



University of
South Australia

International Centre for
Allied Health Evidence

ICAHE

A member of the Sansom Institute

Traumatic Brain Injury Review

**A systematic review of the evidence for
paediatric traumatic brain injury, and for
adults with mild traumatic brain injury**

Prepared for the:

ACC Traumatic Brain Injury Strategy
New Zealand

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1 INTRODUCTION

This report provides a comprehensive review of the currently available secondary evidence (guidelines and systematic reviews) to inform the ACC Traumatic Brain Injury (TBI) Strategy. This review focuses on two areas identified as gaps in current understanding:

1. Paediatric TBI (0-15 years)
2. Adults with mild TBI

ACC research had provided subsection questions for each of these focus areas, making a total of 20 search questions to be addressed by this evidentiary review.

1. Paediatric TBI (0-15 years): Consider the issues specific to paediatric TBI throughout their developmental milestones and the continuum of care.
 - 1.1 Initial acute care
 - 1.2 In-patient and out-patient rehabilitation
 - 1.3 Transitions of care
 - 1.4 Cognitive, Educational and training issues
 - 1.5 Community integration
 - 1.6 Challenging behaviour
 - 1.7 Growth and developmental issues
 - 1.8 Ongoing follow-up care and monitoring
 - 1.9 Needs of carers
2. Mild TBI: Consider the specific issues relevant to mild TBI in adults
 - 2.1 Screening for and early identification of mild TBI
 - 2.2 Initial acute care of those with a mild TBI
 - 2.3 Initial advice and outpatient rehabilitation
 - 2.4 Employment participation
 - 2.5 Community reintegration
 - 2.6 Substance abuse
 - 2.7 Depression
 - 2.8 Challenging behaviour
 - 2.9 Long-term impact and needs of mild TBI person
 - 2.10 Persistent symptoms and Issues specific to mild TBI: fatigue, headaches, pain
 - 2.11 Aging with mild TBI

2 METHODS

An independent research team, from the International Centre for Allied Health Evidence, University of South Australia, undertook an extensive systematic literature search to identify relevant secondary evidence related to the areas listed above. Team members, under the guidance of the project officer, took responsibility for identifying evidence relevant to allotted research questions, appraising the quality of that evidence and then extracting and reporting relevant data. The research team met twice a week for the duration of the project to coordinate the work and ensure high quality, consistent results.

2.1 Search strategy

1. *ACC reports and literature:* The research team was given access to literature known to the ACC Traumatic Brain Injury (TBI) Strategy team.
2. *Independent searching:* A comprehensive literature search was conducted, using a structured and iterative process, through the following databases and grey literature sites:

Databases	Guideline sites	Grey Literature sites
Medline	NICE (UK)	Google Scholar
EMBASE	NHMRC (Australian)	Grey Literature Report
CINAHL	Canadian Medical Assoc.	OIAster
PsychINFO	National Guideline Clearing House (US)	Australian Govt websites
Cochrane Databases	MJA (Australian)	World Health Org
Scopus		PROSPER
Web of Science		
ERIC		

Hand-searching (pearling) was conducted through the reference lists of the included reviews, to identify secondary evidence that had not previously been found.

The search terms comprised MeSH headings and key word text terms. Title and abstract searches were conducted using Boolean operators, wild cards and limiters as appropriate to each database. An example of the search terms and Medline search string for one question is provided in Appendix 1. Search terms were modified to suit each of the 20 subsection questions, and search procedures were modified to suit different databases.

2.2 Inclusion and exclusion criteria

Study selection occurred separately for each of the two focus areas (children with TBI and adults with mild TBI). Broad inclusion criteria applied to both areas:

- Inclusion criteria:
- Systematic reviews, meta-analysis or guidelines
 - Studies conducted on individuals with TBI (an injury to the brain resulting from externally inflicted trauma to the head)
 - Studies evaluating models of care for TBI management
 - Published Jan 2006 – March 2013
- Exclusion criteria:
- Non-English publications
 - Brain injury from other causes (eg. hypoxia, tumour, toxins)
- Inclusions specific to the paediatric TBI section:
- Secondary evidence focused on children or where information pertaining to children can be separated out.
 - Previously healthy children presenting with a TBI, i.e. as an injury to the brain resulting from externally inflicted trauma to the head.
- Exclusions specific to paediatric TBI:
- Brain injury as a result of birth trauma
- Inclusions specific to mild adult TBI section:
- Adult populations
 - Secondary evidence relevant to mild TBI or where information pertaining to mild TBI can be separated out.

