9* did not add results and were omitted from the final search.
ProQuest Health and Medical Complete Library	traumatic brain injury and (Beck Depression Inventory or Zung Self-Rating Depression Scale or Center for Epidemiologic Studies or Patient Health Questionnaire or Structured Clinical Interview for DSM or Hamilton or Hospital Anxiety and Depression Scale or Minnesota Multiphasic Personality Inventory or Diagnostic Interview Schedule or Brief Symptom Inventory or Short Form -36 Health Survey or Neurobehavioral Functioning Inventory or Composite International Diagnostic

[1] NOTE: at a subsequent meeting, the authors decided to only review treatments for depression; the review of depression measures was discontinued.

	Interview or present-state exam or major depression or depressive disorder) Terms were searched as keywords, not ProQuest subject headings. Scale abbreviations were used when appropriate.
Web of Science	traumatic brain injury and (Beck Depression Inventory or Zung Self-Rating Depression Scale or Center for Epidemiologic Studies or Patient Health Questionnaire or Structured Clinical Interview for DSM or Hamilton or Hospital Anxiety and Depression Scale or Minnesota Multiphasic Personality Inventory or Diagnostic Interview Schedule or Brief Symptom Inventory or Short Form -36 Health Survey or Neurobehavioral Functioning Inventory or Composite International Diagnostic Interview or present-state exam or major depression or depressive disorder) Terms were searched as keywords. Scale abbreviations were used when appropriate.
Google Scholar	For this database, we completed multiple searches: Search 1: "traumatic brain injury" major depression Search 2: "traumatic brain injury" depressive disorder Search 3: "traumatic brain injury" depression The search was limited to Medicine, Pharmacology, and Veterinary Science.

Methods of Inclusion and Data Extraction. Abstracts from the initial database search were reviewed by two reviewers who were either graduate research assistants or research staff at the University of Washington Model Systems Knowledge Translation Center (MSKTC). The inclusion criteria were initially created to identify studies with a focus on treating depression in those with TBI. Due to the paucity of studies returned with these criteria, the search was expanded to identify treatment studies in which depressive symptoms were reported as a secondary outcome. The specific criteria included studies with:

- Any treatment modality: Pharmacologic, psychotherapeutic (e.g., individual or group psychotherapy, counseling, psycho-educational approaches), rehabilitation based (e.g., comprehensive/holistic rehabilitation), exercise, electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), etc;
- Depression as a primary outcome: i.e., participants selected for depression and treatment focused on depression;
- Depressive symptoms as a secondary outcome: i.e., participants not necessarily selected for depression, treatment not necessarily focused on depression, but depressive symptoms were measured and reported both pre- and post-intervention;
- Sample is composed of those with TBI, or the sample is not exclusively TBI but results on the TBI subsample are reported separately

Abstracts from 658 articles found in the database search were reviewed by two trained reviewers at the University of Washington Model Systems Knowledge Translation Center (MSKTC). Discrepancies were resolved by consensus of the reviewers. Author and journal names were not masked from the reviewers. If reviewers were unable to determine if the article met the criteria from the abstract, the full article was reviewed. If a study did not meet the criteria, it was excluded from further review. After reviewing the abstracts, 57 of the 658 articles appeared to meet the inclusion criteria.

It was also decided during the full review to exclude studies that did not report *quantitative scores* on a validated depression diagnostic or severity instrument both pre- and post-intervention. At the end of this full review, 26 of the 57 articles met the final criteria. Three external expert reviewers[2] were asked to review the methods and evidence tables and make further recommendations. On the basis of the external reviews, one additional article meeting the final criteria was identified and included in the current review for a total of 27 articles. Figure 1 documents this process.

