

# ***AHRQ Systematic Review Surveillance Program***

**CER #25:** Traumatic Brain Injury and Depression

**Original Release Date:** April 2011

**Surveillance Report:** March 2012

**Surveillance Report:** November 2012

**Surveillance Report:** August 2014

**Surveillance Report:** August 2016

## **Summary of Key Findings from Surveillance Report:**

- Key Question 1: Original systematic review conclusions are likely current.
- Key Question 2: Original systematic review conclusions are likely current.
- Key Question 3: Original systematic review conclusions are likely current.
- Key Question 4: Original systematic review findings of no evidence of non-pharmacological interventions may not be current. Current and previous surveillance reports identified studies examining Cognitive Behavioral Therapy, exercise, and electroencephalography (EEG)-based therapies.
- Key Question 5: Original systematic review conclusions are likely current.
- Key Question 6: Original systematic review conclusions are likely current.

**Signal Assessment:** The signals examined in this surveillance assessment suggest that some conclusions in the original systematic review may not be current.

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**Conflict of Interest:**

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

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## Introduction

The purpose of the surveillance process for the EPC Program is to determine whether the conclusions of a systematic review are current. The surveillance process examines the conclusions to the key questions as written, and does not evaluate the currency of the original scope (i.e., key questions, included interventions). Approximately 25 systematic reviews are selected for surveillance annually based on popularity, use in obtaining continuing medical education certificates, potential impact for changing the field, and use in clinical practice guidelines.

Comparative Effectiveness Review (CER) #25, titled *Traumatic Brain Injury and Depression*, was published in April 2011.<sup>1</sup> Previous surveillance assessments were conducted in March 2012, November 2012,<sup>2</sup> and August 2014.<sup>3</sup>

The key questions for the original CER are as follows:

- **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?
- **Key Question 2.** When should patients who suffer traumatic brain injury be screened for depression, with what tools, and in what setting?
- **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?
- **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?
- **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?
- **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?

Our surveillance assessment began in March 2016. We conducted an electronic search for literature published since the end date of the most recent surveillance report search date. After completing a scan of this literature to identify evidence potentially related to the key questions in this systematic review, we contacted experts involved in the original systematic review to request their opinions as to whether the conclusions had changed.

## Methods

### Prior Surveillance

A surveillance report for the original systematic review was released in August 2014, and included a search for relevant literature published between November 2012 and January 2014,

expert opinion, and a search of U.S. Food and Drug Administration (FDA). The findings from this report are included in our assessment.

### **Literature Searches**

We conducted a literature search of PubMed covering January 2014 to March 2016 using the identical search strategy used for the original review<sup>1</sup> and searching for studies published since the end date of the most recent surveillance search.

The search was conducted to assess the currency of conclusions using journals from among the top 10 journals from relevant specialty subject areas and among those most highly represented among the references for the original review. We included the journals searched in the previous surveillance assessment. The included journals were five high-profile general medical interest journals (Annals of Internal Medicine, The BMJ, JAMA, Lancet, and New England Journal of Medicine) and five specialty journals (American Journal of Psychiatry, Archives of Physical Medical Rehabilitation, Brain Injury, Journal of Head Trauma Rehabilitation, and Journal of Neuropsychiatry and Clinical Neuroscience). The search strategy is reported in Appendix A.

### **Study Selection**

Using the same inclusion and exclusion criteria as the original systematic review (see Appendix B), one investigator reviewed the titles and abstracts of the 10 high-impact journal search results (Appendix C). We included systematic reviews and meta-analyses, whether or not they were included (as a study design) in the original systematic review. For systematic reviews and meta-analyses, we considered findings only if all included studies met criteria that a) all studies were not included or excluded from the original systematic review, b) all studies were not included in a prior surveillance report (if applicable), and c) all studies met inclusion criteria for the original systematic review. Reviews for which one or more study did not meet our criteria were used to identify potentially relevant primary research. Reviews of systematic reviews were not included.

### **Expert Opinion**

We shared the conclusions of the original systematic review and most recent surveillance assessment, findings from the literature analysis, and the newly identified studies with six experts in the field (three original peer reviewers and three local experts) to request their assessment of the currency of the original review conclusions and their recommendations of any relevant new studies. Two subject matter experts responded to our request. Appendix D shows the form experts were asked to complete.

### **FDA Black Box Warnings**

We searched the FDA MedWatch online database website for black box warnings relevant to the key questions in this systematic review.

### **Check for Qualitative Signals**

The authors of the original systematic review conducted qualitative synthesis of data on prevalence, harms and outcomes of depression after Traumatic Brain Injury (TBI). We compared the conclusions of the included abstracts to the conclusions of the original systematic

review and surveillance reports, and assessed expert opinions to identify qualitative signals about the currency of conclusions.

## Compilation of Findings and Conclusions

For this assessment we constructed a summary table (Appendix E) that includes the key questions and conclusions from the original systematic review, findings of the new literature search, FDA black box warnings and the expert assessments that pertained to each key question. Because we did not find any FDA black box warnings relevant to the key questions in this systematic review, we did not include a column for this in the summary table. We categorized the currency of conclusions using a 3-category scheme:

- Original conclusion is still valid and this portion of the systematic review is likely current
- Original conclusion is possibly out of date and this portion of the systematic review may not be current
- Original conclusion is out of date.

We considered the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the systematic review conclusion as still valid, we classified the systematic review conclusion as likely current.
- If we found some new evidence that might change the systematic review conclusion, and /or a minority of responding experts assessed the systematic review conclusion as having new evidence that might change the conclusion, then we classified the systematic review conclusion as possibly not current.
- If we found new evidence that rendered the systematic review conclusion out of date or no longer applicable, we classified the systematic review 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.

## Signal Assessment for Currency of the Systematic Review

We used the following considerations in our assessment of currency of the systematic review:

- **Strong signal:** A report is considered to have a strong signal if new evidence is identified that clearly renders conclusions from the original systematic review out of date, such as the addition or removal of a drug or device from the market or a new FDA boxed warning.
- **Medium signal:** A report is considered to have a medium signal when new evidence is identified which may change the conclusions from the original systematic review. This may occur when abstract review and expert assessment indicates that some conclusions from the original systematic review may not be current, or when it is unclear from abstract review how new evidence may impact the findings from the original systematic review.
- **Weak signal:** A report is considered to have a weak signal if no new evidence is identified that would change the conclusions from the original systematic review. This may occur when no new evidence is identified, or when some new evidence is identified

but it is clear from abstract review and expert assessment that the new evidence is unlikely to change the conclusions of the original systematic review.

## **Results**

### **Prior Surveillance**

The most recent prior surveillance of the topic included two studies and consultation with two subject matter experts, and concluded that conclusions related to all key questions were likely current. However, a prior (March 2012) assessment identified an association between Citalopram and abnormal heart rhythm and a contraindication associated with sertraline and other agents affecting serotonin.

### **Literature Search**

The literature search identified 44 unique titles from the 10 selected high profile general medical and specialty journals (Appendix C). Upon abstract review, 39 studies were rejected because they did not meet the original systematic review inclusion criteria (see Appendix B). The remaining 5 studies<sup>4-8</sup> were examined for potential to change the results of the original systematic review.

### **FDA Black Box Warnings (or Class I Device Recalls and Withdrawals)**

We did not find any FDA black box warnings relevant to the key questions in this systematic review.

### **Expert Opinion**

We shared the conclusions of the original review with six experts in the field (three original peer reviewers and three local experts) to request their assessment of the currency of report conclusions and their recommendations of any relevant new studies. Two subject matter experts responded.

One expert felt that the original review conclusions were current. The second reviewer felt that conclusions associated with all key questions were no longer current, and suggested studies for Key Questions 3,<sup>9</sup> 4,<sup>10</sup> and 6.<sup>9</sup> One study (suggested for both Key Questions 1 and 6), was a cross-sectional examining individuals with TBI broadly, with no data specific to individuals with TBI and depression, and was excluded due to study design and population criteria.<sup>9</sup> The second study, suggested for Key Question 4, was a RCT examining manualized CBT for individuals with TBI and mild to moderate levels of hopelessness and/or suicidal ideation (n=17). Although participants were not explicitly diagnosed with depression, mean baseline Hospital Anxiety and Depression Scale scores (HADS) (treatment M=10.63 [2.67]; waitlist M=9.56 [3.09]) suggest that participants experienced mild-to-moderate depressive symptoms. There was a larger decrease in hopelessness (Beck Hopelessness Scale [BHS] scores) associated with CBT, as compared to waitlist control, with reductions sustained up to three months. There were no significant reduction in depressive symptoms, and a non-significant trend towards lower suicidal ideation associated with CBT<sup>10</sup> (see Appendix E).

### **Identifying Qualitative Signals**

Appendix E shows the original key questions, the conclusions of the original systematic review and the most recent surveillance report, the results of the literature search, expert opinion, and the assessment of the currency of the systematic review.



For Key Question 1, examining the prevalence of depression in individuals with TBI, all conclusions are likely current. We identified two studies examining the TBI Model Systems National Database (TBIMSN),<sup>5,7</sup> one which found that at 5 years post discharge, 7.5% of individuals with TBI experienced moderate or severe depressed mood, and that depression was the most common in individuals 40-49 years of age.<sup>5</sup> The second study examined individuals deployed to Afghanistan, and found that the association between deployment acquired TBI and past 30-day major depressive episode was significant at 3 months post deployment, but not at 9 months.<sup>7</sup> In addition, we identified one study which found that higher Patient Health Questionnaire-9 (PDQ-9) scores in Blacks and Hispanics as compared to Whites and Asian/Pacific Islanders. Studies identified in prior surveillance assessments examined prevalence (9), the effect of injury severity on risk of depression, prevalence by subpopulations (1), and imaging (7). None of the studies identified in prior surveillance assessments were determined to affect the currency of the original review.