2.3 Selection process

1. Initially titles identified from the database and website searches were examined, and clearly irrelevant items were eliminated. Of the remaining titles, abstracts were read and all potentially relevant articles for any of the search questions were identified. Details were entered into Excel spread sheets to track decisions about relevance and quality. Full copies of these potentially applicable articles were obtained for detailed examination.
2. The second step in selection considered the full text articles in terms of their relevance to each of the search questions. Articles that met the inclusion criteria and contributed information to either of the two focus areas were mapped against their relevance to the 20 search questions.
3. In the third step of the selection process, potentially relevant articles were critically appraised for quality. Systematic reviews were appraised using the CEBM critical appraisal tool (Appendix 2), and guidelines were appraised using the AGREE II tool (<http://www.agreetrust.org/?o=1397>). The critical appraisals were conducted by trained members of the iCAHE team, who underwent preliminary reliability testing. Summaries of critical appraisals for all key literature are provided in Appendix 3 (guidelines) and Appendix 4 (systematic reviews).

Systematic reviews were described as excellent quality if their CEBM score= 5/5; high quality 4/5, moderate quality 3/5, poor quality 0-2/5. Guidelines were described as excellent quality if their overall AGREE II score=7/7, high quality 5-6/7, moderate quality 4/7 and poor quality 0-3/7.

4. The final selection of secondary evidence for inclusion in this report was based on the relevance to the search question, the quality of the review/guideline, and the currency of the publication. For each of the 20 search questions, the highest ranked relevant articles underwent data extraction. Arbitrary quality cut off scores were determined to help decide on the most trustworthy secondary evidence to include in the report. Systematic reviews with CEBM scores <3 were excluded from detailed data extraction, as were guidelines with < 50% AGREE II percentage scores.

2.4 Data extraction and reporting

Recommendations or findings of the highest ranked guidelines and systematic reviews were extracted and reported in detail.

For clarity of reporting some of the 20 search questions were broken down into sub-sections. For example Question 2.1 on screening and early identification of mild TBI is addressed in seven subsections: Recommendations for initial screening; Indications for referral to hospital; Indications for referral for head CT scan; Recommendations to emergency department clinicians; Indication for admission to hospital; Recommendations for initial assessment; Indications for referral to the neurosurgical unit.

Information on the relevant primary evidence, which underpinned the key points of guideline/systematic reviews, was extracted and reported when this was provided in the article (the unavailability of primary evidence details is noted when this occurred). The quality of the primary evidence was also extracted and reported when this was made available by the authors. A variety of quality appraisal tools had been used by the guideline and review authors including:

- Downs & Black criteria (1998). Quality score out of 26
- The Centre for Evidence Based Medicine, 5 levels of evidence (CEBM)
- PEDro Score (for RCTs). Quality scored out of 10
- EAST Primer - 3 Classes of evidence
- Newcastle-Ottawa Scale (NOS). Quality score out of 9

A strength grading of recommendations, and the definition of the grading, is provided when this was made available in the guideline or systematic review. Strength grading definitions differed between publications.

For each of the 20 search questions or subsections, executive summaries are provided along with an evidence statement on the quality of the body of evidence found by the research

team. This evidence statement refers to the NHMRC Form Matrix (items 1-3) and the NHMRC Evidence Hierarchy levels. Copies of the NHMRC rating tools are provided in Appendix 5 and 6

2.5 Mapping against the existing NZ guideline

The final step of reporting was to map the results of the evidentiary review against the New Zealand Traumatic brain injury 2007 guidelines. The aim of this was to highlight where new evidence was available that either potentially changed previous recommendations or supported new recommendations, supported previous recommendations, or where gaps in evidence remained.

3 RESULTS

3.1 Overview

The following flow diagram provides a breakdown of the literature identification and selection for this report (Figure 1).