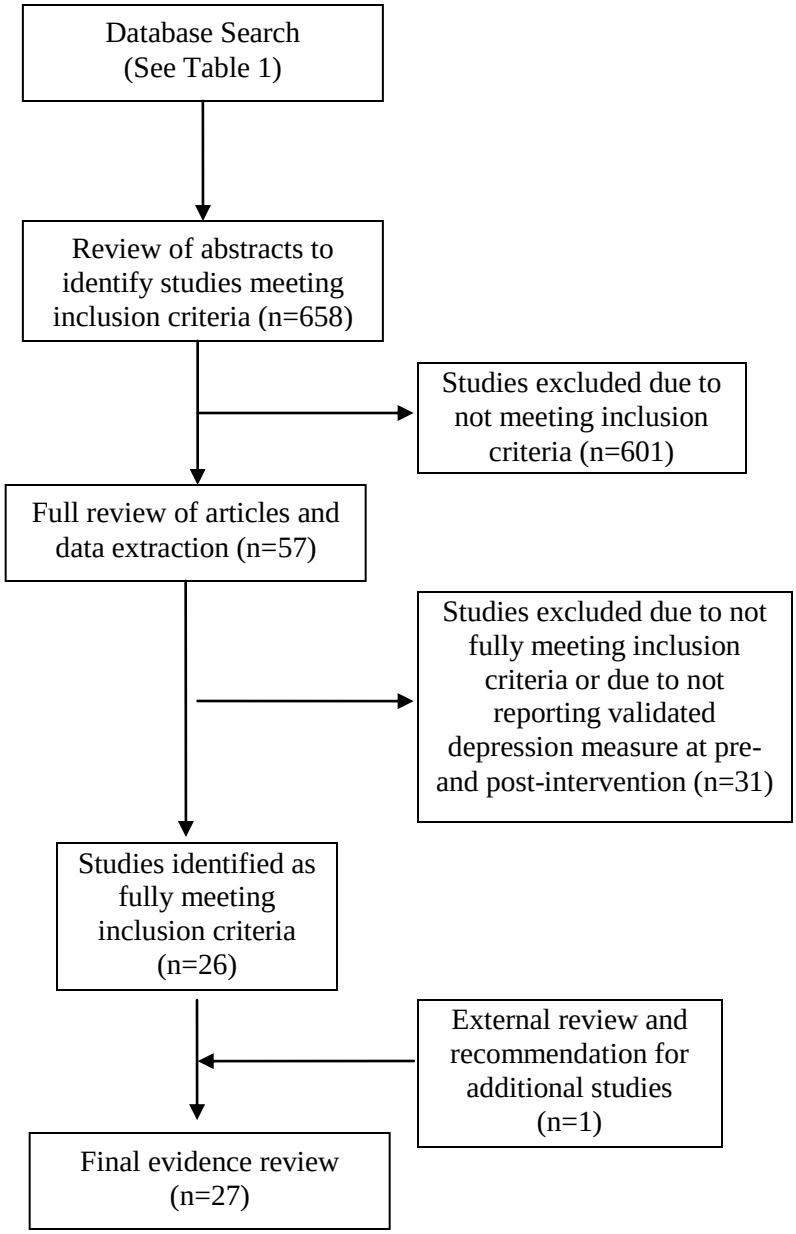

Figure 1: Study Selection

[2] The expert panel included: Theresa Ashman, PhD, Mount Sinai school of Medicine, Brain Injury Research Center; Jonathan M. Silver, MD, New York University School of Medicine and Vani Rao, MD, Johns Hopkins School of Medicine

The level of evidence included in this review was categorized according to the American Academy of Neurology criteria for classifying therapeutic studies. A final review of each the 27 articles was performed by one of the investigators to rate the evidence of the articles, with consultation between investigators as needed for accurate coding and interpretation. Studies were further categorized into the following groups based on depression inclusion criteria:

A. Prospectively enrolled depressed patients
B. Depressed patients retrospectively identified at baseline and results reported for them separately
C. Pre-post scores on depression measure were reported, but there was no selection for depressed patients as a sub-group

The resulting tables of evidence are presented in Tables 2 and 3.

