

# ***AHRQ Comparative Effectiveness Review Surveillance Program***

## **CER #25:**

### **Traumatic Brain Injury and Depression**

#### **Original release date:**

**April 2011**

**Surveillance Report 1<sup>st</sup> Assessment:** March 2012

**Surveillance Report 2nd Assessment:** November 2012

#### **Key Findings 1<sup>st</sup> Assessment:**

- All conclusions for KQ1-6 are still considered valid
- New significant safety concerns were identified including warnings about contraindications for one medication
- Several new studies were identified, including imaging studies aimed at linking neural changes to depression, a study assessing markers to predict treatment response, and several studies on non-pharmacological treatment modalities

The findings were unchanged from the 1st assessment

### **Summary Decision**

This CER's priority for updating is **Low (This is unchanged from the last assessment)**

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# Traumatic Brain Injury and Depression

## 1. Introduction

Comparative Effectiveness Review (CER) #25, Traumatic Brain Injury and Depression, was released in April 2011.<sup>1</sup> It was therefore due for a surveillance assessment in October, 2011. The first assessment was completed in March 2012. This re-assessment was completed in November 2012.

## 2. Methods

### 2.1 Literature Searches

Using the search strategy employed for the original report, we conducted a limited literature search of Medline for the years 2010-October 20, 2011 (first assessment) and 10/2011-10/2012 (re-assessment). This search included five high-profile general medical interest journals (Annals of Internal Medicine, British Medical Journal, Journal of the American Medical Association, Lancet, and the New England Journal of Medicine) and five specialty journals (American Journal of Psychiatry, Archives of Physical Medicine and Rehabilitation, Brain Injury, Journal of Head Trauma and Rehabilitation, and Journal of Neuropsychiatry and Clinical Neurosciences). The specialty journals were those most highly represented among the references for the original report. Because Medline does not index the *Journal of Neuropsychiatry and Clinical Neurosciences* and *Archives of Physical Medicine and Rehabilitation*, searches of these journals were performed using the Web of Science. Appendix A includes the search methodology for this topic.

### 2.2 Study selection

In general we used the same inclusion and exclusion criteria as the original CER.

### 2.3 Expert Opinion

We shared the conclusions of the original report with 16 experts in the field (including the original project leader, suggested field experts, original technical expert panel (TEP) members, and peer reviewers) for their assessment of the need to update the report and their recommendations of any relevant new studies; four subject matter experts responded (three of the four responded to the re-assessment questionnaire). Appendix C shows the questionnaire matrix that was sent to the experts.

### 2.4 Check for qualitative and quantitative signals

After abstracting the study conditions and findings for each new included study into an evidence table, we assessed whether the new findings provided a signal according to the Ottawa Method and/or the RAND Method, suggesting the need for an update. The criteria are listed in the table below.<sup>2,3</sup>

<b>Ottawa Method</b>	
<b>Ottawa Qualitative Criteria for Signals of Potentially Invalidating Changes in Evidence</b>	
A1	Opposing findings: A pivotal trial or systematic review (or guidelines) including at least one new trial that characterized the treatment in terms opposite to those used earlier.
A2	Substantial harm: A pivotal trial or systematic review (or guidelines) whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making.
A3	A superior new treatment: A pivotal trial or systematic review (or guidelines) whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.
<b>Criteria for Signals of Major Changes in Evidence</b>	
A4	Important changes in effectiveness short of “opposing findings”
A5	Clinically important expansion of treatment
A6	Clinically important caveat
A7	Opposing findings from discordant meta-analysis or nonpivotal trial
<b>Quantitative Criteria for Signals of Potentially Invalidating Changes in Evidence</b>	
B1	A change in statistical significance (from nonsignificant to significant)
B2	A change in relative effect size of at least 50 percent
<b>RAND Method Indications for the Need for an Update</b>	
1	Original conclusion is still valid and this portion of the original report does not need updating
2	Original conclusion is possibly out of date and this portion of the original report may need updating
3	Original conclusion is probably out of date and this portion of the original report may need updating
4	Original conclusion is out of date

## 2.5 Compilation of Findings and Conclusions

For this assessment we constructed a summary table that included the key questions, the original conclusions, and the findings of the new literature search, the expert assessments, and any reports of the US Food and Drug Administration (FDA), Health Canada, or the United Kingdom’s Medicines and Health Care Products Regulatory Agency (MHRA) that pertained to each key question. To assess the conclusions in terms of the evidence that they might need updating, we used the 4-category scheme described in the table above for the RAND Method.

In making the decision to classify a CER conclusion into one category or another, we used the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still valid.

- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.
- If we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably out of date.
- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

## 2.6 Determining Priority for Updating

We used the following two criteria in making our final conclusion for this CER:

- How much of the CER is possibly, probably, or certainly out of date?
- How out of date is that portion of the CER? For example, would the potential changes to the conclusions involve refinement of original estimates or do the potential changes mean some therapies are no longer favored or may not exist? Is the portion of the CER that is probably or certainly out of date an issue of safety (a drug withdrawn from the market, a black box warning) or the availability of a new drug within class (the latter being less of a signal to update than the former)?

## 3. Results

### 3.1 Search

The March 2012 literature search identified 98 titles. After title and abstract review, we further reviewed the full text of 18 journal articles. The remaining 80 titles were rejected because they were editorials, letters, or did not include topics of interest. In addition to the searches, we also reference-mined articles that met inclusion criteria as well as non-systematic reviews identified by the literature searches but found no other articles. Eleven additional articles were reviewed at the suggestion of the experts. Thus, through literature searches and expert recommendations, 29 articles went on to full text review. Of these, 15 articles were rejected because they were non-systematic reviews or did not include a comparison of interest. Thus, 14 articles were abstracted into an evidence table (Appendix B).<sup>4-17</sup>

The October 2012 literature search identified 50 articles. After title and abstract review, we further reviewed the full text of 10 journal articles. The remaining 40 titles were rejected because they were editorials, letters, or did not include topics of interest. Experts identified 8 additional articles. Of the 18 articles that went on for full-text review, 12 were accepted; one was rejected because it included no measurement of depression, one was a duplicate of a study included in the

first update assessment, two were rejected because they were non-systematic reviews that did not address a key question, and two were rejected because they were original studies that did not address a key question. Summaries of the 12 accepted articles were added to the summary table (Table 1) and the articles were abstracted into the evidence table (Appendix B).<sup>18-29</sup>

### **3.2 Expert Opinion**

The three experts were in agreement that none of the conclusions changed based on new evidence.

### **3.3 Identifying qualitative and quantitative signals**

Table 1 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, the recommendations of the Southern California Evidence-based Practice Center (SCEPC) regarding the need for update, and qualitative signals.

**Table 1: Summary Table**

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
					Previous Assessment	Cumulative Assessment
<b>Key Question 1: What is the prevalence of depression after traumatic brain injury, and does the area of the brain injured, the severity of the injury, the mechanism or context of injury, or time to recognition of the traumatic brain injury or other patient factors influence the probability of developing clinical depression?</b>						
The prevalence of [depression among individuals with] traumatic brain injury is approximately 30 percent across multiple time points up to and beyond a year. Based on structured clinical interviews, on average 27 percent met criteria for depression 3 to 6 months from injury; 32 percent at 6 to 12 months; and 33 percent beyond 12 months.	<b>March 2012:</b> 2 new studies confirmed prevalence findings from original report <sup>5,16</sup> <b>November 2012:</b> 5 new studies found increased prevalence of depression among athletes with confirmed recent concussion or history of repeated concussion. <sup>18,20-22,24</sup>	NR	<b>March 2012:</b> 4/4: No new evidence that would change conclusions; 1 of 4 experts recommended 2 new studies 1 expert suggested stratifying data by age, whether head injury closed or open, and nature of accident (e.g. car accident vs. fall). <b>November 2012:</b> No new evidence that would change conclusions	Original conclusion is still valid and this portion of the original report does not need updating	Up-to-date	Up-to-date
Data are sparse to assess whether severity of injury influences risk of depression;	<b>March 2012:</b> 1 new study finds no association of injury (TBI) severity (GCS score or post-traumatic amnesia duration) with risk for depression <sup>16</sup> <b>November 2012:</b> Nine-year risk of depression increased with increasing number of prior concussions among retired NFL players. <sup>23</sup> Depressive symptoms, as measured by BDI-II, correlated with decreasing cognitive abilities (indicative of severity of TBI). <sup>22</sup> Self-reported depression	NR	<b>March 2012:</b> NR <b>November 2012:</b> No new evidence that would change conclusions	Original conclusion is still valid and this portion of the original report does not need updating	Up-to-date	Up-to-date

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
					Previous Assessment	Cumulative Assessment
	injury severity. <sup>29</sup>					
Stratification of prevalence by explanatory factors such as age, gender, area of brain injured, or mechanism of injury is not possible within the current body of literature	<p><b>March 2012:</b> 1 new study found no association between age, gender, time since injury and development of depression<sup>8</sup></p> <p>1 new study found that female gender, lower education, postinjury unemployment, and longer time since injury were associated with a non-significant increase in the risk for depression, but length of education and current work status combined were a significant risk factor<sup>4</sup></p> <p>1 new study found that race and education had no association with depression; (younger) age, (female) sex, and cause of injury (intentional) were a major risk for depression; occupational status at time of injury showed a trend toward significance<sup>16</sup></p> <p>1 new study found that development of depression was associated with poorer progress in resuming preinjury lifestyle; timing suggests functional status contributes to depression<sup>11</sup></p> <p>1 new study using cross-lagged analysis suggests poor functional status at 6 months post TBI may predict development of depression at 12 months post TBI<sup>9</sup></p> <p><b>November 2012:</b></p>	NR	<p><b>March 2012:</b> NR</p> <p><b>November 2012:</b> No new evidence that would change conclusions</p>	Original conclusion is still valid and this portion of the original report does not need updating	Up-to-date	Up-to-date

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
					Previous Assessment	Cumulative Assessment
	<p>1 new study found that women had a slightly higher risk for depression after TBI.<sup>25</sup></p> <p>1 new study found that older age was associated with depression in mild TBI patients.<sup>27</sup></p>					
History of alcohol and substance abuse increase risk. Pain, involvement in litigation related to the injury, and perceived stress have been reported as risk factors among those entering rehabilitation care and in prospective cohorts	<p><b>March 2012:</b> 1 new study identified preinjury depression as a significant risk factor for postinjury depression and confirmed a (non-significant) association with pain;<sup>4</sup> 1 new study found that preinjury substance abuse, and preinjury mental health tx, were all significantly related to depression (p&lt;0.005)<sup>16</sup></p> <p>1 new study found the prevalence of axis 1 disorders (MDD, substance abuse) relatively high in the 12 months preceding a TBI, but significantly higher than the US population only for alcohol dependence<sup>14</sup></p> <p><b>November 2012:</b> No new information</p>	NR	<p><b>March 2012:</b> NR</p> <p><b>November 2012:</b> No new evidence that would change conclusions</p>	Original conclusion is still valid and this portion of the original report does not need updating	Up-to-date	Up-to-date
Imaging research about the areas of the brain injured and the relationship to depression risk yields inconsistent results. In aggregate for all those with TBI, onset of major	<p><b>March 2012:</b> 1 new study found no association between lesions in the frontal, temporal, or parietal lobes, sublobular lesions, or limbic lesions on MRI and depression. However, the ratio of right to left frontal lobe and parietal lobe volume ratios predicted depression with high accuracy. What is not clear is whether TBI contributes to</p>	NR	<p><b>March 2012:</b> No new evidence that would change conclusions but 1 expert cited<sup>15</sup>, 1 cited research from literature on strokes as indicating an association between lesion location and depression risk, and 1 cited several military studies, including<sup>12</sup></p> <p><b>November 2012:</b></p>	Original conclusion is still valid and this portion of the original report does not need updating	Up-to-date	Up-to-date