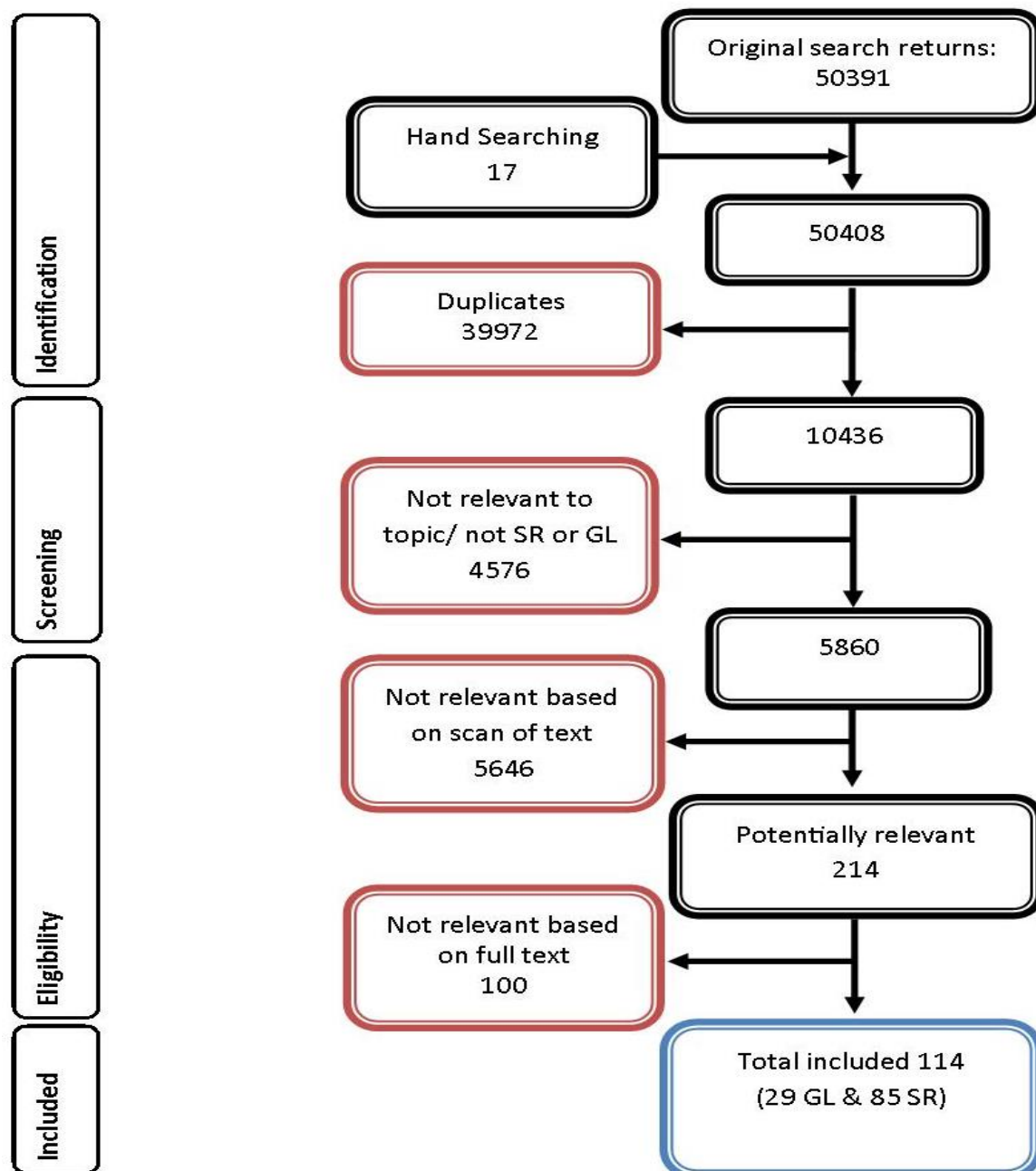


Figure 1. PRISMA flow chart of search results.

3.2 Summary

A total of 50408 articles and guidelines were found in the original searching process across all questions. Of these 39972 were excluded as duplicate references, a further 4576 were deemed irrelevant to the topic or were not secondary evidence (ie a systematic review or a guideline), based on title and abstract scan. The remaining 5860 articles were retrieved and scanned by five researchers for relevance to the questions posed, with a further 5646 found not relevant to the specific questions and/ or the TBI group of interest (either adult mild TBI or paediatric (0-15 years) TBI of any severity). A total of 214 articles were found to be potentially relevant to at least one of the 20 research questions, and went on to full review and quality appraisal (179 systematic reviews and 35 guidelines). Of these 214 potentially relevant results, 114 articles (29 guidelines and 85 systematic reviews) answered at least one of the 20 research questions.

Quality of the secondary evidence was quite variable. From the appraisal process 123 systematic reviews (of the 179 appraised) scored at or above the quality cut off CEBM score of 3/5, and 19 guidelines (of the 35 appraised) scored above the 50% AGREE II cut off score. The full results of this appraisal process are presented in Appendices 4 and 5.