Table 2. Overview of Pharmacologic and Other Biological Intervention Studies for Depression in persons with TBI (N=19)

Authors	AAN Evi-dence Level	Depression Inclusion Score	Total N	TBI sample: n Severity Acuity	Depression Entry criteria	Depression Instruments	Design & Intervention	Results & Conclusions
Pharmaco-logic Interven-tions								
Ashman et al (in press)	I	A	52	52 35.5% mild, 38.7% moderate, 25.8% severe TBI Mean 17.7±13.7 years post TBI	DSM-IV MDD (SCID) HAM-D>17	HAM-D	Double-blind RCT of sertraline (25-200 mg/d) or placebo for 10 wks	Among the 41 who completed the trial, HAM-D, Beck Anxiety Inventory, and Life-3 Quality of Life scores improved significantly from pre- to post-treatment, but there were no group differences. 59% in sertraline group and 32% in the placebo group had a 50% drop in baseline HAM-D score (p=.15).
Lee et al, 2005	II	A	30	30 Mild to moderate TBI Within 1 yr of TBI	DSM-IV MDD BDI≥18	HAM-D BDI	double-blind RCT of methylphenidate (20 mg/d), sertraline (100 mg/d) or placebo for 4 wks	Both drugs improved HAM-D scores more than placebo; methylphenidate improved cognition, alertness, and PCS more than sertraline
Saran, 1985	III	A	22	10 minor TBI vs. 12 non-TBI controls LOC ≤ 20 min, Hospitalized ≤ 48 hrs Normal EEG and CT <1 yr post TBI	DSM III MDD with melancholia	HAM-D SDS	Open trial amitriptyline (200-300 mg/d, mean 175 mg/d) for 4 wks. Amitriptyline non-responders (n=10) had 3-7 day washout, then trial of phenelzine (60-90 mg/d, mean 65 mg/d)	No significant improvement (50% drop in HAM-D) observed with either drug among subjects with TBI, whereas, all non-TBI controls improved on amitriptyline. Controls also improved on SDS affective, psychomotor, and psychological subtests. Improvement in headaches was correlated with improvement in depression
Wroblewski et al, 1996	III	A	10	10 Severe TBI, PTA ≥1 wk, Rancho Los Amigos Head Injury Scale cognitive function level 4 to 6 0.5-2.5 yrs post TBI	DSM III-R depression of at least 2 months duration	DSM III-R 9-item symptom checklist 25-item affect/mood scale	Blind random assignment to desipramine (n=6) (150-300 mg/d) for at least 1 mo or to placebo (n=4) with blinded cross-over for placebo group at 1 mo if non-responder	None in the placebo group had significant improvement (50% drop in 9-item DSM-III-R symptom checklist) and all were crossed over to desipramine. 6 of 7 study completers on desipramine had significant improvement. Affect/mood scale improved overall (p=.001). 2 dropped out and 1 refused diagnostic interview. Duration of desipramine treatment ranged from 1.5 to 3 mos.

Authors	AAN Evi-dence Level	Depression Inclusion Score	Total N	TBI sample: n Severity Acuity	Depression Entry criteria	Depression Instruments	Design & Intervention	Results & Conclusions
Dinan et al, 1992	IV	A	26	13 men with minor closed head injury (LOC < 20 min, negative neuro exam, hosp < 3d) vs. 13 non-head injured controls (matched for age, sex, duration of symptoms, HAM-D score)	DSM III HAM-D>17	HAM-D CGI	Open trial of amitriptyline (100-250 mg/d, TBI group mean 158 mg/d, control group mean 179 mg/d) for 6 wks	4/13 persons with TBI vs. 11/13 non-TBI controls "significantly improved" on CGI. Significantly more controls responded (50% drop in HAM-D or final score < 12) compared to TBI group ($p<.01$), though specific HAM-D response rates were not provided. Mean HAM-D in TBI group dropped from 25.0 ± 7.2 to 18.8 ± 6.8.
Fann et al, 2000	IV	A	15	15 Mild TBI Mean 10.6 mos (range 3-24) post TBI	DSM III-R MDD on DIS HAM-D>17	HAM-D CGI	Non-randomized, single-blind, placebo run-in trial of sertraline (25-150 mg/d, mean 75 mg/d) lasting 8 weeks	Response rate (50% drop in HAM-D) was 86.7% and remission rate (final HAM-D $\leq$ 7) was 66.7%. There were significant improvements in psychological distress, PCS, cognitive functioning, and QOL.
Horsfield et al, 2002	IV	C	5	5 Multiple TBIs ranging from mild to severe TBI acuity not noted	No depression criteria noted Nonspecific behavioral, psychiatric, and cognitive complaints No history of antidepressant treatment	HAM-D	Open trial of fluoxetine (20-60 mg/d) for 8 mos	Significant reduction in HAM-D scores from baseline (18 ± 7.07) to 8 mos (9.8 ± 8.07) ($p<.05$)
Kanetani et al, 2003	IV	A	10	10 Mild to moderate TBI (GCS 12-15, 7 had brain lesions on CT) Mean 152.8 days post TBI	DSM-IV (MINI) minor (n=3) or major (n=7) depression	HAM-D-21	Open trial of Milnacipran (30-150 mg/d) for 6 wks	Response rate (50% drop in HAM-D) was 66.7% and remission rate (final HAM-D $\leq$ 7) was 44.4%. There was significant improvement in cognition on MMSE.
Khateb et al, 2005	IV	C	10	10 Moderate to severe TBI At least 6 mos, mean 42 ± 33 mos from TBI	No depression criteria noted Exclusion: "unstable psychiatric disorders"	HADS	Open trial of donepezil x 3 mos: 5 mg/d for 1 mo, then 10 mg/d for 2 mos	Nonsignificant reduction in HADS-depression scores from baseline (6.8 ± 4.4) to 3 mos (5.0 ± 3.0). Significant improvement in processing speed, learning, and attention on neuropsychological testing.