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
					Previous Assessment	Cumulative Assessment
depression within 3 months of injury has been reported to be sevenfold as common (95 percent CI: 1.36 to 43.48) among those with abnormal CT scans after injury compared with normal imaging.	<p>hemispheric imbalances in neural activity (unless it results from brain atrophy)<sup>8</sup></p> <p>1 new study found that the pathophysiology of post-TBI depression in terms of brain atrophy in 3 regions on MRI overlaps with that of spontaneous depression<sup>15</sup></p> <p>1 new study that used diffusion tensor imaging and functional MRI to examine structural and functional neural correlates of MDD in combat vets with TBI found that those with depression had greater activity during fear matching trials in the amygdala and other emotion procession areas and several other differences but the study could not prove that blast injury caused either the lesions or depression<sup>12</sup></p> <p>November 2012: Imaging studies (MRI and MRSI) suggest association between reduction in gray matter in particular regions (as well as choline/creatine ratio and n-acetyl-aspartate/creatine ratio) and post TBI-depression.<sup>28</sup></p> <p><b>November 2012:</b> 1 new study found an association of frontal subdural hemorrhage with increased risk for mild TBI.<sup>27</sup></p> <p>1 new study found that in patients with TBI, mood disorders were associated with decreased N-acetyl aspartate/creatine ratios in the left anterior cingulate cortex.<sup>19</sup></p>		No new evidence that would change conclusions			
<b>Key Question 2. When should patients who suffer traumatic brain injury be screened for depression, with what tools, and in what setting?</b>						
Prevalence of	<b>March 2012:</b>	NR	<b>March 2012:</b>	Original conclusion is	Up-to-date	Up-to-date

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
					Previous Assessment	Cumulative Assessment
depression is high at multiple time points after TBI. No evidence provides a basis for targeting screening to one timeframe over another.	No new information <b>November 2012:</b> Increased levels of depression at 2, 7, and 14 days post-concussion in one new study support early post-injury screening. <sup>24</sup>		No new evidence that would change the conclusions <b>November 2012:</b> No new evidence that would change conclusions	still valid and this portion of the original report does not need updating		
The literature is insufficient to determine whether tools for detecting depression that have been validated in other populations can accurately identify depression in individuals with TBIs.	<b>March 2012:</b> 1 new study showed that no item of the PHQ-9 demonstrated statistically significant or meaningful differential item functioning attributable to TBI. Findings suggest PHQ-9 is a valid screener for MDD in people with TBI and that all items can be counted without concern regarding possible overdiagnosis. <b>November 2012:</b> No new information	NR	<b>March 2012:</b> NR <b>November 2012:</b> No new evidence that would change conclusions	Original conclusion is still valid and this portion of the original report does not need updating	Up-to-date	Up-to-date
The literature does not support any one tool over the others.	<b>March 2012:</b> No new information <b>November 2012:</b> No new information	NR	March 2012: NR November 2012: No new evidence that would change conclusions	Original conclusion is still valid and this portion of the original report does not need updating	Up-to-date	Up-to-date
<b>Key Question 3: Among individuals with TBI and depression, what is the prevalence of concomitant psychiatric/behavioral conditions, including anxiety disorders, post-traumatic stress disorder (PTSD), substance abuse, and major psychiatric disorders?</b>						
When conditions were reported individually, anxiety disorder was most prevalent and affected from 31 to 61 percent of study participants in four papers.	<b>March 2012:</b> 1 new study found that among individuals with TBI and depression, 23.5% had a substance use disorder and 73.5% had an anxiety disorder <sup>5</sup>  1 new study found that among individuals with TBI and depression, 13% and pre-existing anxiety disorder and 41% had a pre-existing substance use disorder <sup>4</sup>		March 2012: No new evidence that would change conclusions November 2012: No new evidence that would change conclusions	Original conclusion is still valid and this portion of the original report does not need updating	Up-to-date	Up-to-date

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
					Previous Assessment	Cumulative Assessment
	1 new study reported that 3 to 6 months post TBI, 13% had both depressive and anxiety disorders and that at 6 to 12 months, 20% had both. November 2012: No new research identified					
PTSD, a major anxiety disorder, was observed in 37 percent of depressed patients and in no patients without depression.	<b>March 2012:</b> 1 new study found that 10 of 11 patients with post-TBI MDD also had PTSD, compared with 9 of 11 TBI patients without MDD <sup>12</sup> <b>November 2012:</b> No new information	NR	<b>March 2012:</b> NR <b>November 2012:</b> No new evidence that would change conclusions	Original conclusion is still valid and this portion of the original report does not need updating	Up-to-date	Up-to-date
Panic disorder was seen in 15 percent of patients with major depression, but not measured in those without depression.	<b>March 2012:</b> 1 new study found that 6 of 11 patients with post-TBI MDD also had panic disorder compared with 4 of 11 patients without MDD <sup>12</sup> <b>November 2012:</b> No new information	NR	<b>March 2012:</b> NR <b>November 2012:</b> No new evidence that would change conclusions	Original conclusion is still valid and this portion of the original report does not need updating	Up-to-date	Up-to-date
Consideration of potential for coexisting psychiatric conditions is warranted.	<b>March 2012:</b> No new research <b>November 2012:</b> No new information	NR	<b>March 2012:</b> NR <b>November 2012:</b> No new evidence that would change conclusions	Original conclusion is still valid and this portion of the original report does not need updating	Up-to-date	Up-to-date
<b>Key Question 4. What are the outcomes (short and long term, including harm) of treatment for depression among traumatic brain injury patients utilizing psychotropic medications, individual/group psychotherapy, neuropsychological rehabilitation, community-based rehabilitation, complementary and alternative medicine, neuromodulation therapies, and other therapies?</b>						
Only two publications addressed treatment for individuals diagnosed with depression after a traumatic brain	<b>March 2012:</b> 1 new study found that a 12-week aerobics program improved HAM-D scores in individuals taking antidepressant medications such that the range of symptoms fell from moderate-severe and severe to mild-moderate and no symptoms. Scores	<b>March 2012:</b> MedWatch warning on taking sertraline with other agents that affect serotonin: Co-administration of Zoloft with other drugs which enhance the effects of serotonergic neurotransmission, such as tryptophan, fenfluramine, fentanyl,	<b>March 2012:</b> No new evidence that would change conclusions but 1 expert cited <sup>10</sup> <b>November 2012:</b> No new evidence that would change conclusions	Original conclusion is still valid and this portion of the original report does not need updating	Up-to-date	Up-to-date

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
					Previous Assessment	Cumulative Assessment
injury: Both were studies of antidepressant efficacy (one a controlled trial of sertraline and one an open-label trial of citalopram). The sertraline trial showed no significant effect compared with placebo, and the citalopram study did not show improvement in a majority of participants.	<p>on the Rosenberg Self-Esteem scale also improved, and the exercise had no adverse effects.<sup>7</sup></p> <p>1 new study found that a 6-week, internet-based cognitive behavioral therapy program decreased CES-D scores by a significant 1.03 points for each week completed. At 12 months followup, mean scores were 20.6±4.7 and PHQ-9 scores were 11.6±2.4, significantly lower than at baseline. 4/16 completers had symptoms that declined to below MDD criteria.<sup>6</sup></p> <p>1 new study examined the effects of a double-blind placebo-controlled continuation of a 16-week open-label study of citalopram for TBI-associated depression in individuals who achieved remission. 1 participant dropped out due to side effects (diarrhea); all participants described at least 1 adverse event. Mean compliance was 91.9%. The relapse rate did not differ between treated and untreated participants (52%)<sup>10</sup></p> <p><b>November 2012:</b> Flexyx Neurotherapy System, a therapy that delivers electromagnetic pulses, significantly decreased depressive symptoms in a very small sample of TBI patients with depression.<sup>26</sup></p>	<p>5-HT agonists, or the herbal medicine St. John's Wort (<i>hypericum perforatum</i>) should be undertaken with caution and avoided whenever possible due to the potential for pharmacodynamic interaction. (<a href="http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm271273.htm">http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm271273.htm</a>)</p> <p>FDA MedWatch Precaution on lab tests: False-positive urine immunoassay screening tests for benzodiazepines have been reported in patients taking sertraline. This is due to lack of specificity of the screening tests. False positive test results may be expected for several days following discontinuation of sertraline therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish sertraline from benzodiazepines.</p> <p>Health Canada: Citalopram - Association with abnormal heart rhythms (January 25, 2012)</p> <ul style="list-style-type: none"> <li>• A QT study showed that citalopram causes dose-dependent QT prolongation.</li> <li>• Citalopram should no longer be used in doses greater than 40mg/day</li> <li>• 20mg/d is the maximum recommended for patients with hepatic impairment, patients 65 years or older,</li> </ul>				

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
					Previous Assessment	Cumulative Assessment
		<p>patients who are CYP2C19 poor metabolizers, or patients who are taking cimetidine or another CYP2C19 inhibitor</p> <ul style="list-style-type: none"> <li>Citalopram is contraindicated in patients with congenital long QT syndrome or known QT interval prolongation</li> </ul> <p><a href="http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2012/celexa_2_hpc-cps-eng.php">http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2012/celexa_2_hpc-cps-eng.php</a></p> <p>Medicines and Healthcare products Regulatory Agency (MHRA) Drug Safety Update: Antidepressants: Risk of Fractures (May 2010)            Summary: Healthcare professionals should be aware of epidemiological data showing a small increased risk of fractures associated with the use of TCAs and SSRIs, and should take this risk into account in their discussions with patients and in prescribing decisions. Based on 9 observational studies in adults over 50.  <a href="http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON085136">http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON085136</a></p>				
<b>Key Question 5. Where head-to-head comparisons are available, which treatment modalities are equivalent or superior with respect to benefits, short- and long-term risks, quality of life, or costs of care?</b>						
No head-to-head trials were identified that	<b>March 2012:</b> NR <b>November 2012:</b>	NR	<b>March 2012:</b> No evidence <b>November 2012:</b>	Original conclusion is still valid and this portion of the original	Up-to-date	Up-to-date

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Validity of CER conclusion(s)	
					Previous Assessment	Cumulative Assessment
compared the effectiveness of two or more modalities for treating depression that follows TBI. Such studies are needed	No new information		No new evidence that would change conclusions	report does not need updating		
<b>Key Question 6: Are the short- and long-term outcomes of treatment for depression after TBI modified by individual characteristics, such as age, preexisting mental health status or medical conditions, functional status, and social support?</b>						
No studies were identified that assessed the impact of demographic or other potentially modifying characteristics on treatment effectiveness. Future research needs to address this issue.	<b>March 2012:</b> In the citalopram blinded, placebo-controlled continuation study, <sup>10</sup> relapse was not predicted by age, sex, employment status or overall baseline or post-treatment HDRS scores. However 2 HDRS variables did predict higher risk for relapse: agitation and greater than mild psychic anxiety <b>November 2012:</b> No new information	NR	<b>March 2012:</b> No new evidence that would change conclusions but 1 expert cited <sup>13</sup> <b>November 2012:</b> No new evidence that would change conclusions	Original conclusion is still valid and this portion of the original report does not need updating	Up-to-date	Up-to-date
	<b>March 2012:</b> In the original open-label citalopram study, certain small nuclear polymorphisms (SNPs) in genes associated with serotonin transport and metabolism predicted greater response to treatment and occurrence of adverse events. <sup>13</sup> <b>November 2012:</b> No new information					