For Key Question 2, examining screening and tools, all conclusions are likely current. We identified no studies relevant to the key question. Prior surveillance identified a study that found increased levels of depression at 2, 7, and 14 days post-concussion, concluding that early screening is warranted, and another study that found that no items on the PHQ-9 demonstrated statistically significant or meaningful differential item functioning attributable to TBI. None of the studies identified in prior surveillance assessments were determined to affect the currency of the original review.

For Key Question 3, examining comorbid conditions, all conclusions are likely current. We identified one RCT which found that 13 of 43 participants with TBI and a DSM IV-TR diagnosis of a depressive disorder or BDI-II score >20 met criteria for a DSM-IVTR anxiety disorder at baseline.<sup>4</sup> Prior surveillance identified one study which found higher rates of comorbid PTSD and panic disorder than reported in the original systematic review; however, the sample size was small (n=11).

For Key Question 4, examining the benefits and harms of treatment, the original review's findings of no evidence for non-pharmacological interventions is no longer current. We identified one study comparing a home based walking program to nutritional education, which found a significant reduction in depressive symptoms associated with the walking intervention,<sup>8</sup> and an expert suggested a small RCT examining CBT in individuals with TBI, experiencing hopelessness and/or suicidal ideation. The study found a significant reduction in hopelessness associated with CBT; however, there was no significant reduction in depressive symptoms or suicidal ideation.<sup>10</sup> Prior surveillance included studies examining aerobic exercise, internet based CBT, and an electroencephalography (EEG)-based therapy, as well as one study examining the effectiveness of citalopram. In addition, the March 2012 assessment identified FDA warnings for the combination of sertraline and other agents affecting serotonin, false positives for benzodiazepines associated with sertraline, a Health Canada warning of abnormal heart rhythms associated with citalopram, and a MHRA warning of increased risk of fractures associated with antidepressants. None of the studies identified in prior surveillance assessments were determined to affect the currency of the original review.

For Key Question 5, examining the comparative effectiveness of interventions, all conclusions are likely current. We identified one study that found no difference between Cognitive Behavioral Therapy (CBT) and supportive psychotherapy on remission and quality of life (QOL). No studies were identified in any of the prior surveillance assessments.

For Key question 6, examining potential moderators, all conclusions are likely current. We identified no studies relevant to the key question. Two studies in the March 2012 surveillance assessment examined citalopram, and found no association of gender, sex, education, and baseline/post-treatment Hamilton Depression Rating Scale (HDRS) scores on remission, but that agitation and psychic anxiety HDRS subscales were predictive of remission, and that certain small nuclear polymorphisms (SNPs) in genes associated with serotonin transport and metabolism predicted greater response to treatment and occurrence of adverse events. None of the studies identified in prior surveillance assessments were determined to affect the currency of the original review.

## **Signal Assessment**

The conclusions based on the results of the prior surveillance assessment, literature published since the original report, FDA black box warnings, and expert assessment is that:

- Key Question 1: Original systematic review conclusions are likely current.
- Key Question 2: Original systematic review conclusions are likely current.
- Key Question 3: Original systematic review conclusions are likely current.
- Key Question 4: Original systematic review findings of no evidence of non-pharmacological interventions may not be current. Current and previous surveillance reports identified studies examining Cognitive Behavioral Therapy, exercise, and electroencephalography (EEG)-based therapies.
- Key Question 5: Original systematic review conclusions are likely current.
- Key Question 6: Original systematic review conclusions are likely current.

The signal for this report is medium suggesting that the conclusions in the original systematic review may not be current.

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# **Appendices**

**Appendix A: Search Strategy**

**Appendix B: Inclusion and Exclusion Criteria from Original Systematic Review**

**Appendix C: Literature Search Results**

**Appendix D: Questionnaire Sent to Expert Reviewers**

**Appendix E: Summary Table**

## Appendix A. Search Strategy

Top Journals used for surveillance of this topic:

Annals of Internal Medicine  
 British Medical Journal  
 Journal of the American Medical Association  
 Lancet  
 New England Journal of Medicine  
 American Journal of Psychiatry  
 Archives of Physical Medicine and Rehabilitation  
 Brain Injury  
 Journal of Head Trauma and Rehabilitation  
 Journal of Neuropsychiatry and Clinical Neurosciences

MEDLINE via PubMed searched March 31, 2016

Original Search from previous Report	((((((((((((((((depressive[Title/Abstract]) OR depression[Title/Abstract]) OR depressed[Title/Abstract]) OR sadness[Title/Abstract]) OR sad[Title/Abstract]) OR hopelessness[Title/Abstract]) OR suicidal[Title/Abstract]) OR suicide[Title/Abstract]) OR mood [Title/Abstract])) OR (("Depressive Disorder"[Mesh] OR "Depression"[Mesh] OR "Mental Disorders"[Mesh:noexp])) AND (((((((((((depressive[Title/Abstract]) OR depression[Title/Abstract]) OR depressed[Title/Abstract]) OR sadness[Title/Abstract]) OR sad[Title/Abstract]) OR hopelessness[Title/Abstract]) OR suicidal[Title/Abstract]) OR suicide[Title/Abstract]) OR mood[Title/Abstract])) AND (((((((((((TBI[Title/Abstract]) OR head injuries[Title/Abstract]) OR head injury[Title/Abstract]) OR traumatic brain injury[Title/Abstract]) OR traumatic brain injuries[Title/Abstract]) OR neurotrauma[Title/Abstract]) OR diffuse axonal injury[Title/Abstract]) OR brain trauma[Title/Abstract]) OR head trauma[Title/Abstract])) OR (((((((("Brain Concussion"[Mesh] OR "Brain Injuries"[Mesh:noexp] OR "Brain Hemorrhage, Traumatic"[Mesh] OR "Epilepsy, Post-Traumatic"[Mesh] OR "Head Injuries, Closed"[Mesh] OR "Head Injuries, Penetrating"[Mesh] OR "Intracranial Hemorrhage, Traumatic"[Mesh] OR "Craniocerebral Trauma"[Mesh] OR "Diffuse Axonal Injury"[Mesh])) AND Humans[Mesh] AND English[lang])) NOT (((((((("Case Reports"[Publication Type] OR "Letter"[Publication Type] OR "Comment"[Publication Type] OR "Editorial"[Publication Type] OR "Practice Guideline"[Publication Type]) C-1)
AND	
Journal Limits	((((((((((("Annals of internal medicine"[Journal]) OR "British medical journal"[Journal]) OR "British medical journal (Clinical research ed.)"[Journal]) OR "BMJ (Clinical research ed.)"[Journal]) OR "Journal of the American Medical Association"[Journal]) OR "JAMA"[Journal]) OR "Lancet"[Journal]) OR "The New England journal of medicine"[Journal]) OR "The American journal of psychiatry"[Journal]) OR (Archives of physical medicine[Journal] AND rehabilitation[Journal])) OR Brain injury : [BI] OR (journal of head trauma[Journal] AND rehabilitation[Journal])) OR (journal of neuropsychiatry[Journal] AND clinical neurosciences[Journal]))
AND	
Date Limits	("2014/01/30"[Date - Entrez] : "3000"[Date - Entrez])
N=1 PMID 26327036	

## Appendix B. Inclusion and Exclusion Criteria from Original Systematic Review

Our inclusion/exclusion criteria were developed in consultation with the Technical Expert Panel (TEP). Criteria are summarized below.

\*Note: Original inclusion/exclusion criteria extracted from Effective Health Care Program, CER

Category	Criteria
Study population	Adults age $\geq 16$ years old
Study settings and geography	Developed nations: United States, Canada, United Kingdom, Western Europe, Japan, Australia, New Zealand, Israel, South America
Publication languages	English only
Admissible evidence (study design and other criteria)	<p><u>Admissible designs</u> Randomized controlled trials, cohorts with comparison, case-control, and case series (n<math>\geq</math>50)</p> <p><u>Other criteria</u> Original research studies that provide sufficient detail regarding methods and results to enable use and adjustment of the data and results Patient populations must include participants that have been diagnosed with depression following a traumatic brain injury received in adulthood Studies must address one or more of the following for depression after traumatic brain injury: Treatment modality Symptom management approach Short- and long-term outcomes and quality of life Relevant outcomes must be able to be abstracted from data presented in the papers</p>

#25, *Traumatic Brain Injury and Depression*, pps. 8-9.

We limited the review to studies published in developed countries to better approximate the United States health care system in terms of access to screening and treatment services. We did not have translation services available to us to review non-English papers, and our TEP agreed that the vast majority if not all of the relevant literature would be published in English. Furthermore, this review is intended to inform U.S. health care, and most research in this population is published in studies. Empirical evidence on the potential for bias created by excluding non-English studies also suggests little effect. All study designs except individual case reports were included in order to be inclusive and identify all possible prevalence, screening, and treatment studies. The decision to require at least 50 participants in each study was made in concert with our TEP, and resulted in the exclusion of only 36 studies, of which one was a randomized controlled trial. The adult trauma population is defined at the Level I trauma center as 16 years old or older. Short- and long-term outcomes in traumatic brain injury in children are pathologically distinct from the adult population. We chose to limit this study to the adult population of traumatic brain injury and outcomes associated with depression. In order to ascertain prevalence and to further assess potential modifiers of likelihood of being depressed, it was important that studies use an acceptable means of diagnosing depression. We accepted a structured clinical interview or any validated diagnostic tool, excluding for these questions any

studies that relied only on self-report of depressed status or that did not describe their approach to depression diagnosis.