Authors	AAN Evi-dence Level	Depression Inclusion Score	Total N	TBI sample: n Severity Acuity	Depression Entry criteria	Depression Instruments	Design & Intervention	Results & Conclusions
Newburn et al, 1999	IV	A	26	26 Severity not noted Mean 4.67 years post TBI	DSM-III-R MDD HAM-D≥17 Moderate depression on CGI	HAM-D CGI	Open trial of moclobemide (450-600 mg/d) either as single dose or 3 divided doses, for 3-6 weeks	Baseline HAM-D=23.4 (range 17-29), mean HAM-D reduction was 81%. 23/26 defined as responders (HAM-D<10 or 50% reduction). Irritability scores dropped by 57% and pain scores dropped by 39%.
Perino et al, 2001	IV	A	20	20 Severe TBI 11 < 6 mos post TBI 9 between 24-36 mos post TBI	DSM-IV MDD	BPRS CGI	Open trial of citalopram (20 mg/d) and carbamazepine (600 mg/d) for 12 weeks	Significant reductions in BPRS ($p<.05$) and CGI ($p<.005$) scores overall; post-acute subgroup had worse outcomes than group treated early
Rappaport et al, 2008	IV	A	54	54 Mild to moderate TBI < 1 yr post TBI	DSM-IV MDD (SCID)	HAM-D CGI	Open trial of citalopram at 20 mg/d for 6 wks (n=29) or 20-50 mg/d for 10 wks (n=26)	At 6 wks (n=54), 27.7% responded (50% drop in HAM-D) and 24.1% remitted (HAM-D ≤ 7). At 10 wks (n=26), 46.2% responded and 26.9% remitted.
Turner-Stokes et al, 2002	IV	A	21	3 Severity not noted Mean time from admission to acute rehabilitation was 63.3 days	DSM IV Major depressive-like episode (n=1) Depressive features (n=2)	BDI-II	Open trial of sertraline (50-100 mg) for 4-6 weeks	Marked clinical response in patient with major depressive-like episode (BDI-II dropped from 30 to 10). Some improvement in 2 patients with depressive features (BDI-II dropped from 16 to 9 in one patient, the other was untestable)
Other Biological Interven-tions								
Schoenberg-er et al, 2001	II	C	12	12 CHI with reported substantial cognitive difficulties 9 mild, 3 moderate 36 mos to 21 yrs from CHI	None	BDI	RCT of Flexys Neurotherapy System of biofeedback (EEG recording with photic feedback) for 25 sessions over 5-8 weeks - 6 active treatment - 6 waitlist controls	Significantly greater pre-post improvement on BDI in intervention group (22.5±9.9 to 7.0±5.3) vs. control group (16.7±9.8 to 16.2±12.2) Within subjects (n=12), BDI scores significantly improved from pre-treatment (19.3±11.1) to post-treatment (7.9±6.9) and 3-mo follow-up (7.8±6.7)