It was noted that several paediatric secondary evidence articles were excluded due to the project's inclusion criteria of age 0 – 15 years (ie. excluded if information relevant to subjects 15 years and younger could not be separated out of a wider age range). It was also noted that the reference list of one included guideline (MAA NSW 2008) had some inconsistencies/errors that may subsequently have affected our reporting accuracy of those sections.

For some research questions considerable recent, good quality evidence was found, whereas little was found for other questions (for example ageing with mild TBI, and community reintegration). Table 1 below maps the new evidence found during this project against the recommendations/evidence available in the *New Zealand Guideline Group (2007) Traumatic brain injury: Diagnosis, acute management and rehabilitation*.

Table 1 Mapping the evidence against the existing NZ Guidelines (2007)

NZ Guideline 2007	New evidence supports previous recommendations		New evidence potentially changes previous/ adds new recommendations		No new evidence	
	Paediatrics	Adult mild	Paediatrics	Adult mild	Paediatrics	Adult mild
Pre-hospital assessment - acute	✓	✓	✓	✓		
Initial advice & information		✓		✓	✓	
Assessment of need for medical attention	✓	✓				
Non-accidental injury	✓		✓			✓
Organisation of trauma services		✓			✓	
Emergency Department assessment	✓	✓	✓	✓		
Primary investigation for suspected TBI	✓	✓		✓		
Imaging of people with a suspected TBI	✓	✓	✓	✓		
Use of corticosteroids & barbituates - acute TBI	✓		✓			✓
Surgical interventions	✓					NA
Other acute interventions			✓			✓
Transfer from secondary to tertiary care settings	✓	✓	✓			
Indications for hospital admission	✓	✓		✓		
In-hospital observation	✓	✓	✓			
Discharge from hospital	✓	✓	✓			
Rehabilitation organisation of services	✓		✓	✓		

NZ Guideline 2007	New evidence supports previous recommendations		New evidence potentially changes previous/ adds new recommendations		No new evidence	
	Paediatrics	Adult mild	Paediatrics	Adult mild	Paediatrics	Adult mild
Case coordination				✓	✓	
Rehabilitation teams & services		✓				
Rehabilitation assessment	✓	✓		✓		
Rehabilitation – physical intervention				✓		
Rehabilitation - function				✓	✓	
Rehabilitation - continence					✓	✓
Rehabilitation – sensory impairment			✓			✓
Rehabilitation – language & communication			✓			✓
Rehabilitation - cognitive		✓	✓	✓		
Rehabilitation – psychosocial & behavioural	✓	✓	✓	✓		
Rehabilitation – daily living tasks				✓	✓	
Vocational rehabilitation		✓		✓	NA	
Equipment & adaptations	✓			✓		NA
Sleep & fatigue	✓	✓		✓		
Leisure & recreation					✓	✓
Persistent symptoms -prevention					✓	✓
Persistent symptoms – assessment & management		✓	✓	✓		
Return to work or study/school	✓	✓	✓	✓		

NZ Guideline 2007	New evidence supports previous recommendations		New evidence potentially changes previous/ adds new recommendations		No new evidence	
	Paediatrics	Adult mild	Paediatrics	Adult mild	Paediatrics	Adult mild
Follow-up	✓	✓		✓		
Continuing care & support		✓	✓	✓		
Transitions	✓					NA
Needs of carers			✓			NA
Community integration		✓	✓			✓
Driving		✓			NA	
Substance abuse				✓	NA	
Challenging behaviour	✓	✓	✓	✓		
Depression		✓	✓	✓		
Immediate management of concussion	✓	✓	✓	✓		
Growth & development in children/ Long term impact in adults	✓	✓	✓	✓	✓	
Ageing with mild TBI						✓

NZ Guideline 2007	New evidence supports previous recommendations		New evidence potentially changes previous/ adds new recommendations		No new evidence	
	Paediatrics	Adult mild	Paediatrics	Adult mild	Paediatrics	Adult mild
Case coordination				✓	✓	
Rehabilitation teams & services		✓				
Rehabilitation assessment	✓	✓		✓		
Rehabilitation – physical intervention				✓		
Rehabilitation - function				✓	✓	
Rehabilitation - continence					✓	✓
Rehabilitation – sensory impairment						✓
Rehabilitation – language & communication					✓	✓
Rehabilitation - cognitive	✓	✓		✓		
Rehabilitation – psychosocial & behavioural		✓		✓		
Rehabilitation – daily living tasks				✓		
Vocational rehabilitation		✓		✓		
Equipment & adaptations				✓		
Sleep & fatigue		✓		✓		
Leisure & recreation					✓	✓
Persistent symptoms -prevention						✓
Persistent symptoms – assessment & management		✓		✓		
Return to work or study/school	✓	✓	✓	✓		