Additional criteria:

In order to answer KQ1, studies had to provide some measure of prevalence. We excluded studies that did not provide prevalence data (e.g., for which only mean depression scores were available).

In order to answer KQ2, studies had to provide data that allowed prevalence to be assessed in accordance with a specific timeframe, setting, or tool (or some combination of these). Studies that did not provide any information about when depression screening took place relative to injury were excluded from the weighted average for depression prevalence calculations for specific time points.

In order to answer KQ3, we required that studies present data on comorbid psychiatric conditions within the depressed population separately from the nondepressed population, as our intent was not to measure these conditions in the general TBI population but to explain their specific relationship to depression.

This review focused on the prevalence of diagnosed depression in populations that had sustained a documented traumatic brain injury, and on the treatment of those populations. We excluded studies of individuals with penetrating head injuries because penetrating injury, such as gunshot wounds, create specific and severe tissue damage along the course of the injury as well as associated bleeding and inflammation. The mechanism of injury associated with blunt force trauma to the head more often leads to a diffuse pattern of injury that may affect the entirety of the brain. Although long-term outcomes may be similar in some penetrating head injury cases, our focus on the more global nature of blunt-force trauma and its consequences lead us to exclude studies of penetrating head injuries from this review.

## Appendix C. Literature Search Results

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## Appendix D. Questionnaire Sent to Expert Reviewers

# ***AHRQ Systematic Review Surveillance Program***

## **Reviewer Form**

**Title of Original Systematic Review:** Traumatic Brain Injury and Depression

[Link to Report](#)

**Most Recent Prior Surveillance Published:** August 2014

[Link to Surveillance Report](#)

**Name of Reviewer:** \_\_\_\_\_

### **Instructions:**

The Agency for Healthcare Research and Quality (AHRQ) Scientific Resource Center (SRC) periodically conducts surveillance of published AHRQ systematic reviews to assess the currency of review conclusions. The goal of this process is to identify signals that a report may be out of date. One part of this process includes soliciting expert review of our synthesis of recently published literature and previous surveillance assessments.

The original systematic review was published in April 2011. The original systematic review search dates went through November 2010. Previous surveillance was conducted in March 2010, November 2010, and August 2014, with the most recent search extending through January 2014. We conducted a bridged literature search of select high impact journals from January 2014 to January 2016 and identified evidence potentially related to the key questions of the original systematic review.

The table below highlights the conclusions from the original systematic review, the findings of prior surveillance assessments, and a summary of the relevant recently published literature. Abstracts from relevant literature are included at the end of the document. If you would like a list of our full search results, please let us know.

Please review the table and provide responses to the questions for each key question below. The primary goal of this review is to identify any important new studies, drugs, interventions, or devices you know of that we may have missed in our literature search and to understand if any new evidence exists which may alter the conclusions of the original systematic review.

### **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 of recognition of

the traumatic brain injury or other patient factors influence the probability of developing clinical depression?

**Prior Surveillance Assessment: August 2014**

- All conclusions are likely current.
  - Identified studies examined prevalence (two studies), gender prevalence, and imaging. No studies had the potential to change the conclusions of the original review.
  - Studies identified in March and November 2012 surveillance assessments examined prevalence (seven), the effect of injury severity on risk of depression, prevalence by subpopulations (seven), and imaging (six).

**Current Literature Analysis:**

- Prevalence:
  - A retrospective cohort study of the TBIMS-NDB found that at five years post discharge, 7.5% experienced moderate or severe depressed mood.<sup>5</sup>
  - A prospective cohort study (Army PPDS) found that 20% reported deployment acquired TBI. The association between deployment-acquired TBI and past 30-day major depressive episode was significant at three, but not nine months post deployment.<sup>7</sup>
- Subpopulations:
  - A retrospective cohort study of the TBIMS-NDB found that at five years post discharge, of individuals aged 40-49, 15.9% experienced moderate or severe depressed mood (PHQ-9  $\geq 15$ ). Rate of depressed mood decreased both with older and younger age.<sup>5</sup>
  - Another analysis of the TBIMS found that in year two, both Blacks and Hispanics had higher scores on the PHQ-9 than Whites and Asian/Pacific Islanders. There was no difference in depressive symptoms between Blacks and Hispanics, and Whites and Asian/Pacific Islanders.<sup>6</sup>

**Reviewer Questions:**

1. Are the original report conclusions still supported by the current evidence?

[Click here to enter text.](#)

2. Are there any published or unpublished studies that you know of that we may have overlooked?

[Click here to enter text.](#)

**Key Question 2:**

When should patients who suffer traumatic brain injury be screened for depression, with what tools, and in what setting?

**Prior Surveillance Assessment: August 2014**

- All conclusions are likely current.
  - One study found that no items on the PHQ-9 demonstrated significant item functioning attributable to TBI.
  - One study identified in March 2012 surveillance assessment found that increased levels of depression at two, seven, and 14 days post-concussion support early post- injury screening.

**Current Literature Analysis:**

- No studies were identified.

**Reviewer Questions:**

1. Are the original report conclusions still supported by the current evidence?

[Click here to enter text.](#)

2. Are there any published or unpublished studies that you know of that we may have overlooked?

[Click here to enter text.](#)

**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?

**Prior Surveillance Assessment: August 2014**

- All conclusions are likely current.
  - Three identified studies examined the prevalence of comorbid anxiety (three studies), with findings consistent with the original systematic review.
  - One study identified in March 2012 surveillance assessment examined the prevalence of comorbid PTSD and panic disorder. Rates of comorbidity were higher than in the original systematic review; however, the sample size was small (n=11).

**Current Literature Analysis:**

- In one RCT (n=43) of participants with TBI and a DSM IV-TR diagnosis of a depressive disorder, or BDI-II score >20, 13 met criteria for a DSM-IVTR anxiety disorder at baseline.<sup>4</sup>

**Reviewer Questions:**

1. Are the original report conclusions still supported by the current evidence?

[Click here to enter text.](#)

2. Are there any published or unpublished studies that you know of that we may have overlooked?

[Click here to enter text.](#)

**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?

**Prior Surveillance Assessment: August 2014**

- All conclusions are likely current.

- No studies were identified in the August 2014 assessment.
- Studies identified in March and November 2012 surveillance assessments examined aerobic exercise prevalence, internet based CBT, citalopram, and an electroencephalography (EEG)-based therapy. In addition, the March 2012 assessment identified FDA warnings for the combination of sertraline and other agents affecting serotonin, false positives for benzodiazepines associated with sertraline, a Health Canada warning of abnormal heart rhythms associated with citalopram, and a MHRA warning of increased risk of fractures associated with antidepressants.

**Current Literature Analysis:**

- A randomized crossover study comparing a home based exercise program to nutrition education among individuals with TBI and depressive found a significant reduction in depressive symptoms following the walking intervention.<sup>8</sup>

**Reviewer Questions:**

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

**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?

**Prior Surveillance Assessment: August 2014**

- All conclusions are likely current.
  - No studies were identified.

**Current Literature Analysis:**

- A RCT compared CBT to supportive psychotherapy over 16 weeks and found that while there was a significant reduction in scores on the BDI-II for the CBT group, severity reduction did not differ significantly between groups. There was no difference in remission rates. All participants improved on a measure of QOL, with no significant differences between groups.<sup>4</sup>

**Reviewer Questions:**

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

**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?

**Prior Surveillance Assessment: August 2014**

- All conclusions are likely current.
  - No studies were identified in the August 2014 assessment.
  - The March 2012 assessment included two studies examining moderators of citalopram. Relapse was not predicted by age, sex, employment status or overall baseline or post-treatment HDRS scores, but was predicted by small nuclear polymorphisms (SNPs) in genes associated with serotonin transport.

**Current Literature Analysis:**

- No studies were identified.

**Reviewer Questions:**

1. Are the original report conclusions still supported by the current evidence?

2. Are there any published or unpublished studies that you know of that we may have overlooked?

## Original Systematic Review Conclusions and Literature Analysis

**Title of Original Systematic Review:** Traumatic Brain Injury and Depression

**Original Systematic Review Published:** April 2011

**Original Systematic Review Search Dates:** January 1966 to May 2010

**Surveillance Report Published:** March 2012

**Surveillance Report Search Dates:** May 2010 to October 2011

**Surveillance Report Published:** November 2012

**Surveillance Report Search Dates:** November 2010 to October 2012

**Surveillance Report Published:** August 2014

**Surveillance Report Search Dates:** November 2012 to January 2014

**Current Literature Search Dates:** January 2014 to March 2016

The conclusions from the original systematic review, the findings and assessment of the prior surveillance assessment, and a summary of the relevant recently published literature are outlined below. Abstracts are provided at the end of the document.

Table 1. 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 of recognition of the traumatic brain injury or other patient factors influence the probability of developing clinical depression?