Authors	AAN Evi-dence Level	Depression Inclusion Score	Total N	TBI sample: n Severity Acuity	Depression Entry criteria	Depression Instruments	Design & Intervention	Results & Conclusions
Baker-Price & Persinger, 2003	III	A	11	11 Closed head injury 4 had LOC Mean 2 years after injury	Chronic depression diagnosed by professional or self-response to local newspaper, unresponsive to antidepressant	BDI	Open 2-group study of Magnetic field (1 microtesla burst, once a week for 6 weeks) - 7 subjects across left frontal lobe (3 dropped out) - 7 subjects across bilateral temporal lobes	BDI scores significantly decreased from baseline (19.7±8.6) to 6 weeks (14.1±5.2) and 6 weeks after end of treatment (15.1±7.6). No difference between region of application of magnetic field
Baker-Price & Persinger, 1996	IV	A	4	4 Acquired brain injury with mild to moderate impairment on neuropsych testing 2 within 1yr 1 within 3 yrs 1 about 6 yrs from injury	Persistent or frequently intermittent depression diagnosed by physician unresponsive to antidepressant	BDI SCL-90	Open study of Magnetic field (1 microtesla burst, once a week for 5 weeks) across bilateral temporal lobes	Significant decrease in BDI over 5 weeks: mean 33±9 to 17±9 SCL-90 depression scale dropped by 1.5 SD, but not statistically significant
Donnellan, 2006	IV	C	1	Severe TBI with multiple injuries and significant pain Approximately 5 mos after TBI	None	HADS	Classical Chinese medicine acupuncture points on limbs and thorax (7 treatments over 6 weeks)	No change in pre-post HADS depression (7/21) or anxiety (9/21) score, despite subjective improvement in anxiety and mood and significant improvement in pain scores.
Kant et al, 1999	IV	B	11	11 Mild to severe (4 with multiple CHI) Within 7-48 months of injury	DSM-IIIR criteria for neuropsychiatric conditions 4 had MDD (all antedating CHI), 5 had mood disorder secondary to CHI, 1 had chronic delirium, 1 had delusional disorder secondary to CHI	MADRS CGI	Retrospective study of Electroconvulsive therapy (ECT) 3 times per week (total treatments ranged from 4-20, mean 10). 8 patients received continuation ECT (total treatments ranged from 3-62, mean 18).	8 responders (i.e., MADRS≤15, 50% reduction in pre-ECT MADRS, CGI≤3) 2 partial responders (1/3 criteria met; both responded after continuation ECT) 1 nonresponder Among 9 with mood disorders, MADRS dropped from 33.4±6.4 to 11.2±8.5.

Authors	AAN Evi-dence Level	Depression Inclusion Score	Total N	TBI sample: n Severity Acuity	Depression Entry criteria	Depression Instruments	Design & Intervention	Results & Conclusions
					All unresponsive to medications or prior responders to ECT			
Martino et al, 2008	IV	A	1	1 Severe TBI 6 yrs post TBI	MDD	HAM-D (24-item)	8 bifrontal ECT treatments, followed by 4 continuation treatments over 6 wks	HAM-D dropped from 25 at baseline to 12 after acute treatment to 7 after continuation treatment. Neuropsychological battery showed stable or improved scores on all tests except MMSE and Trails B.

[1] Depression Selection Score

A. Prospectively enroll depressed patients
B. Depressed patients retrospectively identified at baseline
C. Pre-post depression scores only, with no selection for depressed patients at baseline

BDI-Beck Depression Inventory
BPRS=Brief Psychiatric Rating Scale
CGI=Clinical Global Impressions Scale
CHI=Closed Head Injury
DIS=Diagnostic Interview Schedule
DSM=Diagnostic and Statistical Manual of Mental Disorders
HADS-Hospital Anxiety and Depression Scale
HAM-D=Hamilton Rating Scale for Depression
LOC=Loss of consciousness
MADRS=Montgomery-Asberg Depression Rating Scale
MINI= Mini-International Neuropsychiatric Interview
MMSE=Mini-mental State Exam
PCS=Post-concussive Symptoms
QOL=Quality of life
SCID=Structured Clinical Interview for DSM
SDS=Zung Self-Rating Depression Scale
SCL-90-R=Symptom Checklist-90-Revised