Legend: PTSD= Post-Traumatic Stress Disorder; TBI=Traumatic Brain Injury; SNPs=Small Nuclear Polymorphisms; MRI=Magnetic Resonance Imaging; MDD= Major Depressive Disorder; NSSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant

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# **Appendices**

**Appendix A: Search Methodology**

**Appendix B: Evidence Table**

**Appendix C: Questionnaire Matrix**

## Appendix A. Search Methodology

### DATABASE SEARCHED & TIME PERIOD COVERED:

PubMed – 09/01//2011-09/12/2012

### LANGUAGE:

English

### SEARCH STRATEGY:

Brain Concussion[mh] OR brain injuries[mh:noexp] OR Brain Hemorrhage, Traumatic[mh] OR Epilepsy, Post-Traumatic[mh] OR Head Injuries, Closed[mh] OR Head Injuries, Penetrating[mh] OR Intracranial Hemorrhage, Traumatic[mh] OR Craniocerebral Trauma[mh] OR TBI[tiab] OR head injuries[tiab] OR head injury[tiab] OR traumatic brain injury[tiab] OR traumatic brain injuries[tiab] OR neurotrauma[tiab] OR diffuse axonal injury[mh] OR diffuse axonal injury[tiab] OR brain trauma[tiab] OR head trauma[tiab]  
AND

Depressive Disorder[mh] OR Depression[mh] OR depressive[tiab] OR depression[tiab] OR depressed[tiab] OR sadness[tiab] OR sad[tiab] OR hopelessness[tiab] OR suicidal[tiab] OR suicide[tiab] OR Mental Disorders[mh:noexp] OR mood[tiab]  
AND

"Lancet Neurol"[Journal] OR "BMJ"[Journal] OR "BMJ (Int Ed)"[Journal] OR "JAMA"[Journal] OR "N Engl J Med"[Journal] OR "Ann Intern Med"[Journal] OR "Lancet"[Journal] OR "Journal of head trauma rehabilitation" OR J Head Trauma Rehabil OR american journal of psychiatry OR brain injury[journal]

**NUMBER OF RESULTS: 31**

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### DATABASE SEARCHED & TIME PERIOD COVERED:

Web of Science - SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH – 09/01/2011–09/12/2012

### LANGUAGE:

English

### SEARCH STRATEGY:

Topic=(Brain Concussion\* OR brain injuries OR brain injury OR Traumatic Brain Hemorrhage OR Post-Traumatic Epilepsy OR Head Injuries OR Intracranial Hemorrhage OR Craniocerebral Trauma OR TBI OR head injuries OR head injury OR traumatic brain injury OR traumatic brain injuries OR neurotrauma OR diffuse axonal injury OR diffuse axonal injury OR brain trauma OR head trauma)  
AND

Topic=(depressive OR depression OR depressed OR sadness OR sad OR hopelessness OR suicid\* OR Mental Disorders OR mood)  
AND

Publication Name=(journal of neuropsychiatry and clinical neurosciences OR archives of physical medicine and rehabilitation)

**NUMBER OF RESULTS: 6**

## Appendix B. Evidence Table

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effectiveness of Tx)
KQ1 What is the prevalence of depression after traumatic brain injury, and does the area of the brain injured, the severity of the injury, the mechanism or context of injury, or time to recognition of the traumatic brain injury or other patient factors influence the probability of developing clinical depression?				
<p>Author: Whelan-Goodinson, 2009 <sup>5</sup></p> <p>Country, Setting: Monash University, Melbourne NSW; rehab hospital</p> <p>Enrollment Period: All admissions since inception</p> <p>Design: Observational study, cross- sectional, survey and medical record review</p> <p>Time from Injury: 0.5-5.5 years, mean of 3 yrs</p> <p>Length of Follow-up: NA</p> <p>Depression Scale/tool: SCID-I</p>	<p>Inclusion Criteria: Minimum age 17 years at the time of injury and maximum of 75 at time of interview; English proficiency, no history of previous TBI or serious neurological disorder e.g., stroke, epilepsy, brain tumor, or neurodegenerative disease; however patients with premorbid psychiatric Hx were not excluded.</p> <p>Exclusion Criteria: NR</p> <p>TBI Definition: NR</p>	<p>Group(s)</p> <p>N Screened: NR N eligible: NR N included: 100 N completed: 100</p> <p>Depression: Prior to injury: 17% At time of injury: unclear (20%? 3%? 17%?)</p> <p>Other pre-existing psychiatric conditions: Any anxiety disorder 13%, Any psychiatric disorder: 1% Substance use disorder: 41% Eating disorder: 2%</p> <p>Age: 38±16.96 (19-67)</p> <p>Severity of TBI: Mean Glasgow coma Score at 1 year post injury 8.53±4.35 Mechanism/type of injury: NR Area of Brain injured:</p>	<p>Depression: NR but according to DSM-IV criteria</p> <p>Other co-morbidities: NR</p> <p>HRQOL or functional status: NR</p>	<p>46% of participants had depression at some time post injury, and 74% of those were depressed at the time of assessment. 8 people with current depression had a comorbid substance use disorder (23.5%) and 25 had a comorbid anxiety disorder (73.5%). 51.1% of those with depression were receiving medication and/or counseling, and 31.3% (5) of those whose depression had resolved were receiving counseling and/or medication.</p>

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effectiveness of Tx)
<p>Author: Whelan-Goodinson, 2010 <sup>4</sup></p> <p>Country, Setting: Monash University, Melbourne NSW; rehab hospital</p> <p>Enrollment Period: All admissions since inception</p> <p>Design: Observational study, cross- sectional, survey and medical record review</p> <p>Time from Injury: 0.5-5.5 years, mean of 3 yrs</p> <p>Length of Follow-up: NA</p> <p>Depression Scale/tool: SCID-I</p>	<p>Inclusion Criteria: Glasgow Scale &lt;15, considered cognitively capable of giving informed consent and being reliable historians as deemed by the treating doctor or neuropsychologist, and sufficiently proficient in English to complete the interview</p> <p>Exclusion Criteria: Previous TBI or serious neurological disorder, e.g., stroke, epilepsy, brain tumor, or neurodegenerative disease</p> <p>TBI Definition: NR</p>	<p>NR</p> <p>Group(s)</p> <p>N Screened: NR N eligible: NR N included: 100 N completed: 100</p> <p>Depression: Prior to injury: 17% At time of injury: unclear (see<sup>5</sup>)</p> <p>Other pre-existing psychiatric conditions: Any anxiety disorder: 13%, Any psychiatric disorder: 1% Substance use disorder: 41% Eating disorder: 2%</p> <p>Age: 38±16.96 (19-67)</p> <p>Severity of TBI: Mean Glasgow coma Score at 1 year post injury 8.53±4.35</p> <p>Mechanism/type of injury: NR Area of Brain injured: NR</p>	<p>Depression: NR but according to DSM-IV criteria</p> <p>Other co-morbidities: NR HRQOL or functional status: NR Glasgow Outcome Scale Extended</p>	<p>Predictors of postinjury disorders: The odds of developing depression were nearly 5 times higher in those with a history of preinjury depression; 13 of 17 cases with depression at some time in their lives prior to injury developed postinjury depression.</p> <p>Female gender, lower education, pain, postinjury unemployment, and longer time since injury were associated with greater likelihood of postinjury depression. In the logistic regression, history of preinjury depression was the only significant predictor of postinjury depression; however, longer time postinjury, pain, , and lower education approached significance in relation to postinjury depression. Current employment status and gender did not make significant individual contributions to this model. When length of education was combined with current work status (which are inter-</p>

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effectiveness of Tx)
				related) were entered together, they made a significant contribution. Also, when history of preinjury depression was omitted, gender made a significant contribution (women were at higher risk for preinjury depression)
<p>Author: Hart, 2011<sup>16</sup>  Country, Setting:  US, multisite (academic, 19 nsites) participants in the Traumatic Brain Injury Model System [TBIMS] National Database</p> <p>Enrollment Period:  Within 72 hours of injury, all enrollees from 10/06-06/09</p> <p>Design:  Before and after, at 1-year follow-up?</p> <p>Time from Injury:  1 year  Length of Follow-up:  1 year  Depression Scale/tool:  Patient Health Questionnaire (PHQ)-9 measures each of the 9 DSM-IV symptoms of major depression)</p>	<p>Inclusion Criteria:  Receipt of medical care in a TBIMS-affiliated trauma center within 72 hours of injury, age &gt;16, penetrating or non-penetrating TBI with at least 1 of the following characteristics: Glasgow Coma Scale score &lt; 13 on emergency admission (not due to intubation, intoxication or sedation), loss of consciousness of more than 30 minutes (not due to sedation or intoxication), posttraumatic amnesia (PTA) more than 24 hours, or trauma related intracranial abnormality on neuroimaging</p> <p>Exclusion Criteria:  Inability to complete PHQ-9, either due to inability to speak English or severe cognitive impairment</p> <p>TBI Definition:  Score&lt;13 on GCS,</p>	<p>Group(s)</p> <p>N Screened:2,274  N eligible:  N included:1570  N completed:1570 (+ 350 who did not provide self-report depression data at follow-up)</p> <p>Depression:  Prior to injury:  NR  At time of injury:  NR</p> <p>Other pre-existing psychiatric conditions:  43.2% positive for substance abuse pre-injury  19.6% positive for receipt of mental health treatment</p> <p>Age:  39.9±18.8</p>	<p>Depression:  Minor depression defined as 2-4 positive symptoms, major depression defined as ≥5 positive symptoms  With at least 1 postivie cardinal symptom (depressed mood or anhedonia)</p> <p>Other co-morbidities:  NR</p> <p>HRQOL or functional status:  FIM measured within 72 hours of injury and at 1-year</p>	<p>Prevalence:  52% of sample: reported no significant depression  22% reported minor depression  26% reported major depression</p> <p>Correlates:  Race, education had no association with depression; PTA duration and FIM at rehab discharge also were not associated with depression; GCS scores also were not associated with depression. (Younger) age, (female) sex, preinjury substance abuse, preinjury mental health tx, and cause of injury (intentional) were all significantly related to depression (p&lt;0.005)  Occupational status at time of injury showed a trend toward significance (p=0.006)</p>