<b>Conclusions from Original Systematic Review</b> <a href="#">Link to Review</a>	<b>Findings and Assessment from Prior Surveillance Assessment (August 2014)</b> <a href="#">Link to Report</a>	<b>Literature Analysis (March 2016)</b>
The prevalence of depression among individuals with traumatic brain injury is approximately 30% across multiple time points up to and beyond a year. Based on structured clinical interviews, on average 27% met criteria for depression three to six months from injury; 32% at six to 12 months; and 33% beyond 12 months ( <b>Moderate SOE</b> ).	<p><b>August 2014</b> <b>Assessment: Current</b> Two studies yielded similar results and do not have the potential to significantly change original report findings.<sup>11,12</sup></p> <p><b>November 2012</b> <b>Assessment: Current</b> Five new studies found increased prevalence of depression among athletes with confirmed recent concussion or history of repeated concussion.<sup>13-17</sup></p>	<p>A retrospective cohort study of the TBIMS-NDB (patients admitted and discharged between 10/01-12/07; n=4064) found that at five years post discharge, 7.5% experienced moderate or severe depressed mood (PHQ-9 <math>\geq 15</math>).<sup>5</sup></p> <p>A prospective cohort study (Army PPDS; n=4645) of individuals deployed to Afghanistan found that 20% reported deployment acquired TBI. The association between deployment acquired TBI and past 30-day major</p>



<b>Conclusions from Original Systematic Review</b> <a href="#">Link to Review</a>	<b>Findings and Assessment from Prior Surveillance Assessment (August 2014)</b> <a href="#">Link to Report</a>	<b>Literature Analysis (March 2016)</b>
	<p><b>March 2012</b>  <b>Assessment: Current</b>  Two new studies confirmed prevalence findings from original report<sup>18,19</sup></p>	depressive episode was significant at three months post deployment, but not at nine months. <sup>7</sup>
Data are sparse to assess whether severity of injury influences risk of depression.	<p><b>November 2012</b>  <b>Assessment: Current</b>  Nine-year risk of depression increased with increasing number of prior concussions among retired NFL players.<sup>20</sup> Depressive symptoms, as measured by BDI-II, correlated with decreasing cognitive abilities (indicative of severity of TBI).<sup>16</sup> Self-reported depression injury severity.<sup>21</sup></p> <p><b>March 2012</b>  <b>Assessment: Current</b>  One new study finds no association of injury (TBI) severity (GCS score or post-traumatic amnesia duration) with risk for depression.<sup>18</sup></p>	No studies were identified
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>August 2014</b>  <b>Assessment: Current</b>  One study on gender and TBI severity does not have the potential to significantly change original report and previous surveillance report findings.<sup>12</sup></p> <p><b>November 2012</b>  <b>Assessment: Current</b>  One new study found that women had a slightly higher risk for depression after TBI.<sup>22</sup></p> <p>One new study found that older age was associated with depression in mild TBI patients.<sup>23</sup></p> <p><b>March 2012</b></p>	<p>A retrospective cohort study of the TBIMS-NDB (patients admitted and discharged between 10/01-12/07; n=4064) found that at five years post discharge, of individuals aged 40-49, 15.9% experienced moderate or severe depressed mood (PHQ-9 ≥15). Rate of depressed mood decreased both with older and younger age.<sup>5</sup></p> <p>Another cohort study (TBIMS; n=1662) of individuals with TBI found that in year two, both Blacks (p=.022; p=.007) and Hispanics (p=.037; p=.001) had higher scores on the PHQ-9 than Whites and Asian/Pacific Islanders respectively. There was no difference in depressive symptoms between Blacks and Hispanics, and Whites and</p>

<b>Conclusions from Original Systematic Review</b> <a href="#">Link to Review</a>	<b>Findings and Assessment from Prior Surveillance Assessment (August 2014)</b> <a href="#">Link to Report</a>	<b>Literature Analysis (March 2016)</b>
	<p><b>Assessment: Current</b>            One new study found no association between age, gender, time since injury and development of depression.<sup>24</sup></p> <p>One new study found that female gender, lower education, post-injury 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>25</sup></p> <p>One 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>18</sup></p> <p>One new study found that development of depression was associated with poorer progress in resuming preinjury lifestyle; timing suggests functional status contributes to depression.<sup>26</sup></p> <p>One new study using cross-lagged analysis suggests poor functional status at six months post TBI may predict development of depression at 12 months post TBI.<sup>27</sup></p>	Asian/Pacific Islanders. <sup>6</sup>
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 depression within three months of injury has been reported to be sevenfold as common (95% CI: 1.36 to 43.48) among those with abnormal CT scans	<p><b>August 2014</b>  <b>Assessment: Current</b>            One study of 14 patients undergoing diffusion tensor imaging does not have the potential to significantly change original report and previous surveillance report findings.<sup>14</sup></p>	No studies were identified

<b>Conclusions from Original Systematic Review</b> <a href="#">Link to Review</a>	<b>Findings and Assessment from Prior Surveillance Assessment (August 2014)</b> <a href="#">Link to Report</a>	<b>Literature Analysis (March 2016)</b>
<p>after injury compared with normal imaging.</p>	<p><b>November 2012</b>  <b>Assessment: Current</b>            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>One new study found an association of frontal subdural hemorrhage with increased risk for mild TBI.<sup>23</sup></p> <p>One 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>29</sup></p> <p><b>March 2012</b>  <b>Assessment: Current</b>            One 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 hemispheric imbalances in neural activity (unless it results from brain atrophy).<sup>24</sup></p> <p>One new study found that the pathophysiology of post-TBI depression in terms of brain atrophy in three regions on MRI overlaps with that of spontaneous depression.<sup>30</sup></p> <p>One new study that used diffusion tensor</p>	

Conclusions from Original Systematic Review <a href="#">Link to Review</a>	Findings and Assessment from Prior Surveillance Assessment (August 2014) <a href="#">Link to Report</a>	Literature Analysis (March 2016)
	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>31</sup>	

*Abbreviations:* BDI-II=Beck Depression Inventory-2; CT=Computed Tomography; GCS=Glasgow Coma Scale; MDD=Major Depressive Disorder; MRI=Magnetic Resonance Imaging; MRSI=Magnetic Resonance Spectroscopy Imaging; PHQ-9=Patient Health Questionnaire-9; PPDS=Pre/Post Deployment Study; SOE=Strength of Evidence; TBI=Traumatic Brain Injury; TBIMS-NDB=Traumatic Brain Injury Model Systems- National Database

Table 2. Key Question 2: When should patients who suffer traumatic brain injury be screened for depression, with what tools, and in what setting?

Conclusions from Original Systematic Review <a href="#">Link to Review</a>	Findings and Assessment from Prior Surveillance Assessment (August 2014) <a href="#">Link to Report</a>	Literature Analysis (March 2016)
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><b>August 2014</b> <b><u>Assessment: Current</u></b> No new studies identified.</p> <p><b>November 2012</b> <b><u>Assessment: Current</u></b> Increased levels of depression at two, seven, and 14 days post-concussion in one new study support early post- injury screening.<sup>17</sup></p> <p><b>March 2012</b> <b><u>Assessment: Current</u></b> No new information</p>	No studies were identified
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.	<p><b>August 2014</b> <b><u>Assessment: Current</u></b> No new studies identified.</p> <p><b>November 2012</b> <b><u>Assessment: Current</u></b></p>	No studies were identified

Conclusions from Original Systematic Review <a href="#">Link to Review</a>	Findings and Assessment from Prior Surveillance Assessment (August 2014) <a href="#">Link to Report</a>	Literature Analysis (March 2016)
	<p>No new information</p> <p><b>March 2012</b> <b><u>Assessment: Current</u></b> One 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 over-diagnosis.</p>	
<p>The literature does not support any one tool over the others, nor in what setting (<b>SOE Low</b>).</p>	<p><b>August 2014</b> <b><u>Assessment: Current</u></b> No new studies identified.</p> <p><b>November 2012</b> <b><u>Assessment: Current</u></b> No new information</p> <p><b>March 2012</b> <b><u>Assessment: Current</u></b> No new information</p>	<p>No studies were identified</p>

*Abbreviations:* MDD=Major Depressive Disorder; PHQ-9=Patient Health Questionnaire-9; SOE=Strength of Evidence; TBI=Traumatic Brain Injury

Table 3. 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?

Conclusions from Original Systematic Review <a href="#">Link to Review</a>	Findings and Assessment from Prior Surveillance Assessment (August 2014) <a href="#">Link to Report</a>	Literature Analysis (March 2016)
<p>When conditions were reported individually, anxiety disorder was most prevalent and affected from 31% to 61% of study participants in four papers.</p>	<p><b>August 2014</b> <b><u>Assessment: Current</u></b> No new studies identified.</p> <p><b>November 2012</b> <b><u>Assessment: Current</u></b> No new research identified</p>	<p>In one RCT (n=43) of participants with TBI and a DSM-IV-TR diagnosis of a depressive disorder, or BDI-II score &gt;20, 13 met criteria for a DSM-IV-TR anxiety disorder at baseline.<sup>4</sup></p>

<b>Conclusions from Original Systematic Review</b> <a href="#">Link to Review</a>	<b>Findings and Assessment from Prior Surveillance Assessment (August 2014)</b> <a href="#">Link to Report</a>	<b>Literature Analysis (March 2016)</b>
	<p><b>March 2012</b>  <b><u>Assessment: Current</u></b>            One 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>19</sup></p> <p>One 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>25</sup></p> <p>One new study reported that three to six months post-TBI, 13% had both depressive and anxiety disorders and that at six to 12 months, 20% had both.</p>	
<p>PTSD, a major anxiety disorder, was observed in 37% of depressed patients and in no patients without depression.</p>	<p><b>August 2014</b>  <b><u>Assessment: Current</u></b>            No new studies identified.</p> <p><b>November 2012</b>  <b><u>Assessment: Current</u></b>            No new information</p> <p><b>March 2012</b>  <b><u>Assessment: Current</u></b>            One new study found that 10 of 11 patients with post-TBI MDD also had PTSD, compared with nine of 11 TBI patients without MDD.<sup>31</sup></p>	<p>No studies were identified.</p>
<p>Panic disorder was seen in 15% of patients with major depression, but not measured in those without depression.</p>	<p><b>August 2014</b>  <b><u>Assessment: Current</u></b>            No new studies identified.</p> <p><b>November 2012</b>  <b><u>Assessment: Current</u></b>            No new information</p>	<p>No studies were identified</p>