Table 3. Overview of Psychotherapeutic and Rehabilitation Intervention Studies for Depression in persons with TBI (N=8)

Authors	AAN Evi-dence Level	Depression Selection Score	Total N	TBI: n Severity Acuity	Depression Entry criteria	Depression Instruments	Design & Intervention	Results & Conclusions
Powell et al, 2002	I	C	110	110 At least moderate TBI (PTA > 24h or neurosurgical intervention); nearly all had PTA > 1 wk; majority had PTA > 1 mo 3 mo – 20 yr post; TBI median 1.37 yr	No depression criteria 15% scored > 13 on HADS pre treatment	BICRO-39 Psychological wellbeing subscale rated by participants and carers-given to 75 participants HADS- given to 46 participants with sufficient cognitive ability	RCT with masked outcome assessment Experimental = Individualized, goal-planning oriented multi-disciplinary team treatment in home or community setting, 2-6 hrs/ wk x mean of 28 wk Control = Information condition: 1 home visit with individualized resource booklet	1° Outcome = Barthel Index & BICRO-39 at mean 2 yr post randomization; experimental > control on both measures (p<.05) 68% of experimental & 50% of control group improved on BICRO-39 psych subscale (p<.05) 50% of experimental and 54% of control group improved on HADS (ns)
McMillan et al, 2002	II	C	145	145 TBI (any severity) with attention complaints or deficits on neuropsychological testing; mean PTA ~ 1 mo 3 – 12 mo post TBI	No depression criteria	HADS	RCT with masked outcome assessment Experimental = Attention Control Training: 5 45-min sessions supervised practice using audiotape x 4 wk; daily independent practice with tape Control 1 = Physical fitness training with same amount of therapist contact and independent practice Control 2 = No treatment, no therapist contact	1° Outcome not specified No significant group differences were found on HADS or other measures. Pre-treatment HADS 7 ±5 ACT group, 5 ± 4 exercise group, 5 ± 4 control group; Post-treatment HADS 5 ± 4 ACT group, 4 ± 4 exercise group, 6 ± 5 control group

Authors	AAN Evi-dence Level	Depression Selection Score	Total N	TBI: n Severity Acuity	Depression Entry criteria	Depression Instruments	Design & Intervention	Results & Conclusions
Tiersky et al, 2005	II	C	20	20 Mild/ moderate TBI (GCS > 8, LOC </= 4 hr); 40% had no LOC At least 1 yr post TBI; mean 6 yr	No specific depression criteria Inclusion: complaints of emotional distress on SCL-90R	SCL-90-R depression scale	RCT with masked outcome assessment Experimental = "Comprehensive neuropsychological rehabilitation:" Cognitive remediation (attention process training, memory notebook, problem solving) + CBT; 2 50-min individualized sessions, w/ daily 30-min homework, 3x/wk x 11 wks Control = Waitlist/ attention control x 11 wk, w/ total of 2 or 3 45-min contacts from PI	1° Outcome = SCL-90-R GSI; experimental < control ($p < .05$) Depression scale on SCL-90-R, experimental < control ($p < .05$) Authors noted that post treatment means remained above "caseness" levels
Anson & Ponsford, 2006	IV	C	33	33 Mean PTA 32 d; ~90% had PTA < 1 wk 46 d – 7 yr post TBI	No depression criteria	HADS	Pre-Post Treatment Design (data were pooled from 2 groups with different baselines) Experimental = CBT-based coping skills group, 10 sesssions (2 90-min sessions/ wk) over 5 wk + homework assignments Control = Baseline phase x 5 wk	1° Outcome not specified Change in HADS depression from pre to post treatment = ns (% change = 1.3 ± 41) Authors report several variables correlated with higher % improvement in depression, e.g. greater self-awareness, less severe injury, higher premorbid intelligence