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effectiveness of Tx)
	Duration of PTA (number of days between the TBI and the 1 <sup>st</sup> of 2 occasions within 72 hours that the participant was fully oriented, i.e., a score > 76 on the Galveston Orientation and Amnesia Test)	Severity of TBI:  Mechanism/type of injury: 9.5% intentional cause of injury 62.1% vehicle-related 24.6% falls-related  Area of Brain injured:		[this paper also investigated the relationship of depression to 1-year outcomes such as cognitive and physical disability, global outcomes, and satisfaction with life, but these outcomes are beyond the scope of the review]
<p>Author: Koponen 2011 <sup>14</sup> Country, Setting: Finland; academic medical center Enrollment Period: consecutive patients who visited emergency facility for TBI</p> <p>Design: Prospective observational study Time from Injury: &lt; 3 days</p> <p>Length of Follow-up: 12 months</p> <p>Depression Scale/tool: SCAN and SCID-II</p>	<p>Inclusion Criteria: (1) Acute brain trauma (&lt; 3 days onset) that included one or more of the following: a. loss of consciousness for at least 1 minute (eye-witnessed by someone), b. post-traumatic amnesia (PTA) for at least 30 minutes; c. neurological signs or symptoms of brain injury during the first 3 days (excluding headache and nausea), or d. neuro-radiological findings indicating acute TBI; and (2) age between 16 and 70. Exclusion Criteria: Other CNS diseases TBI Definition: Glasgow coma scale at arrival combined with duration of PTA as follows: Mild TBI: GCS 13-15 and PTA &lt; 24 hrs.; Moderate TBI:</p>	<p>Group(s) 1 group only N Screened:45 N eligible:39 N included:39 N completed:38 (1 lost to FU)</p> <p>Depression: see findings Prior to injury: At time of injury:</p> <p>Other pre-existing psychiatric conditions: See findings Age: 41.6±17.0 (range 16-67) Severity of TBI: 27 (71.1%) mild, 6 (15.8%), moderate, 3 (7.9%) severe; 2 (5.3%) very severe</p> <p>Mechanism/type of injury: 26 (68.4%) falls; 10 (26.3%) 1 assault (2.6%), 1 other...</p>	<p>Depression: NR Other co-morbidities: NR HRQOL or functional status: NR</p>	<p>During the 12 months preceding TBI, occurrence of axis 1 disorders was relatively high: alcohol abuse n=7 (18.4%); MDD n=4 (10.5%, 95% CI 2.9 to 24.8), Any Axis 1 disorder: n=15 (39.5%, 95% CI 24.0 to 56.6) When all disorders were taken into account (both pre-existing and new onset), 47.4% had any axis 1 disorder, and 6 had MDD (15.8%, 95% CI 6.0 to 31.3). Of those with onset after TBI, 5 had depressive disorders (13.2%, 95% CI 4.4 to 28.1). Of these 5, two developed depression NOS after TBI with no Hx of affective disorders. One participant developed his first major depressive episode. Remaining two developed a major depressive episode</p>

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effectiveness of Tx)
	GCS 9-12 or PTA 1-7 days; Severe TBI: GCS≤8 or PTA>7 days; Very severe: PTA>4wks	Area of Brain injured: NR		after TBI(?). [so before TBI, alcoholism tended to be high, after TBI, depression tended to be high] Study also assessed axis II disorders. Rate was 29.0% (95% CI 15.4 to 45.9)  Rate of Axis I disorders pre TBI was high but did not differ from that of the US community except for alcohol dependence (18.4%, 95% CI 7.7 to 34.3 vs. 3.9% and 1.3% in the community in Finland and the US, respectively).
<p>Author: Ownsworth, 2011 <sup>11</sup></p> <p>Country, Setting: NSW, major metropolitan hospital</p> <p>Enrollment Period: 9/07-7/09</p> <p>Design: Prospective longitudinal observational study</p> <p>Time from Injury: Varied (hospital discharge and +3 months)</p> <p>Length of Follow-up: 3 months from hospital</p>	<p>Inclusion Criteria: TBI from any cause, 18-60 years of age, hospitalized at least 4 days prior to discharge, adequate English skills</p> <p>Exclusion Criteria: NR</p> <p>TBI Definition: NR</p>	<p>Group(s)</p> <p>N Screened: 196</p> <p>N eligible: N included: 129</p> <p>N completed: 96 (22 w/d or loss to followup, 11 missing data)</p> <p>Depression: Prior to injury: At time of injury:</p> <p>Other pre-existing psychiatric conditions:</p> <p>Age:</p>	<p>Depression: DASS score ≥10</p> <p>Other co-morbidities: NR</p> <p>HRQOL or functional status: Ability and Adjustment Index of the Mayo Portland Adaptability Inventory-4 (MPAI-4)</p>	<p>Proportion clinically depressed at discharge and 3 months later: 24%, 27% resp. At 3 months, 11.5% shifted from normal to clinically depressed and 11.55 had shifted from depressed to normal.</p> <p>Discharge DASS score was correlated with 3-month DASS score.</p> <p>Total transition events (Sentinel Events Questionnaire) correlated significantly with DASS-21 depression score at 3 months and with the MPAI-4 change</p>

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effectiveness of Tx)
<p>discharge</p> <p>Depression Scale/tool: Depression, Anxiety, and Stress Scales 21 (DASS-21)</p>		<p>Mean age 35.37±13.07 (18-60)</p> <p>Severity of TBI: Mean GCS (initial) 9.15±4.29 (3-15)</p> <p>Mechanism/type of injury: Traffic related (47.9%) Fa.; (27.1%) Assault (17.7%) Sporting injury (7.3%)</p> <p>Area of Brain injured: NR</p>		<p>score.</p> <p>Patients who progressed from normal to clinical depression had significantly poorer progress in resuming pre-injury lifestyle. Findings suggest the lack of progress in resuming normal lifestyle activities contributes to the postdischarge depressive symptoms through an influence on perceived function.</p>
<p>Author: Schönberger 2011<sup>9</sup></p> <p>Country, Setting: NSW</p> <p>Enrollment Period:</p> <p>Design: Time from Injury: Length of Follow-up: Depression Scale/tool: SCIDI</p>	<p>Inclusion Criteria: Complicated mild to severe TBI, age 16-80 at injury, no previous TBI or other neurological disorder, residence in Australia, sufficient cognitive and English ability to complete interviews</p> <p>Exclusion Criteria: TBI Definition:</p>	<p>Group(s)</p> <p>N Screened: 430 N eligible:276 N included: 172 N completed: (no differences between participants and those who declined except participants had more years of education)</p> <p>Depression: Prior to injury: NR At time of injury: NR 3-6 mos post injury: 19% had depressive disorder 6-12 mos post injury: 31% had a depressive disorder</p> <p>Other pre-existing psychiatric</p>	<p>Depression: NR</p> <p>Other co-morbidities: Anxiety: 3-6 mos: 13% of participants had both depression and anxiety 6-12 mos: 20% had both HRQOL or functional status: Extended Glasgow Outcome Scale (GOSE)</p>	<p>At 6 months post injury, 7% of participants had a severe disability in terms of functionality. 74% had moderate disability, 20% had good recovery.</p> <p>Cross-lagged analysis of depression and functional status showed that at 6 and 12 mos, poor functional status was not significantly related to the occurrence of depression. Poor functional status at 12 months was predicted by poor functional status at 6 months but not by depression at 6 months.</p> <p><i>Occurrence of depression between 6 and 12 months post injury was predicted by</i></p>

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effectiveness of Tx)
		<p>conditions: NR</p> <p>Age: 34.9±16.2 (median 28.3; range 16-77) Severity of TBI: 9.2±4.3 (median 9, range 3-15)</p> <p>Mechanism/type of injury: NR</p> <p>Area of Brain injured: NR</p>		<p><i>depression at 6 months and by poor functional status at 6 months (p&lt;0.048), but depression (and anxiety) at 6 months did not predict later functional status, and the prediction of depression at 12 months from functional status at 6 months was not significantly stronger than the prediction of functional status at 12 months from depression at 6 months.[seems somewhat contradictory; abstract emphasizes positive finding]</i></p>
<p>Author: Schönberger 2011<sup>8</sup></p> <p>Country, Setting: NSW Academic medical center</p> <p>Enrollment Period: NR</p> <p>Design: Cross-sectional Time from Injury: 2.2 yrs post-injury (0.3-5.7)</p> <p>Length of Follow-up: Not relevant Depression Scale/tool: SCID-IV</p>	<p>Inclusion Criteria: TBI with rehab at Epworth Hospital, absence of neurological conditions other than TBI, age 17-75, sufficient proficiency in English to complete structured psychiatric interview, suitability for MRI scanning, and no pre-injury hx of depression (via SCID-IV)</p> <p>Exclusion Criteria: NR</p> <p>TBI Definition: Glasgow Coma Scale</p>	<p>Group(s)</p> <p>N Screened:NR N eligible:NR N included:54 N completed:54</p> <p>Depression: Prior to injury: none per inclusion criterion At time of injury: same</p> <p>Other pre-existing psychiatric conditions: NR</p> <p>Age: Mean 35.0, median 28.3, range 17-73, 61% 17-33</p>	<p>Depression: Per SCID-IV</p> <p>Other co-morbidities:</p> <p>HRQOL or functional status: NR</p>	<p>13 (24%) developed a novel depressive disorder post-injury: 9 (69%) had a major depressive disorder and 4 (31%) had a DDNOS.</p> <p>91% of participants had gray or white matter lesions on MRI. 80%: frontal lobe 65% temporal lobe 50% parietal lobe 67% sublobar 65% limbic</p> <p>No association was seen between DD and any of these lesions.</p> <p>Most participants had larger</p>

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effectiveness of Tx)
		<p>Severity of TBI: Mild to severe with most in the moderate-to severe range</p> <p>Mechanism/type of injury: NR</p> <p>Area of Brain injured: See results</p>		<p>right frontal than left frontal lobes...DD was associated with a significantly more pronounced difference. (Cohen's <math>d=0.9</math>) Most participants also had larger right parietal than left parietal lobes: this difference was significantly smaller in individuals with DD. Both of these differences was independently associated with risk for DD. Age, gender, and time since injury did not predict DD. Frontal volume ratios predicted 31% of DD correctly, parietal volumes predicted 39%, and both predicted 46%. Non-depressed individuals were predicted with high accuracy using all three. However, it has not been definitively confirmed that TBI contributes to hemispheric imbalances in neural activity (unless the imbalance is the result of brain atrophy)</p>
<p>Author: Hudak 2011<sup>15</sup></p> <p>Country, Setting: US, Academic medical center</p> <p>Enrollment Period:</p>	<p>Inclusion Criteria: 16-65 years of age, required admission to hospital for TBI</p> <p>Exclusion Criteria: 1) Preexisting neurological or psychiatric disorder or TBI;</p>	<p>Group(s)</p> <p>N Screened: N eligible: 72 N included: 58 N completed:25 (remaining participants eliminated)</p>	<p>Depression: Defined as BDI score &gt;13</p> <p>Other co-morbidities: NR</p> <p>HRQOL or functional status:</p>	<p>Structural imaging found some suggestive evidence that the pathophysiology of post-TBI depression overlaps with that of spontaneous depression. Atrophy(from 0 to 6 months post injury) in 3</p>

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effectiveness of Tx)
<p>2005-2008</p> <p>Design: Observational study on convenience sample</p> <p>Time from Injury: NR (mean time to 1<sup>st</sup> scan 3 days)</p> <p>Length of Follow-up: 6 months</p> <p>Depression Scale/tool: Beck Depression Index</p>	<p>cognitive dysfunction; any condition that could result in an abnormal MRI; 2) presence of focal lesions; 3) contraindications to MRI; 4) prisoners, homeless, pregnant women</p> <p>TBI Definition:</p>	<p>because one scan missing)</p> <p>Depression: Prior to injury: No At time of injury:</p> <p>Other pre-existing psychiatric conditions: None</p> <p>Age: Median 23 (interquartile range [IQR] 19-37)</p> <p>Severity of TBI: Median 8 (IQR 3-14)</p> <p>Mechanism/type of injury: (64% motor vehicle collision, 9% motor cycle collision, 9% motor-pedestrian collision)</p> <p>Area of Brain injured: NR</p>	<p>Glasgow Outcome Scale-Extended: median 7</p> <p>Functional status exam: Median 13</p>	<p>regions of interest correlated significantly with depressive symptoms; these regions have been associated with spontaneous depression also.</p>
<p><b>Author:</b> Liossi, 2009<sup>25</sup></p> <p><b>Country, Setting:</b> UK, academic medical center</p> <p><b>Time from Injury:</b> 185-1,460 days (matched)</p> <p><b>Length of Follow-up:</b> NR</p> <p><b>Depression Scale/tool:</b> Beck Depression Inventory</p>	<p><b>Inclusion Criteria:</b> Head injury and abnormal CT scan</p> <p><b>Exclusion Criteria:</b> Previous hx of head injury; neurological or psychiatric disorder; hx of serious medical condition; alcohol or drug abuse; speech, motor, or perceptual deficit likely to interfere with neuropsych assessment</p>	<p><b>Group(s)</b> Male and female head-injured patients</p> <p><b>N Screened:</b> 520 (162 women, 358 men)</p> <p><b>N eligible:</b> 377</p> <p><b>N included:</b> 150 (75 pairs)</p> <p><b>N completed:</b></p>	<p>NA</p>	<p><b>Age and cognitive decline were related for women but not men.</b></p> <p><b>Women had marginally elevated depression and anxiety scores compared to men but neither were significant.</b></p>