Conclusions from Original Systematic Review <a href="#">Link to Review</a>	Findings and Assessment from Prior Surveillance Assessment (August 2014) <a href="#">Link to Report</a>	Literature Analysis (March 2016)
	<p><b>March 2012</b> <b>Assessment: Current</b> One new study found that six of 11 patients with post-TBI MDD also had panic disorder compared with four of 11 patients without MDD.<sup>31</sup></p>	
Consideration of potential for coexisting psychiatric conditions is warranted.	<p><b>August 2014</b> <b>Assessment: Current</b> No new studies identified.</p> <p><b>November 2012</b> <b>Assessment: Current</b> No new information</p> <p><b>March 2012</b> <b>Assessment: Current</b> No new information</p>	No studies were identified

*Abbreviations:* BDI-II=Beck Depression Inventory-2; DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders-4 Text Revision; MDD=Major Depressive Disorder; PTSD=Post-Traumatic Stress Disorder; RCT=Randomized Controlled Trial; TBI=Traumatic Brain Injury

Table 4. 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?

Conclusions from Original Systematic Review <a href="#">Link to Review</a>	Findings and Assessment from Prior Surveillance Assessment (August 2014) <a href="#">Link to Report</a>	Literature Analysis (March 2016)
Only two publications addressed treatment for individuals diagnosed with depression after a traumatic brain 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 ( <b>Pharmacologic treatment SOE Low</b> ).	<p><b>August 2014</b> <b>Assessment: Current</b> No new studies identified.</p> <p><b>November 2012</b> <b>Assessment: Current</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>32</sup></p>	A randomized crossover study comparing a home based exercise program to nutrition education among individuals with TBI and depressive symptoms (CES-D M=16 [mild depression]; n=67) found a significant reduction in depressive symptoms following the walking intervention. <sup>8</sup>

<b>Conclusions from Original Systematic Review</b> <a href="#">Link to Review</a>	<b>Findings and Assessment from Prior Surveillance Assessment (August 2014)</b> <a href="#">Link to Report</a>	<b>Literature Analysis (March 2016)</b>
	<p><b>March 2012</b>  <b>March 2012 Assessment: Current</b>            One 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 on the Rosenberg Self-Esteem scale also improved, and the exercise had no adverse effects.<sup>33</sup></p> <p>One new study found that a six-week, internet-based cognitive behavioral therapy program decreased CES-D scores by a significant 1.03 points for each week completed. At 12 months follow-up, mean scores were 20.6±4.7 and PHQ-9 scores were 11.6±2.4, significantly lower than at baseline. Four out of 16 completers had symptoms that declined to below MDD criteria.<sup>34</sup></p> <p>One 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. One participant dropped out due to side effects (diarrhea); all participants described at least one adverse event. Mean compliance was 91.9%. The relapse rate did not differ between treated and untreated participants (52%).<sup>35</sup></p> <p>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,</p>	



<b>Conclusions from Original Systematic Review</b> <a href="#">Link to Review</a>	<b>Findings and Assessment from Prior Surveillance Assessment (August 2014)</b> <a href="#">Link to Report</a>	<b>Literature Analysis (March 2016)</b>
	<p>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 pharmacodynamic interaction.</p> <p><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, patients who are CYP2C19 poor metabolizers, or patients who are taking cimetidine or another CYP2C19 inhibitor</li> <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-">http://www.hc-sc.gc.ca/dhp-</a></p>	

Conclusions from Original Systematic Review <a href="#">Link to Review</a>	Findings and Assessment from Prior Surveillance Assessment (August 2014) <a href="#">Link to Report</a>	Literature Analysis (March 2016)
	<p><a href="https://www.mhra.gov.uk/medeff/advisories-avis/prof/2012/celexa_2_hpc-cps-eng.php">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 nine observational studies in adults over 50.</p> <p><a href="http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON085136">http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON085136</a></p>	

*Abbreviations:* CES-D=Centre for Epidemiological Studies-Depression; FDA=Food and Drug Administration; HAM-D=Hamilton Rating Scale for Depression; MDD=Major Depressive Disorder; MHRA=Medicines and Healthcare Products Regulatory Agency; PHQ-9=Patient Health Questionnaire-9; SOE=Strength of Evidence; SRI=Selective Serotonin Reuptake Inhibitor; TCA=Tricyclic Antidepressant; TBI=Traumatic Brain Injury

Table 5. 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?

Conclusions from Original Systematic Review <a href="#">Link to Review</a>	Findings and Assessment from Prior Surveillance Assessment (August 2014) <a href="#">Link to Report</a>	Literature Analysis (March 2016)
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.	<p><b>August 2014</b> <b>Assessment: Current</b> No new studies identified.</p> <p><b>November 2012</b> <b>Assessment: Current</b> No new information</p> <p><b>March 2012</b> <b>Assessment: Current</b> No new information</p>	A RCT (n=77) compared CBT to SPT over 16 weeks and found that while there was a significant reduction in scores on the BDI-II for the CBT group, severity reduction did not differ significantly between groups. There was no difference in remission rates. All participants improved on a measure of QOL, with no significant differences between groups. <sup>4</sup>

*Abbreviations:* BDI-II=Beck Depression Inventory-2; CBT=Cognitive Behavioral Therapy; QoL=Quality of Life; RCT=Randomized Controlled Trial; SPT=Supportive Psychotherapy; TBI=Traumatic Brain Injury

Table 6. 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>Conclusions from Original Systematic Review</b> <a href="#">Link to Review</a>	<b>Findings and Assessment from Prior Surveillance Assessment (August 2014)</b> <a href="#">Link to Report</a>	<b>Literature Analysis (March 2016)</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.	<p><b>August 2014</b> <b><u>Assessment: Current</u></b> No new studies identified.</p> <p><b>November 2012</b> <b><u>Assessment: Current</u></b> No new information</p> <p><b>March 2012</b> <b><u>Assessment: Current</u></b> In the citalopram blinded, placebo- controlled continuation study, relapse was not predicted by age, sex, employment status or overall baseline or post-treatment HAM-D scores. However, two HAM-D variables did predict higher risk for relapse: agitation and greater than mild psychic anxiety.<sup>35</sup></p>	No studies were identified.

*Abbreviations:* HAM-D=Hamilton Depression Rating Scale; TBI=Traumatic Brain Injury

## Abstracts from Relevant Literature/References

1. Corrigan JD, Cuthbert JP, Harrison-Felix C, et al. US population estimates of health and social outcomes 5 years after rehabilitation for traumatic brain injury. *The Journal of head trauma rehabilitation*. Nov-Dec 2014;29(6):E1-9.

**OBJECTIVE:** To estimate the number of adults in the United States from 2006 to 2012 who manifest selected health and social outcomes 5 years following a traumatic brain injury (TBI) that required acute inpatient rehabilitation. **DESIGN:** Secondary data analysis. **SETTING:** Acute inpatient rehabilitation facilities. **PARTICIPANTS:** Patients 16 years and older receiving acute inpatient rehabilitation for a primary diagnosis of TBI. **MAIN OUTCOME MEASURES:** Mortality, functional independence, societal participation, subjective well-being, and global outcome. **RESULTS:** Annually from 2001 to 2007, an average of 13 700 patients

aged 16 years or older received acute inpatient rehabilitation in the United States with a primary diagnosis of TBI. Approximately 1 in 5 patients had died by the 5-year postinjury assessment. Among survivors, 12% were institutionalized and 50% had been rehospitalized at least once. Approximately one-third of patients were not independent in everyday activities. Twenty-nine percent were dissatisfied with life, with 8% reporting markedly depressed mood. Fifty-seven percent were moderately or severely disabled overall, with 39% having deteriorated from a global outcome attained 1 or 2 years postinjury. Of those employed preinjury, 55% were unemployed. Poorer medical, functional, and participation outcomes were associated with, but not limited to, older age. Younger age groups had poorer mental and emotional outcomes. Deterioration in global outcome was common and not age-related. CONCLUSIONS: Significant mortality and morbidity were evident at 5 years postinjury. The deterioration in global outcomes observed regardless of age suggests that multiple influences contribute to poorer outcomes. Public health interventions intended to reduce post-acute inpatient rehabilitation mortality and morbidity rates will need to be multifaceted and age-specific.

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2. Stein MB, Kessler RC, Heeringa SG, et al. Prospective longitudinal evaluation of the effect of deployment-acquired traumatic brain injury on posttraumatic stress and related disorders: results from the Army Study to Assess Risk and Resilience in Service members (Army STARRS). *The American journal of psychiatry*. Nov 1 2015;172(11):1101-1111.