Authors	AAN Evi-dence Level	Depression Selection Score	Total N	TBI: n Severity Acuity	Depression Entry criteria	Depression Instruments	Design & Intervention	Results & Conclusions
Bedard et al, 2003	IV	C	13	13 Severity not noted At least 1 yr post TBI	No depression criteria Exclusion: "major concurrent mental illness," suicidal ideation	BDI-II	Pre-Post Treatment Design Experimental = Weekly group x 12 wk based on mindfulness meditation Control = None; data from 3 treatment drop-outs used as comparison group	1° Outcome not specified Change on BDI-II pre (18.4 ± 12.2) to post treatment (9.7 ± 10.6) = ns Group x time interaction for BDI-II approached significance (p = .06); treatment completers scored lower and treatment dropouts scored higher (worse) at follow-up
Gurr & Coetzer, 2005	IV	C	20	20 (13 for 3 mo follow-up) 9 mild, 3 moderate, 8 severe At least 6 mo post TBI; range 7-474 mo	No depression criteria Exclusion: "psychiatric conditions"	HADS	Pre-Post Treatment Design (data from a pre-treatment baseline phase were presented but not analyzed) Experimental = CBT-based treatment focused on headache management; 3 weekly relaxation groups + 6 30-min individual sessions every other week + 1 follow-up session Control = Pre-treatment baseline x 10 wk (data presented but not analyzed)	1° Outcome = Headache frequency & intensity; decreased after treatment Change in HADS pre (9.7 ± 4.1) to post treatment (8.5 ± 4.6) = ns

Authors	AAN Evi-dence Level	Depression Selection Score	Total N	TBI: n Severity Acuity	Depression Entry criteria	Depression Instruments	Design & Intervention	Results & Conclusions
Ownsworth, 2005	IV	n/a	1	1 Severe TBI; coma 6 d; PTA 12 d 4.5 yr post TBI	n/a	DASS	Case report with masked outcome assessment 13 weekly psychotherapy sessions with brain injury education and CBT skills with focus on defensive denial, + attendance at 3 TBI group sessions	1° Outcome not specified Pre treatment depression on DASS extremely severe (34/42); 1 wk post treatment depression in normal range (2/42)
Svendsen et al, 2004	IV	C	143	38 Severity not noted; 8 had "pure frontal injury" per neuroimaging Acuity not noted	No depression criteria Exclusion: "psychiatric or progressive neurodegenerative illness"	EBIQ Depression subscale completed by participants and relatives	Pre-Post Treatment Design Experimental = Interdisciplinary, holistic day treatment administered in "classes" of 16 participants; daily x 4 mo + 8 mo close monitoring in community Control = None	1° Outcome not specified EBIQ Depression scores converted to z scores by comparing to uninjured controls; pre treatment z = -1.1, post treatment z = -.5 Similar results for self and relative ratings Authors note that z scores changed significantly pre to post treatment but remained worse than controls

[1] Depression Inclusion Criteria

A. Prospectively enrolled depressed patients
B. Depressed patients retrospectively identified at baseline
C. Pre-post depression scores only, with no selection for depressed patients at baseline

AAN=American Academy of Neurology
BDI=Beck Depression Inventory
BICRO-39=Brain Injury Community Rehabilitation Outcome-39 scales
CBT=Cognitive Behavioral Therapy
DASS=Depression Anxiety Stress Scale
DSM=Diagnostic and Statistical Manual of Mental Disorders
EBIQ=European Brain Injury Questionnaire

HADS-Hospital Anxiety and Depression Scale
GCS=Glasgow Coma Scale
LOC=Loss of consciousness
PTA=Post-traumatic Amnesia
RCT=Randomized Controlled Trial
SCL-90-R=Symptom Checklist-90-Revised
TBI=Traumatic Brain Injury

Finally, the reference list includes all articles examined for inclusion in this systematic review.

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1. Clinical Question Development:

a) Problem/Issue to be addressed:

To conduct a structured, evidence-based systematic literature review and evaluation of depression measures[3] and interventions for adults with TBI.

b) To what patient population does this apply?

The target patient population studied adults with TBI and depression.
If the population is mixed acquired brain injury (traumatic + other such as stroke, anoxia, etc.), the focus will be on traumatic brain injury.

c) What is the intervention (therapy, test, risk factor)?

Depression measures and interventions in people with TBI.

d) What are the outcomes of interest?