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effectiveness of Tx)
		<p>150</p> <p><b>Depression:</b>  <b>Prior to injury: No</b>  <b>At time of injury: No</b></p> <p><b>Other pre-existing psychiatric conditions:</b>  <b>None</b></p> <p><b>Age:</b>  <b>Mean age men: 43.44</b>  <b>Mean age women: 39.61</b></p> <p><b>Severity of TBI:</b>  <b>Mean GCS 12.79 for men,</b>  <b>10.88 for women</b></p> <p><b>Mechanism/type of injury:</b>  <b>Motor vehicle accident,</b>  <b>falls, assault, pedestrian injury</b></p> <p><b>Area of Brain injured:</b>  <b>Frontal hemorrhagic or contusional injuries</b></p>		
<p><b>Author:</b>  <b>Rao, 2010<sup>27</sup></b></p> <p><b>Country, Setting:</b>  <b>US, academic medical center</b></p> <p><b>Time from Injury:</b></p>	<p><b>Inclusion Criteria:</b>  <b>1<sup>st</sup> closed head injury, clear hx of altered mental status or GCS &lt;15 soon after injury; admission to inpatient unit for assessment of brain injury; age ≥18, ability to give</b></p>	<p><b>Group(s)</b>  <b>N Screened: NA</b>  <b>N eligible: NA</b>  <b>N included: 43</b>  <b>N completed: 43</b></p> <p><b>Depression:</b>  <b>Prior to injury: No</b></p>	<p><b>DSM-IV criteria</b></p>	<p><b>8 (18.6%) of enrollees met criteria for mood disorder due to general medical condition during the 1<sup>st</sup> year of trauma.</b></p> <p><b>7 of the 8 were diagnosed on the first assessment.</b></p>

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effectiveness of Tx)
<p>≤3 months, preferably 2 weeks</p> <p>Length of Follow-up: 3 months</p> <p>Depression Scale/tool: SCID</p>	<p>consent</p> <p>Exclusion Criteria: Prior TBI; open head injury; hx of any other type of brain illness or mental disorder; duration of loss of consciousness &gt; 30 minutes</p>	<p>At time of injury: No</p> <p>Other pre-existing psychiatric conditions: None Age: mean=44.5±17.5(SD)</p> <p>Severity of TBI: NR (mild TBI)</p> <p>Mechanism/type of injury: Motor vehicle accidents, falls, assaults</p> <p>Area of Brain injured: Assessed but not reported</p>		<p>When enrollees were divided into 2 groups based on mood disorder (depressed, non-depressed), depression was associated with greater age and presence of frontal subdural hemorrhage.</p>
<p>Author: Capizzano, 2010<sup>19</sup></p> <p>Country, Setting: US, academic medical center</p> <p>Time from Injury: 26-4,923 days (mean 55 months)</p> <p>Length of Follow-up: NR</p> <p>Depression Scale/tool: HAM-D</p>	<p>Inclusion Criteria: TBI</p> <p>Exclusion Criteria: Penetrating TBI, injury-related complications, having undergone a neurosurgical procedure</p>	<p>Group(s) N Screened: NR N eligible: NR N included: 20 TBI pts., 13 age- and sex-matched controls</p> <p>N completed: 20TBI pts.</p> <p>Depression:  Prior to injury: NR At time of injury: NR</p> <p>Other pre-existing psychiatric conditions: NR Age: 18-75</p>	<p>Case definition of TBI: CDC guidelines for Surveillance of CNS Injury</p>	<p>5 pts fulfilled clinical criteria for major depression; all had reduced N-acetyl aspartate/creatine ratios in the left anterior cingulate cortex cf. pts without mood disorders. However, when they controlled for time, this difference disappeared.</p>

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effectiveness of Tx)
		<p><b>Severity of TBI:</b> Mean GCS score 11.65, range 5-15</p> <p><b>Mechanism/type of injury:</b> Motor vehicle accident, fall</p> <p><b>Area of Brain injured:</b> Varied: 11 had left frontal injury, 2 had right frontotemporal lesions, 5 had normal MRIs and 2 had MRIs consistent with diffuse axonal injury</p>		
<p><b>Author:</b> Rao 2010<sup>28</sup></p> <p><b>Country, Setting:</b> US, Academic medical center</p> <p><b>Time from Injury:</b> 3-60 months</p> <p><b>Length of Follow-up:</b> NA</p> <p><b>Depression Scale/tool:</b> SCID-1</p>	<p><b>Inclusion Criteria:</b> Age ≥18 years, closed head injury, date of TBI between 3 and 60 months prior to evaluations, MMSE score &gt;18, stable medical history prior to injury, sufficient cognitive capacity to provide consent, meeting DSM-IV criteria for a major depressive disorder (for depressed participants)</p> <p><b>Exclusion Criteria:</b> Hx of diagnosable mood disorder prior to TBI</p>	<p><b>Group(s)</b> Depressed and non-depressed</p> <p>N Screened: NR N eligible: NR N included: 10 cases, 7 controls N completed: NR</p> <p><b>Depression:</b> Prior to injury: No At time of injury: No</p> <p><b>Other pre-existing psychiatric conditions: (no)</b> Age: Cases: mean age 52.4 Controls mean age 27.3</p> <p><b>Severity of TBI:</b></p>	<p><b>TBI:</b> Glasgow Coma Scale</p> <p><b>Depression:</b> SCID-1/DSM-IV criteria for depression</p>	<p><b>Cognitive performance:</b> depressed patients had significantly poorer cognitive function than controls (Part B of trail-making test, Brief visuo-spatial memory Test, total recall, trend toward worse delayed recall but better performance on Wisconsin card sorting test.</p> <p><b>Regional Brain Volumes (MRI):</b> Reduction in gray matter volume in right frontal and total left occipital lobe; trend toward lower gray matter volumes in total brain, left frontal cortex, bilateral temporal cortex, and right parietal</p>

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effectiveness of Tx)
		<p>Cases: 40% had moderate to severe TBI            Controls: 100% had moderate to severe TBI</p> <p>Mechanism/type of injury: NR            Area of Brain injured: NR</p>		<p>cortex.</p> <p>MRSI: right basal ganglia choline/creatine ratio and n-acetyl-aspartate/creatine decreased in cases.</p> <p>Suggest possible role for frontotemporal lobe, basal ganglia pathology in post-TBI depression</p>
<p><b>Author:</b> Amen 2011<sup>18</sup>  <b>Country, Setting:</b> US, Multisite academic medical centers  <b>Time from Injury:</b> varied  <b>Length of Follow-up:</b> varied  <b>Depression Scale/tool:</b> DSM-IV</p>	<p><b>Inclusion Criteria:</b> 3 or more seasons playing in NFL  <b>Exclusion Criteria:</b> In ability to refrain from taking psychoactive medications for duration of study</p>	<p><b>Group(s)</b></p> <p>N Screened: NR            N eligible: NR            N included: 100            N completed: 100</p> <p><b>Depression:</b>            Prior to injury: NR            At time of injury: NR</p> <p><b>Other pre-existing psychiatric conditions:</b> NR            Age:25-82 (mean 57.27)</p> <p><b>Severity of TBI:</b>            NR; inferred from self-reports of head injury, concussion, loss of consciousness  <b>Mechanism/type of injury:</b>            Closed head injury from playing pro football  <b>Area of Brain injured:</b> NR</p>	<p><b>TBI:</b> inferred from head injury  <b>Depression:</b>            DSM-IV criteria or under treatment for depression</p>	<p>28% of players had diagnosed depression or were under treatment for depression, far higher than the general population. They identified consistent changes in quantitative EEG, which did not differentiate between depressed and non-depressed individuals.</p>

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effectiveness of Tx)
<p><b>Author:</b> Kontos 2012<sup>24</sup></p> <p><b>Country, Setting:</b> US academic medical center</p> <p><b>Design:</b> 2-year prospective study on concussion and post-injury depression in the 2 weeks following injury</p> <p><b>Time from Injury:</b> 2-14 days</p> <p><b>Length of Follow-up:</b> 14 days</p> <p><b>Depression Scale/tool:</b> Beck Depression Inventory II</p>	<p><b>Inclusion Criteria:</b> Sports-related concussion diagnosed by a sports-medicine professional</p> <p><b>Exclusion Criteria:</b> History of treatment for substance abuse, psychiatric disorder, special education, years repeated in school, speech problems, and current baseline score of 20 or greater on the Beck Depression Inventory II</p>	<p><b>Group(s)</b></p> <p>N Screened: NR N eligible: NR N included: 75 N completed: 75</p> <p><b>Depression:</b> Prior to injury: None At time of injury: None</p> <p><b>Other pre-existing psychiatric conditions:</b> NR</p> <p><b>Age:</b> 54 high school (mean age 15.74) and 21 college (19.68) athletes</p> <p><b>Severity of TBI:</b> n/a</p> <p><b>Mechanism/type of injury:</b> Concussion</p> <p><b>Area of Brain injured:</b></p>	<p><b>TBI:</b> n/a</p> <p><b>Depression:</b> BDI-II&gt;20 (moderate or greater)</p> <p><b>Concussion:</b> “a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces.”</p> <p>Neurocognitive changes assessed using the ImpACT computerized neurocognitive test battery.</p>	<p><b>Athletes with concussions exhibited significantly higher (within subject) levels of depression from baseline at 2 (p&lt;0.001), 7 (p=0.006), and 14 days (p=0.04) post-concussion.</b></p> <p>Verbal memory was significantly worse at 2 days post-concussion, cf. baseline (p=0.03)</p> <p>Visual memory was significantly lower at 2 days (p=0.01) and 14 days (p=0.001).</p> <p>Reaction time was significantly slower at 2 days (p=0.001) and 14 days (p=0.001).</p> <p>No differences in motor processing speed.</p> <p>No difference between males and females except for visual memory.</p> <p>Depression scores correlated with neurocognitive decrements in reaction time and visual memory. Somatic depression (e.g., tiredness) was more salient with</p>

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effectiveness of Tx)
				respect to decrements in neurocognitive performance
<p><b>Author:</b> Kerr, 2012<sup>23</sup>  <b>Country, Setting:</b> US, academic medical center  <b>Enrollment Period:</b> 2001  <b>Design:</b> Prospective cohort survey  <b>Time from Injury:</b> varying  <b>Length of Follow-up:</b> 9 years  <b>Depression Scale/tool:</b> General Health Survey (GHS) and SF-36 (including PCS)  (outcome = 9-year risk of depression)</p>	<p><b>Inclusion Criteria:</b> Having played pro football  <b>Exclusion Criteria:</b> Prior depression</p>	<p><b>Group(s)</b>  N Screened:NR  N eligible: 3729  N included: 2536  N completed: 1316 but 138 excluded for former depression</p> <p><b>Depression:</b>  Prior to injury: No  At time of injury: No</p> <p><b>Other pre-existing psychiatric conditions:</b> NR  Age: NR</p> <p><b>Severity of TBI:</b> NR  <b>Mechanism/type of injury:</b> Concussions secondary to playing football  <b>Area of Brain injured:</b> NR</p>	<p><b>TBI:</b> n/a  <b>Depression:</b> SF-36  <b>Concussion:</b> GHS definition</p>	<p>From 2001 and 2010, 106 (10.2%) were diagnosed as clinically depressed. Of those 68 reported still suffering from depression in 2010.</p> <p>Of the 1044 respondents with no prior depression, 35% reported no concussions, 25.8% reported 1-2 concussions, 19.5% reported 3-4 concussions, 12.9% reported 5-9 concussions, and 6.8% reported 10 or more. The 9-year risk of depression increased with an increasing number of concussions from 3% (no concussions) to 26.8% (10 or more). Multivariate binomial regression revealed that none of the possible confounders affected the finding with the exception of years of retirement and the 2001 SF-36 PCS scores but when these were controlled for, the relationship still remained and independent of the relationship between</p>