OBJECTIVE: Traumatic brain injury (TBI) is increasingly recognized as a risk factor for deleterious mental health and functional outcomes. The purpose of this study was to examine the strength and specificity of the association between deployment-acquired TBI and subsequent posttraumatic stress and related disorders among U.S. Army personnel. METHOD: A prospective, longitudinal survey of soldiers in three Brigade Combat Teams was conducted 1-2 months prior to an average 10-month deployment to Afghanistan (T0), upon redeployment to the United States (T1), approximately 3 months later (T2), and approximately 9 months later (T3). Outcomes of interest were 30-day prevalence postdeployment of posttraumatic stress disorder (PTSD), major depressive episode, generalized anxiety disorder, and suicidality, as well as presence and severity of postdeployment PTSD symptoms. RESULTS: Complete information was available for 4,645 soldiers. Approximately one in five soldiers reported exposure to mild (18.0%) or more-than-mild (1.2%) TBI(s) during the index deployment. Even after adjusting for other risk factors (e.g., predeployment mental health status, severity of deployment stress, prior TBI history), deployment-acquired TBI was associated with elevated adjusted odds of PTSD and generalized anxiety disorder at T2 and T3 and of major depressive episode at T2. Suicidality risk at T2 appeared similarly elevated, but this association did not reach statistical significance. CONCLUSIONS: The findings highlight the importance of surveillance efforts to identify soldiers who have sustained TBIs and are therefore at risk for an array of postdeployment adverse mental health outcomes, including but not limited to PTSD. The mechanism(s) accounting for these associations need to be elucidated to inform development of effective preventive and early intervention programs.

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3. Perrin PB, Krch D, Sutter M, et al. Racial/ethnic disparities in mental health over the first 2 years after traumatic brain injury: a model systems study. *Archives of physical medicine and rehabilitation*. Dec 2014;95(12):2288-2295.

OBJECTIVE: To determine whether racial/ethnic disparities occur in depression, anxiety, and satisfaction with life at 1 and 2 years postdischarge. DESIGN: A prospective, longitudinal, multicenter study of individuals with traumatic brain injury (TBI) participating in the National Institute on Disability and Rehabilitation Research Traumatic Brain Injury Model Systems project. Medical, demographic, and outcome data were obtained from the Model Systems database at baseline, as well as 1 and 2 years postdischarge. SETTING: A total of 16 TBI Model Systems hospitals in the United States. PARTICIPANTS: Individuals with moderate or severe TBI (N=1662) aged 16 years or older consecutively discharged between January 2008 and June 2011 from acute care and comprehensive inpatient rehabilitation at a Model Systems hospital. INTERVENTION: Not applicable. MAIN OUTCOME MEASURES: The Patient Health Questionnaire-9, Generalized Anxiety Disorder 7-item scale, and Satisfaction with Life Scale assessed depression, anxiety, and satisfaction with life at 1 and 2-year follow-ups. RESULTS: After controlling for all possible covariates, hierarchical linear models found that black individuals had elevated depression across the 2 time points relative to white individuals. Asian/Pacific Islanders' depression increased over time in comparison to the decreasing depression in those of Hispanic origin, which was a greater decrease than in white individuals. Black individuals had lower life satisfaction than did white and Hispanic individuals, but only marginally greater anxiety over time than did white individuals and similar levels of anxiety as did Asian/Pacific Islanders and Hispanic individuals. CONCLUSIONS: Mental health trajectories of individuals with TBI differed as a function of race/ethnicity across the first 2 years postdischarge, providing the first longitudinal evidence of racial/ethnic disparities in mental health after TBI during this time period. Further research will be required to understand the complex factors underlying these differences.

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4. Ashman T, Cantor JB, Tsaousides T, Spielman L, Gordon W. Comparison of cognitive behavioral therapy and supportive psychotherapy for the treatment of depression following traumatic brain injury: a randomized controlled trial. *The Journal of head trauma rehabilitation*. Nov-Dec 2014;29(6):467-478.

OBJECTIVE: To determine the efficacy of 2 different interventions (cognitive behavioral therapy [CBT] and supportive psychotherapy [SPT]) to treat post-traumatic brain injury (TBI) depression. PARTICIPANTS: A sample of 77 community-dwelling individuals with a TBI, and a diagnosis of depression. Participants were randomized into treatment conditions either CBT or SPT and received up to 16 sessions of individual psychotherapy. MEASURES: Participants completed the Structured Clinical Interview for DSM-IV and self-report measures of depression (Beck Depression Inventory-Second Edition), anxiety (State-Trait Anxiety Inventory), perceived social support (Interpersonal Support Evaluation List), stressful life events (Life Experiences Survey), and quality of life (QOL) before beginning and immediately following treatment. RESULTS: No significant differences were found at baseline between CBT and SPT groups on demographic factors (sex, age, education, race, and time since injury) or baseline measures of depression, anxiety, participation, perceived social support, stressful life events, or QOL. Analyses of variance revealed significant time effects for the Beck Depression Inventory-Second Edition, State-Trait Anxiety Inventory, and QOL outcome measures but no group effects. Intention-to-treat mixed effects analyses did not find any significant difference in patterns of scores of the outcome measures between the CBT and SPT intervention groups. CONCLUSIONS: Both forms of

psychotherapy were efficacious in improving diagnoses of depression and anxiety and reducing depressive symptoms. These findings suggest that in this sample of individuals with TBI, CBT was not more effective in treating depression than SPT, though further research is needed with larger sample sizes to identify different components of these interventions that may be effective with different TBI populations. ClinicalTrials.gov Identifier: NCT00211835.

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5. Bellon K, Kolakowsky-Hayner S, Wright J, et al. A home-based walking study to ameliorate perceived stress and depressive symptoms in people with a traumatic brain injury. *Brain injury*. 2015;29(3):313-319.

Abstract Objective: To determine whether a 12-week home-based walking programme can decrease perceived stress and depressive symptoms in persons with a traumatic brain injury (TBI). SETTING: Community- and home-based. PARTICIPANTS: Sixty-nine participants with a TBI. DESIGN: Comparative effectiveness cross-over design with random assignment to treatment sequence and blinded post-hoc assessment of outcome where participants completed a 12-week walking intervention and a nutrition education module. The walking intervention utilized pedometers to track the amount of steps each participant walked daily. With the assistance of an assigned coach, weekly goals were given with the intent of increasing the amount of walking that the participant was initially completing. The nutrition control group was created to offset the impact of the coaching calls. MAIN MEASURES: Measurement of perceived stress and depressive symptoms was completed through the use of the Perceived Stress Scale (PSS) and Center for Epidemiological Studies-Depression (CES-D). These measures were collected at three time points: baseline and following each 12-week intervention. RESULTS: RESULTS indicated that both perceived stress and depression symptoms significantly improved following the walking intervention. CONCLUSIONS: While limitations existed with the study, it is evident that walking can be used as an efficient and cost-effective tool to manage perceived stress and depressive symptoms in persons who have sustained a TBI.

## Appendix E. Summary Table

Table 1. 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 of recognition of the traumatic brain injury or other patient factors influence the probability of developing clinical depression?

<b>Conclusions from Original Systematic Review</b> <a href="#">Link to Review</a>	<b>Findings and Assessment from Prior Surveillance Assessment (August 2014)</b> <a href="#">Link to Report</a>	<b>Literature Analysis (March 2016)</b>	<b>Expert Opinion</b>	<b>Surveillance Assessment</b>
<p>The prevalence of depression among individuals with traumatic brain injury is approximately 30% across multiple time points up to and beyond a year. Based on structured clinical interviews, on average 27% met criteria for depression three to six months from injury; 32% at six to 12 months; and 33% beyond 12 months (<b>Moderate SOE</b>).</p>	<p><b>August 2014 Assessment: Current</b>  Two studies yielded similar results and do not have the potential to significantly change original report findings.<sup>11,12</sup></p> <p><b>November 2012 Assessment: Current</b>  Five new studies found increased prevalence of depression among athletes with confirmed recent concussion or history of repeated concussion.<sup>13-17</sup></p> <p><b>March 2012 Assessment: Current</b>  Two new studies confirmed prevalence findings from original report<sup>18,19</sup></p>	<p>A retrospective cohort study of the TBIMS-NDB (patients admitted and discharged between 10/01-12/07; n=4064) found that at five years post discharge, 7.5% experienced moderate or severe depressed mood (PHQ-9 <math>\geq 15</math>).<sup>5</sup></p> <p>A prospective cohort study (Army PPDS; n=4645) of individuals deployed to Afghanistan found that 20% reported deployment acquired TBI. The association between deployment acquired TBI and past 30-day major depressive episode was significant at three months post deployment, but not at nine months.<sup>7</sup></p>	<p>One expert believed the conclusion to be current. The second reviewer felt that the conclusion was no longer current; however, provided no supporting literature.</p>	<p>Conclusions are likely current.</p>
<p>Data are sparse to assess whether severity of injury influences risk of depression.</p>	<p><b>November 2012 Assessment: Current</b>  Nine-year risk of depression increased with</p>	<p>No studies were identified</p>	<p>See above</p>	<p>Conclusions are likely current.</p>