1. Distinguish non-specific distress and TBI physical symptoms from depression.

2. Identify the most reliable, valid and efficient means of identifying persons with clinically significant depression or probable MDD and measuring change in depression severity via self-report measures;

3. Battery of items/scales measuring major depression in those with TBI

4. Interventions able to address depression.

e) State one or more answerable clinical questions that include the population, intervention and outcomes of interest:

1. What are the most reliable, valid and efficient means of screening for, diagnosing and measuring depression, particularly MDD, in people with TBI?

2. What are the efficacious treatments for clinically significant (particularly MDD) depression for people with TBI?

f) Define the construct being studied in operational terms to assist with construct validity:

1. Major Depression--- (as is defined in DSM-IV), Depression,

2. Criteria for Literature Search:

[3] NOTE: at a subsequent meeting, the authors decided to only review treatments for depression; the review of depression measures was discontinued.

a. Key Text words and Index words for the condition or closely related conditions, if appropriate (linked by the word "OR")

- Major Depression/Major depressive disorder, depression
- TBI, head injury, brain injury
- CES-D (Center for Epidemiologic Studies Depression)
- Zung self rating scale
- DSM-IV or III
- Major depressive episode
- SCL-90
- SF-36, SF-16, SF-8, SF-12, MHI-5
- Hamilton
- Present State Exam
- DIS (Diagnostic Interview Schedule)
- MMPI
- PHQ-9 (Patient Health Questionnaire)
- BDI (Beck Depression Inventory)
- Older Adult Mood and Health Questionnaire
- Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID)
- BDI-II
- BSI
- HAD, HADS
- NFI
- CIDI (Composite International Diagnostic Interview
- (there may be others]

b. Key Text words and Index words for the intervention (linked to above by the word "AND"):

- Depressive symptoms
- Depression
-
-
-
-

c. Databases to be searched (e.g. MEDLINE, EMBASE, and Current Contents):

Pubmed, Medline, Psychinfo, Proquest, CINAHL, Google Scholar, Web of Science, Cochrane Library?

d. Years to be included in the search:

Open-ended; must have one published article 1980 or later to meet inclusion criteria.

3. Inclusion and Exclusion Criteria:

a. Include all languages: Yes ___ No **_X_ (Published in English)**

b. Selected study population: Human Subjects: **Y**

Animal Studies: **N**

c. Disease in question or closely related diseases to be included:

Brain injury and Major Depression, Depression,

d. Interventions to be included: Any modality with a depression inclusion criteria and depression outcome: Pharmacologic, Psychosocial (e.g., individual or group psychotherapy, counseling, psychoeducational approaches), exercise, ECT (electroconvulsive therapy), TMS (Transcranial Magnetic Stimulation), etc

e. Interventions to be excluded: Interventions primarily targeting community integration, quality of life, improving functioning, general emotional well-being or non-depressive emotional symptoms such as anxiety, anger, etc.

f. Outcomes to be included:

- Reliability
- Diagnostic Accuracy / Validity
- Prognostic Accuracy / Validity
-Sensitivity to change over time and/or intervention
-Construct validity
-depression treatment efficacy or effectiveness

g. Outcomes to be excluded:

h. Types of studies to be included:

X RCT
X Cohort
X Case Control
X Case Series include Controlled single or multiple-single case studies (ABA, multiple baseline, etc.)
X Review papers
X Meta-analyses
X Instrument Manual, if available?
X Correlational/Survey
□ Book chapters, if available?

i. Standard exclusion criteria:

1. Not relevant to one of the clinical questions (reliability, diagnostic validity, prognostic validity, treatment efficacy/ effectiveness)
2. Outside of study population (not depression or TBI)
3. Article not peer reviewed

j. Additional exclusion criteria:

Theoretical manuscript or non-statistical (e.g. physiopathology) description of DOC

4. Project Timeline:

Project Tasks	Target Date
1. Project Development Plan	June 4, 2007
2. Inclusion/exclusion of Articles	June 30, 2007
3. Table of Evidence/Data Extraction	June-July 15
4. Table of Evidence Review	July-Mid August
5. First Draft of Review	August-September
6. External Review	November