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effectiveness of Tx)
				decreased physical health and depression.
<p><b>Author:</b> Hudak 2012<sup>22</sup></p> <p><b>Country, Setting:</b> US, academic medical center</p> <p><b>Time from Injury:</b> 6-12 months</p> <p><b>Length of Follow-up:</b> 6 months</p> <p><b>Depression Scale/tool:</b> BDI-II</p>	<p><b>Inclusion Criteria:</b> TBI needing hospitalization, age 14-65 yoa, participation in structured telephone interview (or participation of surrogate)</p> <p><b>Exclusion Criteria:</b></p>	<p><b>Group(s)</b> N Screened:1279 N eligible: 1279 N included: 471? N completed:451</p> <p><b>Depression:</b> Prior to injury: At time of injury:</p> <p><b>Other pre-existing psychiatric conditions:</b> NR Age: range 20-60</p> <p><b>Severity of TBI:</b> Median GCS score 11, range 3-15 <b>Mechanism/type of injury:</b> Most commonly motorized vehicle <b>Area of Brain injured:</b> NR</p>	<p><b>TBI:</b> as measured by GCS <b>Additional measures:</b> Functional Status Exam (FSE), Glasgow Outcome Scale-Extended (GOS-E)</p> <p><b>Depression:</b> For those with mild TBI, a BDI score&gt;18; for those with moderate-to-severe TBI, a BDI score &gt;34</p>	<p>Purpose of study was to examine the relationship between functional abilities (FSE) and post-TBI depressive symptoms as a way to monitor for and prevent depression...</p> <p><b>Mild TBI group (GCS 13-15):</b> BDI-II was correlated with duration of hospital stay, GOS-E, and FSE but not age, educational level, time to follow-up, or GCS score. 17% of this group was considered to have clinical depression.</p> <p><b>Moderate-to-severe injury group (GCS&lt;13):</b> BDI-II was correlated with age, GOS-E, and FSE but not educational level, duration of hospital stay, GCS, or time to follow-up. 21% were considered significantly depressed.</p> <p><b>BDI-II scores were correlated with the total FSE and all domains of the FSE. Lower functional status correlated with more depressive symptoms.</b></p>

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effectiveness of Tx)
				<p>Educational level correlated with lower risk for depressive symptoms. No correlation was seen with injury cause (e.g., violence). The hypothesis that improving functional status would be associated with more depressive symptoms was born out only in the mildly depressed group and with the GOS-E but not the FSE</p>
<p><b>Author:</b> Hart 2012 <sup>21</sup> <b>Country, Setting:</b> US, academic medical centers, TBIMS national database <b>Time from Injury:</b> NR <b>Length of Follow-up:</b> 1-2 years <b>Depression Scale/tool:</b> PHQ-9 (Patient Health Questionnaire, based on DSM IV)</p>	<p><b>Inclusion Criteria:</b> ≥16 yoa, GCS score&lt;13, loss of consciousness &gt;30 minutes, post-traumatic amnesia&gt;24 hours, and/or trauma-related intracranial abnormality; able to complete questionnaire <b>Exclusion Criteria:</b> NR</p>	<p><b>Group(s)</b>  N Screened:1975 N eligible:1975 N included:1586 N completed: 1089 (remaining expired or could not complete the questionnaire or were lost to follow up)  <b>Depression:</b> Prior to injury: NR At time of injury: NR  <b>Other pre-existing psychiatric conditions:</b> NR Age: mean=38.6±18.28  <b>Severity of TBI:</b></p>	<p><b>TBI:GCS</b> <b>Depression:</b> Minor depression: 2-4 positive symptoms Major depression: ≥5 positive symptoms</p>	<p>Across follow-up years, 26% of participants reported major depressive disorder; 21% reported minor depression; 53-55% reported no depression in years 1 and 2, resp. There was considerable shifting across categories from year 1 to 2. Of those not depressed in year 1, nearly ¾ remained not depressed in year 2. However 26% developed MDD or minor depression between year 1 and 2, and nearly 1/3 of those with minor depression in year 1 traversed to MDD in year 2. Becoming depressed was associated with lower FIM (Functional</p>

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effectiveness of Tx)
		<p><b>Mechanism/type of injury:</b>  <b>Area of Brain injured:</b></p>		<p>Independence measure) motor and cognitive scores, poor social support, substance abuse, and pre-injury mental health issues. Predictors of change differed according to symptom onset. Supports long-term monitoring for depression...</p>
<p><b>Author:</b>  <b>Spitz 2012</b> <sup>29</sup>  <b>Country, Setting:</b>  Australia, academic medical center  <b>Time from Injury:</b>  Mean=19.29 days post-injury    <b>Length of Follow-up:</b> NR    <b>Depression Scale/tool:</b>  Hospital Anxiety and Depression Scale (HADS-A and -D)</p>	<p><b>Inclusion Criteria:</b>  16-80 yoa, no previous TBI or other neurologic disorder, sufficient cognitive ability to undergo neuropsychological assessment  <b>Exclusion Criteria:</b> NR</p>	<p><b>Group(s)</b>    N Screened: NR  N eligible: NR  N included:97  N completed:    <b>Depression:</b>  <b>Prior to injury:</b>  # NR but not excluded  <b>At time of injury:</b>  NR but not excluded    <b>Other pre-existing psychiatric conditions:</b>  NR  <b>Age:</b>  Mean=35.83±15.79 (range 16-76)    <b>Severity of TBI:</b>  Mean GCS 8.41    <b>Mechanism/type of injury:</b>  NR</p>	<p><b>TBI:</b>  Days of PTA (severe&gt;7 days)  <b>Depression:</b>  HADS-D    <b>Other tests:</b>  Multiple cognitive tests, including sentence completion  Coping Scale for Adults</p>	<p><b>Purpose of study was to assess cognitive function and coping skills after TBI and their relationship with emotion.</b>    <b>Patients with TBI performed more poorly on all cognitive tests than normative samples. However, cognitive processing and HADS scores did not differ significantly by injury severity. Poorer cognitive performance (on tests of memory, executive functions, and attention and info processing) were associated with greater levels of depression and anxiety. Use of adaptive coping strategies moderated the relation between the</b></p>

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effectiveness of Tx)
		Area of Brain injured: NR		Hayling A (a measure of information processing speed) and depression (for individuals with slow information processing).
<p><b>Author:</b> Cernich <sup>20</sup></p> <p><b>Country, Setting:</b> US, government (VA) and academic medical centers</p> <p><b>Time from Injury:</b> NR</p> <p><b>Length of Follow-up:</b> NR</p> <p><b>Depression Scale/tool:</b> Brief screen</p>	<p><b>Inclusion Criteria:</b> OEF/OIF era veterans who screened positive for TBI nad whose charts included 3 mental health screens (PTSD, depression, alcohol abuse)</p> <p><b>Exclusion Criteria:</b></p>	<p><b>Group(s)</b></p> <p>N Screened:423 (charts) N eligible:402 N included:402 N completed:402</p> <p><b>Depression:</b> Prior to injury: NR At time of injury: NR</p> <p><b>Other pre-existing psychiatric conditions:</b> NR</p> <p><b>Age:</b> ~33 yoa</p> <p><b>Severity of TBI:</b> Mild to moderate <b>Mechanism/type of injury:</b> (most to least common): blast injury, motor vehicle accident, fall, wound above shoulder but below head...</p> <p><b>Area of Brain injured:</b> NR</p>	<p><b>TBI:</b> Chart report VA 4-question screener</p> <p><b>Depression:</b> Brief screen?</p>	<p>Of those who screened positive for TBI, 42% screened positive for depression. Those who screened positive for depression were significantly more likely to screen positive for cognitive symptoms, such as poor concentration, forgetfulness, difficulty making decisions, slowed thinking, fatigue and sleep difficulties (as well as headaches and appetite loss) than those who screened negative for depression. They concluded that soldiers who continue to present with symptomatic complaints after TBI should be considered for co-occurring disorders...</p>

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effectiveness of Tx)
KQ2. When should patients who suffer traumatic brain injury be screened for depression, with what tools, and in what setting?				
<p>Author: Cook, 2011 <sup>17</sup></p> <p>Country, Setting: US, Level 1 trauma center and multisite primary care settings</p> <p>Enrollment Period: NR</p> <p>Design: Retrospective differential item functioning (DIF) analysis of data from 2 previous studies, one of primary care patients and one of TBI patients</p> <p>Time from Injury: Immediate up to 1 year</p> <p>Length of Follow-up: 1 year</p> <p>Depression Scale/tool: PHQ-9</p>	<p>Inclusion Criteria: TBI patients: admission to Harborview Medical Center, with TBI and radiologic evidence of acute, traumatically induced brain abnormality or GCS score&lt;13 (lowest score within 24 hours after admission or 1<sup>st</sup> after withdrawal of paralytic agents), age≥18, English-speaking.</p> <p>Exclusion Criteria: TBI patients: uncomplicated mild TBI (GCS 13-15 and no radiologic abnormality), homelessness, no contact info, incarceration, and schizophrenia</p> <p>TBI Definition: GCS&lt;13 or radiologic evidence</p>	<p>Group(s)</p> <p>N Screened: N eligible:</p> <p>N included:3000 primary care pts. and 365 TBI patients N completed: same</p> <p>Depression: Prior to injury: NR At time of injury: NR</p> <p>Other pre-existing psychiatric conditions: NR Age: TBI: 43±17.7 Primary Care: 46±17.2</p> <p>Severity of TBI: NR Mechanism/type of injury: NR Area of Brain injured: NR</p>	<p>Depression: PHQ-9 depression scale criteria Other co-morbidities: NR HRQOL or functional status: NR</p>	<p>The aim of this study was to assess whether any items of the PHQ-9 function differently in persons with TBI than in persons from a primary care sample in a way that would result in over-diagnosis of depression in TBI patients</p> <p>The results were that no PHQ-9 item demonstrated statistically significant or meaningful DIF attributable to TBI. Sensitivity analysis failed to show that the cumulative effects of non-significant DIF resulted in systematic inflation of PHQ-9 total scores. Thus the PHQ-9 is a valid screener of major depressive disorder in people with complicated mild to severe TB and that all symptoms can be counted toward a dx of major depressive disorder, without concern regarding over-diagnosis or unnecessary tx.</p>
<p>Author: Matthews, 2011 <sup>12</sup></p> <p>Country, Setting:</p>	<p>Inclusion Criteria: Experimental group: dx of major depression (MDD),</p>	<p>Group(s)</p> <p>N Screened:NR</p>	<p>Depression:  Other co-morbidities:</p>	<p>Aim of study was to use diffusion tensor imaging (DTI) and fMRI to examine</p>