<b>Conclusions from Original Systematic Review</b> <a href="#">Link to Review</a>	<b>Findings and Assessment from Prior Surveillance Assessment (August 2014)</b> <a href="#">Link to Report</a>	<b>Literature Analysis (March 2016)</b>	<b>Expert Opinion</b>	<b>Surveillance Assessment</b>
	<p>increasing number of prior concussions among retired NFL players.<sup>20</sup> Depressive symptoms, as measured by BDI-II, correlated with decreasing cognitive abilities (indicative of severity of TBI).<sup>16</sup> Self-reported depression injury severity.<sup>21</sup></p> <p><b>March 2012</b>  <b>Assessment: Current</b>            One new study finds no association of injury (TBI) severity (GCS score or post-traumatic amnesia duration) with risk for depression.<sup>18</sup></p>			
<p>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>	<p><b>August 2014</b>  <b>Assessment: Current</b>            One study on gender and TBI severity does not have the potential to significantly change original report and previous surveillance report findings.<sup>12</sup></p> <p><b>November 2012</b>  <b>Assessment: Current</b>            One new study found that women had a slightly higher risk for depression after TBI.<sup>22</sup></p>	<p>A retrospective cohort study of the TBIMS-NDB (patients admitted and discharged between 10/01-12/07; n=4064) found that at five years post discharge, of individuals aged 40-49, 15.9% experienced moderate or severe depressed mood (PHQ-9 <math>\geq</math>15). Rate of depressed mood decreased both with older and younger age.<sup>5</sup></p> <p>Another cohort study</p>	<p>See above</p>	<p>Conclusions are likely current.</p>



<b>Conclusions from Original Systematic Review</b> <a href="#">Link to Review</a>	<b>Findings and Assessment from Prior Surveillance Assessment (August 2014)</b> <a href="#">Link to Report</a>	<b>Literature Analysis (March 2016)</b>	<b>Expert Opinion</b>	<b>Surveillance Assessment</b>
	<p>One new study found that older age was associated with depression in mild TBI patients.<sup>23</sup></p> <p><b>March 2012 Assessment: Current</b></p> <p>One new study found no association between age, gender, time since injury and development of depression.<sup>24</sup></p> <p>One new study found that female gender, lower education, post-injury 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>25</sup></p> <p>One 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</p>	<p>(TBIMS; n=1662) of individuals with TBI found that in year two, both Blacks (p=.022; p=.007) and Hispanics (p=.037; p=.001) had higher scores on the PHQ-9 than Whites and Asian/Pacific Islanders respectively. There was no difference in depressive symptoms between Blacks and Hispanics, and Whites and Asian/Pacific Islanders.<sup>6</sup></p>		

<b>Conclusions from Original Systematic Review</b> <a href="#">Link to Review</a>	<b>Findings and Assessment from Prior Surveillance Assessment (August 2014)</b> <a href="#">Link to Report</a>	<b>Literature Analysis (March 2016)</b>	<b>Expert Opinion</b>	<b>Surveillance Assessment</b>
	<p>toward significance.<sup>18</sup></p> <p>One new study found that development of depression was associated with poorer progress in resuming preinjury lifestyle; timing suggests functional status contributes to depression.<sup>26</sup></p> <p>One new study using cross-lagged analysis suggests poor functional status at six months post TBI may predict development of depression at 12 months post TBI.<sup>27</sup></p>			
<p>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 depression within three months of injury has been reported to be sevenfold as common (95% CI: 1.36 to 43.48) among those with abnormal CT scans after injury compared with normal imaging.</p>	<p><b>August 2014 Assessment: Current</b>  One study of 14 patients undergoing diffusion tensor imaging does not have the potential to significantly change original report and previous surveillance report findings.<sup>14</sup></p> <p><b>November 2012 Assessment: Current</b>  Imaging studies (MRI and MRSI) suggest association between reduction in gray matter in particular regions (as well as choline/creatine</p>	<p>No studies were identified</p>	<p>See above</p>	<p>Conclusions are likely current.</p>

<b>Conclusions from Original Systematic Review</b> <a href="#">Link to Review</a>	<b>Findings and Assessment from Prior Surveillance Assessment (August 2014)</b> <a href="#">Link to Report</a>	<b>Literature Analysis (March 2016)</b>	<b>Expert Opinion</b>	<b>Surveillance Assessment</b>
	<p>ratio and n-acetyl aspartate/creatinine ratio) and post TBI-depression.<sup>28</sup></p> <p>One new study found an association of frontal subdural hemorrhage with increased risk for mild TBI.<sup>23</sup></p> <p>One new study found that in patients with TBI, mood disorders were associated with decreased N-acetyl aspartate/creatinine ratios in the left anterior cingulate cortex.<sup>29</sup></p> <p><b>March 2012 Assessment: Current</b>  One 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 hemispheric imbalances in neural activity (unless it</p>			

<b>Conclusions from Original Systematic Review</b> <a href="#">Link to Review</a>	<b>Findings and Assessment from Prior Surveillance Assessment (August 2014)</b> <a href="#">Link to Report</a>	<b>Literature Analysis (March 2016)</b>	<b>Expert Opinion</b>	<b>Surveillance Assessment</b>
	<p>results from brain atrophy).<sup>24</sup></p> <p>One new study found that the pathophysiology of post-TBI depression in terms of brain atrophy in three regions on MRI overlaps with that of spontaneous depression.<sup>30</sup></p> <p>One 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>31</sup></p>			

*Abbreviations:* BDI-II=Beck Depression Inventory-2; CT=Computed Tomography; GCS=Glasgow Coma Scale; MDD=Major Depressive Disorder; MRI=Magnetic Resonance Imaging; MRSI=Magnetic Resonance Spectroscopy Imaging; PHQ-9=Patient Health Questionnaire-9; PPDS=Pre/Post Deployment Study; SOE=Strength of Evidence; TBI=Traumatic Brain Injury; TBIMS-NDB=Traumatic Brain Injury Model Systems- National Database

Table 2. Key Question 2: When should patients who suffer traumatic brain injury be screened for depression, with what tools, and in what setting?

<b>Conclusions from Original Systematic Review</b> <a href="#">Link to Review</a>	<b>Findings and Assessment from Prior Surveillance Assessment (August 2014)</b> <a href="#">Link to Report</a>	<b>Literature Analysis (March 2016)</b>	<b>Expert Opinion</b>	<b>Surveillance Assessment</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><b>August 2014</b>  <b>Assessment: Current</b>            No new studies identified.</p> <p><b>November 2012</b>  <b>Assessment: Current</b>            Increased levels of depression at two, seven, and 14 days post-concussion in one new study support early post-injury screening.<sup>17</sup></p> <p><b>March 2012</b>  <b>Assessment: Current</b>            No new information</p>	<p>No studies were identified</p>	<p>One expert believed the conclusion to be current. The second reviewer felt that the conclusion was no longer current; however, provided no supporting literature.</p>	<p>Conclusions are likely current.</p>
<p>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.</p>	<p><b>August 2014</b>  <b>Assessment: Current</b>            No new studies identified.</p> <p><b>November 2012</b>  <b>Assessment: Current</b>            No new information</p> <p><b>March 2012</b>  <b>Assessment: Current</b>            One 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</p>	<p>No studies were identified</p>	<p>See above</p>	<p>Conclusions are likely current.</p>

Conclusions from Original Systematic Review <a href="#">Link to Review</a>	Findings and Assessment from Prior Surveillance Assessment (August 2014) <a href="#">Link to Report</a>	Literature Analysis (March 2016)	Expert Opinion	Surveillance Assessment
	all items can be counted without concern regarding possible over-diagnosis.			
The literature does not support any one tool over the others, nor in what setting ( <b>SOE Low</b> ).	<p><b>August 2014</b> <b>Assessment: Current</b> No new studies identified.</p> <p><b>November 2012</b> <b>Assessment: Current</b> No new information</p> <p><b>March 2012</b> <b>Assessment: Current</b> No new information</p>	No studies were identified	See above	Conclusions are likely current.

Abbreviations: MDD=Major Depressive Disorder; PHQ-9=Patient Health Questionnaire-9; SOE=Strength of Evidence; TBI=Traumatic Brain Injury

Table 3. 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?

Conclusions from Original Systematic Review <a href="#">Link to Review</a>	Findings and Assessment from Prior Surveillance Assessment (August 2014) <a href="#">Link to Report</a>	Literature Analysis (March 2016)	Expert Opinion	Surveillance Assessment
When conditions were reported individually, anxiety disorder was most prevalent and affected from 31% to 61% of study participants in four papers.	<p><b>August 2014</b> <b>Assessment: Current</b> No new studies identified.</p> <p><b>November 2012</b> <b>Assessment: Current</b> No new research identified</p> <p><b>March 2012</b> <b>Assessment: Current</b> One new study found that among individuals with TBI</p>	In one RCT (n=43) of participants with TBI and a DSM-IV-TR diagnosis of a depressive disorder, or BDI-II score >20, 13 met criteria for a DSM-IV-TR anxiety disorder at baseline. <sup>4</sup>	One expert believed the conclusion to be current. The second reviewer felt that the conclusion was no longer current, and suggested a cross-sectional study examining demographic-injury profile, outcomes, service utilization, and unmet service needs of individuals with severe	Conclusions are likely current.