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effectiveness of Tx)
<p>US, San Diego VAMC Outpatient Mood clinic</p> <p>Enrollment Period: NR</p> <p>Design: Cross-sectional multimodal neuroimaging study</p> <p>Time from Injury: 2.8 ±1 yr vs. 3.3±1.1 yrs for controls</p> <p>Length of Follow-up: NA</p> <p>Depression Scale/tool: Semi-structured interview based on DSM-IV, Beck Depression Inventory, PHQ-15</p>	<p>prior blast exposure (blast injury) resulting in loss or alteration of consciousness at least 20 minutes</p> <p>Control group: no prior dx of MDD but had blast exposure</p> <p>Exclusion Criteria: Lifetime hx of ADHD, psychotic, bipolar, or chronic pain disorder; active medical problems, claustrophobia, suicidal ideation; alcohol/substance abuse or dependence within 30 days of the study</p> <p>TBI Definition: DVBIC TBI screening tool - blast injury and loss or alteration of consciousness ≥20 minutes</p>	<p>N eligible:NR N included: NR N completed: 11 per group</p> <p>Depression: Prior to injury: None</p> <p>At time of injury: none</p> <p>Other pre-existing psychiatric conditions: (excluded)</p> <p>Age: 26.8 (22-45) vs. controls: 30.3 (22-47)</p> <p>Severity of TBI: NR</p> <p>Mechanism/type of injury: Blast injury</p> <p>Area of Brain injured: NR</p>	<p>PTSD in 10/11 of MDD participants and 9/11 non-MDD participants Panic Disorder (6/11 and 4/11 resp.)</p> <p>HRQOL or functional status: NR</p>	<p>the structural and functional neural correlates of MDD in Iraq combat vets with self-reported history of blast-related concussion.</p> <p>MDD participants showed greater activity during fear matching trials in the amygdala and other emotion processing areas, lower activity in emotion control areas (e.g., dorsolateral prefrontal cortex and lower fractional anisotropy (FA) in several white matter tracts, including the superior longitudinal fasciculus (SLF). Greater MDD symptom severity was negatively correlated with FA in the SLF. Results suggest biological basis for MDD in those with blast-related concussion.</p> <p>Study does not show that blast injury caused either the lesions or MDD</p>
<p><b>Author:</b> Kontos 2012<sup>24</sup></p> <p><b>Country, Setting:</b> US academic medical center</p> <p><b>Design:</b></p>	<p><b>Inclusion Criteria:</b> Sports-related concussion diagnosed by a sports-medicine professional</p> <p><b>Exclusion Criteria:</b> History of treatment for</p>	<p><b>Group(s)</b></p> <p>N Screened: NR N eligible: NR N included: 75 N completed: 75</p>	<p><b>TBI:</b> n/a</p> <p><b>Depression:</b> BDI-II&gt;20 (moderate or greater)</p> <p><b>Concussion:</b> “a complex pathophysiological process affecting the brain, induced</p>	<p><b>Athletes with concussions exhibited significantly higher (within subject) levels of depression from baseline at 2 (p&lt;0.001), 7 (p=0.006), and 14 days</b></p>

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effectiveness of Tx)
<p>2-year prospective study on concussion and post-injury depression in the 2 weeks following injury</p> <p>Time from Injury: 2-14 days</p> <p>Length of Follow-up: 14 days</p> <p>Depression Scale/tool: Beck Depression Inventory II</p>	<p>substance abuse, psychiatric disorder, special education, years repeated in school, speech problems, and current baseline score of 20 or greater on the Beck Depression Inventory II</p>	<p><b>Depression:</b> Prior to injury: None At time of injury: None</p> <p><b>Other pre-existing psychiatric conditions:</b> NR</p> <p><b>Age:</b> 54 high school (mean age 15.74) and 21 college (19.68) athletes</p> <p><b>Severity of TBI:</b> n/a</p> <p><b>Mechanism/type of injury:</b> Concussion</p> <p><b>Area of Brain injured:</b></p>	<p>by traumatic biomechanical forces.”</p> <p>Neurocognitive changes assessed using the ImPACT computerized neurocognitive test battery.</p>	<p>(p=0.04) post-concussion.</p> <p>Verbal memory was significantly worse at 2 days post-concussion, cf. baseline (p=0.03)</p> <p>Visual memory was significantly lower at 2 days (p=0.01) and 14 days (p=0.001).</p> <p>Reaction time was significantly slower at 2 days (p=0.001) and 14 days (p=0.001).</p> <p>No differences in motor processing speed.</p> <p>No difference between males and females except for visual memory.</p> <p><b>Depression scores correlated with neurocognitive decrements in reaction time and visual memory. Somatic depression (e.g., tiredness) was more salient with respect to decrements in neurocognitive performance</b></p> <p>“Mood assessments after concussion are warranted to help monitor and enhance recovery.”</p>

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effectiveness of Tx)
KQ3. Among individuals with TBI and depression, what is the prevalence of concomitant psychiatric/behavioral conditions, including anxiety disorders, post-traumatic stress disorder (PTSD), substance abuse, and major psychiatric disorders?				
See articles under other KQ				
Key Questions 4-6 Treatment				
<p>Author: Schwandt et al., 2010 <sup>7</sup></p> <p>Country, Setting: Canada, Academic rehabilitation center (referrals from outpatient clinic)</p> <p>Enrollment Period: NR</p> <p>Design: Pre-post single group 12-week aerobic program with varying activities, depending on physical limitations. Training intensity was defined by rate of perceived exertion of 5-6 on Borg scale and heart rate 60-75% of age-predicted max. Training intensity maintained at 5-10W below baseline peak</p> <p>Time from Injury: &gt;11 months (11 mos-7.2 yrs)</p> <p>Length of Follow-up:</p>	<p>Inclusion Criteria: 18-55 yrs &gt;6 months since TBI Depression symptoms per MD report Able to communicate and follow instructions in English</p> <p>Exclusion Criteria: Substance abuse Psychiatric dx other than depression Suicidal ideation Medical conditions that would contraindicate participation Musculoskeletal or cognitive impairments</p> <p>TBI Definition: NR</p>	<p>Group(s) Patients with TBI</p> <p>N Screened:28 N eligible:16 N included:5 N completed:4</p> <p>Depression: Prior to injury: At time of injury:</p> <p>Other pre-existing psychiatric conditions: Excluded</p> <p>Age: 19-48 yrs (mean 29)</p> <p>Severity of TBI: Mechanism/type of injury:</p> <p>Area of Brain injured: Varied with patient</p>	<p>Depression: Baseline HAMD scores (10-13: mild; 14-17: mild to moderate; 18-25: moderate to severe; &gt;25: severe):</p> <p>Other co-morbidities: NR</p> <p>HRQOL or functional status: NR</p>	<p>Depression: Baseline HAM-D scores 19-27 (all were taking medication) Post: decreases ranged from 9 to 16 Depression decreased from moderate to severe and severe to mild to moderate and no symptoms</p> <p>Fitness: Change in peak power output indicated improved aerobic fitness, Decreased heart rate in ¾ participants, Borg scores (5-10 →3-7)</p> <p>Rosenberg Self-Esteem Scale: (10-19 pre to 17-25 post) Frequency of attendance: 78%</p> <p>Ability to complete exercise: No adverse effects</p> <p>9-question survey: indicated</p>

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effectiveness of Tx)
<p>12 weeks (end of program)</p> <p>Depression Scale/tool: HAM-D</p>				<p>satisfaction with program; challenging but achievable.</p>
<p>Author: Topolovec-Vranic, 2010 <sup>6</sup></p> <p>Country, Setting: Canada, Outpatient specialty clinic</p> <p>Enrollment Period: 12 mos.</p> <p>Design: Pre-post single group, 6-week internet-delivered CBT program</p> <p>Time from Injury: Mean 2.1 years, (0.1-7.3)</p> <p>Length of Follow-up: 12 months</p> <p>Depression Scale/tool: CES-D, PHQ-9</p>	<p>Inclusion Criteria: Age <math>\geq</math> 16 Dx of mild or moderate TBI (Glasgow Coma Score <math>\geq</math> 9 following injury) English fluency Score <math>\geq</math> 12 on PHQ-9 Regular access to internet, availability for weekly phone calls Originally, fewer than 5 years since TBI</p> <p>Exclusion Criteria: Pre-existing psychopathology (prior to injury), refusal to participate</p> <p>TBI Definition: Based on Glasgow Coma Score</p>	<p>Group(s) Single</p> <p>N Screened:391 N eligible:29 (excluded 88 refusers) N included:21 N completed:13 (16 completed at least 1 assessment; 9 completed 12-month follow-up)</p> <p>Depression: Prior to injury: (exclusion criterion) At time of injury: (exclusion criterion)</p> <p>Other pre-existing psychiatric conditions: (exclusion criterion)</p> <p>Age: Mean 42.5 (19.3-72.3) Severity of TBI: GCS 13-15: 43% GCS &lt;13: 29% NA: 29%</p> <p>Mechanism/type of injury: NR</p>	<p>Depression: Mean CES-D score at baseline for all 21 enrolled was 31.9<math>\pm</math>1.7 Mean PHQ-9 score at baseline for all enrolled was 17.4<math>\pm</math>0.9 Mean CES-D score for completers was 30.7<math>\pm</math>2.3</p> <p>Other co-morbidities: NR HRQOL or functional status: NR</p>	<p>CES-D scores decreased by 1.03 pts for each week of the intervention completed (p&lt;0.0001). At the 12-month followup, mean CES-D score in the 9 participants assessed was 20.6<math>\pm</math>4.7</p> <p>At the 12-month followup, mean PHQ-9 score was 11.6<math>\pm</math>2.4, significantly lower than at baseline (p&lt;0.05), and 4 of the completers had scores&lt;12, indicating symptoms had declined to &lt;major depression criteria. Completion rates were not predicted by any demographic or injury variables assessed.</p> <p>Main challenge reported by those using the site was that it was difficult to read, remember, and sometimes understand</p>

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effectiveness of Tx)
<p>Author: Rapoport, 2010 <sup>10</sup> Country, Setting: Canada, academic TBI clinic Same population as Lanctot et al., 2010 (and Rapoport 2008?).</p> <p>Enrollment Period: Weeks 10-16 of active, open-label treatment</p> <p>Design: Randomized double-blind, placebo-controlled trial following open-label trial. Ten participants were randomly assigned to continue the dose of citalopram they were taking at the end of the open-label trial, and 11 were assigned to taper off over 2 weeks and continue on placebo. Capsules were blinded via overencapsulation.</p> <p>Time from Injury: 3.3±3.2 mos plus 10-16 weeks; only 1/3 of patients assigned at 10 weeks</p> <p>Length of Follow-up:</p>	<p>Inclusion Criteria: Participation in open-label citalopram study and achievement of remission</p> <p>Exclusion Criteria: NR (See Lanctot)</p> <p>TBI Definition: According to Lanctot, mild TBI was defined as loss of consciousness at time of injury of 20 minutes or less, an initial GCS score of 13–15, and post-traumatic amnesia (PTA) of less than 24 hours. Moderate to severe TBI had a GCS score of less than 13, a PTA greater than 24 hours, or an abnormal CT image</p>	<p>Area of Brain injured: NR</p> <p>Group(s)</p> <p>N Screened: NR N eligible: NR N included: 21 N completed: 18</p> <p>Depression: Prior to injury: Excluded At time of injury:</p> <p>Other pre-existing psychiatric conditions: Excluded Age: Mean = 47.67±19.9, range 21-85 Severity of TBI: Mild in 16 participants (76.2%) and moderate in 4 (19.0%); 1 participant had a GCS rating &lt;9 due to hemorrhage from a mesenteric tear and sedation but he was recovering.</p> <p>Mechanism/type of injury: NR</p>	<p>Depression:</p> <p>Other co-morbidities:</p> <p>HRQOL or functional status:</p>	<p>18 of 21 participants completed the study. (reasons for dropping out were side effects [1 participant, diarrhea] or desire to stop taking medication)</p> <p>Mean compliance at the first postrandomization visit (via pill counts) was 91.9% for 16 participants (76.2%). 14 of 16 participants had a compliance of 85% or more. At the final visit, pill counts were available for 18 participants (85.7%) and showed a mean compliance of 94.8%, with all having a compliance of 85% or greater.</p> <p>At baseline, groups differed only in education level and MMSE score (citalopram group had a slightly higher score 28.8±1.0 vs. 25.9±3.9, p=0.036)</p> <p>Relapse was seen in 11 of 21 (52.4%) of participants. Relapse rates did not differ between groups.</p>