<b>Conclusions from Original Systematic Review</b> <a href="#">Link to Review</a>	<b>Findings and Assessment from Prior Surveillance Assessment (August 2014)</b> <a href="#">Link to Report</a>	<b>Literature Analysis (March 2016)</b>	<b>Expert Opinion</b>	<b>Surveillance Assessment</b>
	<p>and depression, 23.5% had a substance use disorder and 73.5% had an anxiety disorder.<sup>19</sup></p> <p>One 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>25</sup></p> <p>One new study reported that three to six months post-TBI, 13% had both depressive and anxiety disorders and that at six to 12 months, 20% had both.</p>		<p>traumatic brain injury. The study did not meet study design criteria, nor did it report comorbidity specific to individuals with TBI and depression.<sup>9</sup></p>	
<p>PTSD, a major anxiety disorder, was observed in 37% of depressed patients and in no patients without depression.</p>	<p><b>August 2014</b>  <b>Assessment: Current</b>            No new studies identified.</p> <p><b>November 2012</b>  <b>Assessment: Current</b>            No new information</p> <p><b>March 2012</b>  <b>Assessment: Current</b>            One new study found that 10 of 11 patients with post-TBI MDD also had PTSD, compared with nine of 11 TBI patients without MDD.<sup>31</sup></p>	<p>No studies were identified.</p>	<p>See above</p>	<p>Conclusions are likely current.</p>

Conclusions from Original Systematic Review <a href="#">Link to Review</a>	Findings and Assessment from Prior Surveillance Assessment (August 2014) <a href="#">Link to Report</a>	Literature Analysis (March 2016)	Expert Opinion	Surveillance Assessment
Panic disorder was seen in 15% of patients with major depression, but not measured in those without depression.	<p><b>August 2014</b> <b><u>Assessment: Current</u></b> No new studies identified.</p> <p><b>November 2012</b> <b><u>Assessment: Current</u></b> No new information</p> <p><b>March 2012</b> <b><u>Assessment: Current</u></b> One new study found that six of 11 patients with post-TBI MDD also had panic disorder compared with four of 11 patients without MDD.<sup>31</sup></p>	No studies were identified	See above	Conclusions are likely current.
Consideration of potential for coexisting psychiatric conditions is warranted.	<p><b>August 2014</b> <b><u>Assessment: Current</u></b> No new studies identified.</p> <p><b>November 2012</b> <b><u>Assessment: Current</u></b> No new information</p> <p><b>March 2012</b> <b><u>Assessment: Current</u></b> No new information</p>	No studies were identified	See above	Conclusions are likely current.

*Abbreviations:* BDI-II=Beck Depression Inventory-2; DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders-4 Text Revision; MDD=Major Depressive Disorder; PTSD=Post-Traumatic Stress Disorder; RCT=Randomized Controlled Trial; TBI=Traumatic Brain Injury

Table 4. 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>Conclusions from Original Systematic Review</b> <a href="#">Link to Review</a>	<b>Findings and Assessment from Prior Surveillance Assessment (August 2014)</b> <a href="#">Link to Report</a>	<b>Literature Analysis (March 2016)</b>	<b>Expert Opinion</b>	<b>Surveillance Assessment</b>
<p>Only two publications addressed treatment for individuals diagnosed with depression after a traumatic brain 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 (<b>Pharmacologic treatment SOE Low</b>).</p>	<p><b>August 2014 Assessment: Current</b> No new studies identified.</p> <p><b>November 2012 Assessment: Current</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>32</sup></p> <p><b>March 2012 March 2012 Assessment: Current</b> One 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 on the Rosenberg Self-Esteem scale also improved, and the exercise had no adverse effects.<sup>33</sup></p> <p>One new study found that a six-week, internet-based</p>	<p>A randomized crossover study comparing a home based exercise program to nutrition education among individuals with TBI and depressive symptoms (CES-D M=16 [mild depression]; n=67) found a significant reduction in depressive symptoms following the walking intervention.<sup>8</sup></p>	<p>One expert believed the conclusion to be current. The second reviewer felt that the conclusion was no longer current, and suggested a RCT examining manualized CBT for individuals with TBI and mild to moderate levels of hopelessness and/or suicidal ideation (n=17). Although participants were not explicitly diagnosed with depression, mean baseline HADS (depression scale) scores (treatment M=10.63 [2.67]; waitlist M=9.56 [3.09]) suggest that participants experienced mild-to-moderate depressive symptoms. There was a larger decrease in hopelessness (BHS scores) associated with CBT, as compared to waitlist control, with reductions sustained up to three months. There were no significant reduction in depressive symptoms, and a non-significant trend towards lower suicidal ideation associated with CBT.<sup>10</sup></p>	<p>The findings on no evidence of non-pharmacological interventions may no longer be current due to studies identified in the March 2012, November 2012, and current surveillance assessments.</p>

<b>Conclusions from Original Systematic Review</b> <a href="#">Link to Review</a>	<b>Findings and Assessment from Prior Surveillance Assessment (August 2014)</b> <a href="#">Link to Report</a>	<b>Literature Analysis (March 2016)</b>	<b>Expert Opinion</b>	<b>Surveillance Assessment</b>
	<p>cognitive behavioral therapy program decreased CES-D scores by a significant 1.03 points for each week completed. At 12 months follow-up, mean scores were 20.6±4.7 and PHQ-9 scores were 11.6±2.4, significantly lower than at baseline. Four out of 16 completers had symptoms that declined to below MDD criteria.<sup>34</sup></p> <p>One 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. One participant dropped out due to side effects (diarrhea); all participants described at least one adverse event. Mean compliance was 91.9%. The relapse rate did not differ between treated and untreated participants (52%).<sup>35</sup></p> <p>MedWatch warning on</p>			

<b>Conclusions from Original Systematic Review</b> <a href="#">Link to Review</a>	<b>Findings and Assessment from Prior Surveillance Assessment (August 2014)</b> <a href="#">Link to Report</a>	<b>Literature Analysis (March 2016)</b>	<b>Expert Opinion</b>	<b>Surveillance Assessment</b>
	<p>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 pharmacodynamic interaction.</p> <p><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</p>			

<b>Conclusions from Original Systematic Review</b> <a href="#">Link to Review</a>	<b>Findings and Assessment from Prior Surveillance Assessment (August 2014)</b> <a href="#">Link to Report</a>	<b>Literature Analysis (March 2016)</b>	<b>Expert Opinion</b>	<b>Surveillance Assessment</b>
	<p>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, patients who are CYP2C19 poor metabolizers, or patients who are taking cimetidine or another CYP2C19 inhibitor</li> <li>• Citalopram is contraindicated in patients with congenital</li> </ul>			

<b>Conclusions from Original Systematic Review</b> <a href="#">Link to Review</a>	<b>Findings and Assessment from Prior Surveillance Assessment (August 2014)</b> <a href="#">Link to Report</a>	<b>Literature Analysis (March 2016)</b>	<b>Expert Opinion</b>	<b>Surveillance Assessment</b>
	<p>long QT syndrome or known QT interval prolongation</p> <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 nine 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>			

*Abbreviations:* CES-D=Centre for Epidemiological Studies-Depression; FDA=Food and Drug Administration; HAM-D=Hamilton Rating Scale for Depression; MDD-Major Depressive Disorder; MHRA=Medicines and Healthcare Products Regulatory Agency; PHQ-9=Patient Health Questionnaire-9; SOE=Strength of Evidence; SRI=Selective Serotonin Reuptake Inhibitor; TCA=Tricyclic Antidepressant; TBI=Traumatic Brain Injury

Table 5. 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?

Conclusions from Original Systematic Review <a href="#">Link to Review</a>	Findings and Assessment from Prior Surveillance Assessment (August 2014) <a href="#">Link to Report</a>	Literature Analysis (March 2016)	Expert Opinion	Surveillance Assessment
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.	<p><b>August 2014 Assessment: Current</b> No new studies identified.</p> <p><b>November 2012 Assessment: Current</b> No new information</p> <p><b>March 2012 Assessment: Current</b> No new information</p>	A RCT (n=77) compared CBT to SPT over 16 weeks and found that while there was a significant reduction in scores on the BDI-II for the CBT group, severity reduction did not differ significantly between groups. There was no difference in remission rates. All participants improved on a measure of QOL, with no significant differences between groups. <sup>4</sup>	One expert believed the conclusion to be current. The second reviewer felt that the conclusion was no longer current; however, provided no supporting literature.	Conclusions are likely current.

*Abbreviations:* BDI-II=Beck Depression Inventory-2; CBT=Cognitive Behavioral Therapy; QoL=Quality of Life; RCT=Randomized Controlled Trial; SPT=Supportive Psychotherapy; TBI=Traumatic Brain Injury

Table 6. 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?

Conclusions from Original Systematic Review <a href="#">Link to Review</a>	Findings and Assessment from Prior Surveillance Assessment (August 2014) <a href="#">Link to Report</a>	Literature Analysis (March 2016)	Expert Opinion	Surveillance Assessment
No studies were identified that assessed the impact of demographic or other	<p><b>August 2014 Assessment: Current</b> No new studies identified.</p>	No studies were identified.	One expert believed the conclusion to be current. The second reviewer felt	Conclusions are likely current.

Conclusions from Original Systematic Review <a href="#">Link to Review</a>	Findings and Assessment from Prior Surveillance Assessment (August 2014) <a href="#">Link to Report</a>	Literature Analysis (March 2016)	Expert Opinion	Surveillance Assessment
potentially modifying characteristics on treatment effectiveness. Future research needs to address this issue.	<p><b>November 2012 Assessment: Current</b> No new information</p> <p><b>March 2012 Assessment: Current</b> In the citalopram blinded, placebo- controlled continuation study, relapse was not predicted by age, sex, employment status or overall baseline or post-treatment HAM-D scores. However, two HAM-D variables did predict higher risk for relapse: agitation and greater than mild psychic anxiety.<sup>35</sup></p>		that the conclusion was no longer current, and suggested a cross-sectional study examining demographic-injury profile, outcomes, service utilization, and unmet service needs of individuals with severe traumatic brain injury. The study did not meet study design criteria, nor did it present data specific to individuals with TBI and depression. <sup>9</sup>	

Abbreviations: HAM-D=Hamilton Depression Rating Scale; TBI=Traumatic Brain Injury

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