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effectiveness of Tx)
<p>40 weeks or until relapse</p> <p>Depression Scale/tool: Hamilton Depression Rating Scale</p>		<p>Area of Brain injured: NR</p>		<p>All participants described at least one AE.</p> <p>Subgroup analysis to try to identify predictors of relapse found no effect of age, sex, employment status or overall baseline or post-treatment HDRS scores. 2 HDRS variables did predict higher risk for relapse: more than mild psychic anxiety and agitation.</p> <p>Thus drug treatment did not decrease risk for relapse...</p>
<p>Author: Lancot 2010 <sup>13</sup></p> <p>Country, Setting: Canada, academic TBI clinic</p> <p>Enrollment Period: Patients recruited from larger cohort of consecutive referrals from 2003-2007</p> <p>Design: Open-label study of citalopram (20mg/d)</p> <p>Time from Injury: 3.3±3.2 mos</p> <p>Length of Follow-up: 6 wks</p> <p>Depression Scale/tool: HAM-D and Depression</p>	<p>Inclusion Criteria: Mild to moderate TBI and dx of major depressive episode.</p> <p>Exclusion Criteria: Individuals with prior focal brain disease (e.g., stroke, tumor), significant acute medical illness, alcohol abuse, CT abnormalities inconsistent with TBI, current antidepressant tx, contraindications to citalopram, or premorbid dx of schizophrenia, BPD, or dementia</p> <p>TBI Definition: Mild TBI was defined as loss of consciousness at time of</p>	<p>Group(s)</p> <p>N Screened: NR N eligible: 560 N included:NR N completed:90</p> <p>Depression: Prior to injury: Excl? At time of injury:</p> <p>Other pre-existing psychiatric conditions: Excluded</p> <p>Age: 39.9±18.0</p> <p>Severity of TBI:</p>	<p>Depression: Depression module of the SCID Axis I disorders</p> <p>Other co-morbidities: 46.7% had focal injuries, 2.2% had atrophy on CT scan HRQOL or functional status: NR</p>	<p>Aim of the study was to assess whether certain small nuclear polymorphisms (SNPs) in 65HTTLPR (serotonin transporter), 5HT1A C..., 5HT2 T-..., MTHFR, brain-derived neurotropic factor (BDNF), val66met, and tryptophan hydroxylase-2(TPH2)... genes associated with serotonin metabolism affected response to treatment (efficacy and adverse events). MTHFR and BDNF SNPs predicted greater tx response (<math>R^2=0.098</math>, <math>p=0.013</math>), and the 5HTTLPR predicted greater occurrence of AEs</p>

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effectiveness of Tx)
module of the SCID Axis I disorders	injury of 20 minutes or less, an initial GCS score of 13–15, and post-traumatic amnesia (PTA) of less than 24 hours. Moderate to severe TBI had a GCS score of less than 13, a PTA greater than 24 hours, or an abnormal CT image	Majority met criteria for mild to moderate TBI Mechanism/type of injury:  Area of Brain injured:		(R2=0.069, p=0.020). Thus SNPs might help predict short term response to and tolerability of citalopram in patients with MDE following TBI.
<p><b>Author:</b> Nelson 2012 <sup>26</sup></p> <p><b>Country, Setting:</b> US, private clinic?</p> <p><b>Time from Injury:</b> NR</p> <p><b>Length of Follow-up:</b> NR, at least 7-11 weeks from first treatment</p> <p><b>Depression Scale/tool:</b> Neurobehavioral Functioning Inventory (NFI) and PTSD Symptom Scale (PSS)</p>	<p><b>Inclusion Criteria:</b> Persistent symptoms of PTSD and TBI, treatment resistance</p> <p><b>Exclusion Criteria:</b> Seizure disorders, sleep apnea, substance abuse</p>	<p><b>Group(s)</b></p> <p>N Screened: NR N eligible: NR N included: 7 N completed: 5</p> <p><b>Depression:</b> Prior to injury: NR At time of injury: NR</p> <p><b>Other pre-existing psychiatric conditions:</b> Age: 23-42</p> <p>Severity of TBI: NR Mechanism/type of injury: 4 blast injuries, rest NR Area of Brain injured: NR</p>	<p><b>TBI: NR</b> <b>Depression: NR</b></p>	<p><b>Study would be excluded based on sample size of less than 50</b></p> <p><b>Purpose of study was to assess efficacy and safety of Flexyx Neurotherapy System, which delivers electromagnetic pulses.</b></p> <p><b>The treatment regimen resulted in a significant decrease in depressive symptoms, based on responses to the NFI. (pre to post-treatment, p&lt;0.02, linear trend with increasing number of sessions, p&lt;0.001).</b></p>
<p>Of minor relevance to KQ5 (not specific to individuals with depression following TBI): FDA (<a href="http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm271273.htm">http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm271273.htm</a>) MedWatch warning on taking sertraline with other agents that affect serotonin: Co-administration of Zoloft with other drugs which enhance the effects of serotonergic neurotransmission, such as tryptophan, fenfluramine, fentanyl, 5-HT agonists, or the herbal medicine St. John's Wort (hypericum perforatum) should be undertaken with caution and avoided whenever possible due to the potential for</p>				

<b>Study Description</b>	<b>Inclusion/Exclusion Criteria</b>	<b>Population and Baseline Characteristics</b>	<b>Study Definitions</b>	<b>Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effectiveness of Tx)</b>
<p>pharmacodynamic interaction.            FDA MedWatch Precaution on lab tests: False-positive urine immunoassay screening tests for benzodiazepines have been reported in patients taking sertraline. This is due to lack of specificity of the screening tests. False positive test results may be expected for several days following discontinuation of sertraline therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish sertraline from benzodiazepines.</p>				

Legend: TBI=Traumatic Brain Injury; TBIMS= Traumatic Brain Injury Model System; PTA= Posttraumatic Amnesia; DASS21= Depression, Anxiety, and Stress Scales 21; IQR= Interquartile Range; SNPs=Small Nuclear Polymorphisms; TPH2=Tryptophan Hydroxylase-2; DTI=Diffusion Tensor Imaging; SLF=Superior Longitudinal Fasciculus; DIF=Differential Item Functioning; DDNOS=Dissociative Disorder Not Otherwise Specified; FA=Fractional Anisotropy; GOSE=Extended Glasgow Outcome Scale; MRI=Magnetic Resonance Imaging

Bold= New studies from the re-assessment

## Appendix C. Questionnaire Matrix

### Surveillance and Identification of Triggers for Updating Systematic Reviews for the EHC Program

**Title: Traumatic Brain Injury and Depression**

The table below provides summaries of the evidence for key questions for which studies were identified.

<b>Conclusions From CER Executive Summary</b>	<b>Is this conclusion almost certainly still supported by the evidence?</b>	<b>Has there been new evidence that may change this conclusion?</b>	<b>Do Not Know</b>
<b>Key Question 1: What is the prevalence of depression after traumatic brain injury, and does the area of the brain injured, the severity of the injury, the mechanism or context of injury, or time to recognition of the traumatic brain injury or other patient factors influence the probability of developing clinical depression?</b>			
<p>The prevalence of depression after traumatic brain injury is approximately 30 percent across multiple time points up to and beyond a year. Based on structured clinical interviews, on average 27 percent of TBI patients met criteria for depression 3 to 6 months from injury; 32 percent at 6 to 12 months; and 33 percent beyond 12 months. Higher prevalence is reported in many study populations. No strong predictors are available to select a screening window or to advise TBI patients or their providers about risk of depression.</p>	<input type="checkbox"/>	<p>New Evidence:</p>	<input type="checkbox"/>
<b>Key Question 2: When should patients who suffer traumatic brain injury be screened for depression, with what tools, and in what setting?</b>			

<b>Conclusions From CER Executive Summary</b>	<b>Is this conclusion almost certainly still supported by the evidence?</b>	<b>Has there been new evidence that may change this conclusion?</b>	<b>Do Not Know</b>
<p>Prevalence of depression is high at multiple time points after TBI. No evidence provides a basis for targeting screening to one timeframe over another.</p> <p>Likewise, the literature is insufficient to determine whether tools for detecting depression that have been validated in other populations can accurately identify depression in individuals with TBIs. Nor does the literature support any one tool over the others.</p>	<input type="checkbox"/>	<p>New Evidence:</p>	<input type="checkbox"/>
<p><b>Key Question 3: Among individuals with TBI and depression, what is the prevalence of concomitant psychiatric/behavioral conditions, including anxiety disorders, post-traumatic stress disorder (PTSD), substance abuse, and major psychiatric disorders?</b></p>			
<p>When conditions were reported individually, anxiety disorder was most prevalent and affected from 31 to 61 percent of study participants in four papers. PTSD, a major anxiety disorder, was observed in 37 percent of depressed patients and in no patients without depression, and panic disorder was seen in 15 percent of patients with major depression, but not measured in those without depression. Consideration of potential for coexisting psychiatric conditions is warranted.</p>	<input type="checkbox"/>	<p>New Evidence:</p>	<input type="checkbox"/>
<p><b>Key Question 4: What are the outcomes (short and long term, including harm) of treatment for depression among traumatic brain injury patients utilizing psychotropic medications, individual/group psychotherapy, neuropsychological rehabilitation, community-based rehabilitation, complementary and alternative medicine, neuromodulation therapies, and other therapies?</b></p>			
<p>Only two publications addressed treatment for individuals diagnosed with depression after a traumatic brain injury: Both were studies of</p>	<input type="checkbox"/>	<p>New Evidence:</p>	<input type="checkbox"/>

<b>Conclusions From CER Executive Summary</b>	<b>Is this conclusion almost certainly still supported by the evidence?</b>	<b>Has there been new evidence that may change this conclusion?</b>	<b>Do Not Know</b>
antidepressant efficacy (one a controlled trial of sertraline and one an open-label trial of citalopram). The sertraline trial showed no significant effect compared with placebo, and the citalopram study did not show improvement in a majority of participants.			
<b>Key Question 5: Where head-to-head comparisons are available, which treatment modalities are equivalent or superior with respect to benefits, short- and long-term risks, quality of life, or costs of care?</b>			
No head-to-head trials were identified that compared the effectiveness of two or more modalities for treating depression that follows TBI. Such studies are needed.	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
<b>Key Question 6: Are the short- and long-term outcomes of treatment for depression after TBI modified by individual characteristics, such as age, preexisting mental health status or medical conditions, functional status, and social support?</b>			
No studies were identified that assessed the impact of demographic or other potentially modifying characteristics on treatment effectiveness. Future research needs to address this issue.	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
<b>Are there new data that could inform the key questions that might not be addressed in the conclusions?</b>			

<b>Conclusions From CER Executive Summary</b>	<b>Is this conclusion almost certainly still supported by the evidence?</b>	<b>Has there been new evidence that may change this conclusion?</b>	<b>Do Not Know</b>