NZ Guideline 2007	New evidence supports previous recommendations		New evidence potentially changes previous/ adds new recommendations		No new evidence	
	Paediatrics	Adult mild	Paediatrics	Adult mild	Paediatrics	Adult mild
Follow-up						
Continuing care & support						
Transitions	?		?		?	
Needs of carers	?				?	
Community integration			✓			✓
Driving		✓				
Substance abuse	?		?			
Challenging behaviour	✓		✓			
Depression	?		?			
Immediate management of concussion		✓		✓		
Growth & development in children/ Long term impact in adults		✓		✓	✓	
Ageing with mild TBI	?		?			

3.3 Research questions

3.1.1 Question 1. Paediatric TBI (0-15 years): Consider the issues specific to paediatric TBI throughout their developmental milestones and the continuum of care

Question 1.1 What is the evidence for initial acute care in children (0-15) with TBI?

This question will be answered in subsections: Initial assessments (scales & scores), Assessment: Imaging and clinical decision rules, Intracranial pressure, Pharmacological treatments, Surgical treatments, Pre-hospital management and treatment, and Other treatments.

Initial assessment (scales & scores)

Executive summary

The evidence reviewed in this project for paediatric assessment scales, assessment scores and clinical decision rules and report mixed findings. All except one (Konigs et al. 2012) suggest the use of the paediatric version of the Glasgow Coma Scale (GCS), under the age of five years or in pre-verbal children. Konigs et al. (2012) suggested measuring post traumatic amnesia duration with the Wechsler Full Scale IQ, Performance IQ and Verbal IQ as a more reliable indicator of intellectual outcomes than the GCS. NICE (2007) also recommend that a grimace alternative be added to the verbal score for pre-verbal children.

Evidence statement

Key question	Rating	Notes
Evidence base	A	Information within high quality guidelines & reviews is based on data from observational studies and government agency reports
Consistency	B	Recommendations were inconsistent across studies, but discrepancies can be explained
Clinical impact	B	Substantial implications due difficulties related to assessing paediatric TBI population

Key guidelines regarding assessment

1. **SIGN 2009 Early management of patients with a head injury. Scottish Intercollegiate Guidelines Network**

AGREE II score 7/7

‘This guideline makes recommendations on the early management of patients with head injury, focusing on topics of importance throughout NHS Scotland.’ Recommendations are made for the management of adults and children.

Recommendations relevant to assessment scales and scores:

- *Great care should be taken when interpreting the Glasgow Coma Scale in the under fives and this should be done by those with experience in the management of the young child (p.12).*
 - The Glasgow Coma Scale is difficult to apply to young children. A modified GCS, the Paediatric Coma Scale and Score, is specific for use in children under the age of five years and lists specific indications for assessing TBI in children in this group (p.12).
 - Recommended best practice based on the clinical experience of the guideline development group.

2. Brain Trauma Foundation 2007. Guidelines for prehospital management of severe TBI

AGREE II score: 6/7

This US guideline updates an earlier 2000 edition. Recommendations are aimed at the pre-hospital management of adults and children with severe TBI, by emergency medical service personnel.

The recommendations for the use of the Glasgow Coma Scale and the Paediatric Glasgow Coma Scale were underpinned by literature from a systematic review, and by literature provided from experts in the field. The literature base for this recommendation was of low (Holmes 2005a) or poor (Johnson 1997; Massagli 1996; White 2001) methodological quality, with indirect evidence.

Recommendations relevant to assessment scales and scores:

- *The GCS and the paediatric GCS are reliable indicators of the severity of TBI in children and should be used repeatedly to identify improvement or deterioration over time.*
- *The adult protocol for standard GCS measurement should be followed in children over 2 years of age. In pre-verbal children, the P-GCS should be employed, with a full verbal score of 5 assigned to infants cooing or babbling.*
- *Prehospital providers should determine the GCS or P-GCS after airway, breathing, and circulation are assessed and stabilised.*
- *The GCS and P-GCS should be measured preferably prior to administering sedative or paralytic agents, or after these drugs have been metabolised (p.S14.)*

Reference	Design	Results		
Brain trauma foundation 2007				
Massagli, 1996	Retrospective review <i>Country:</i> NR <i>Sample:</i> n=33. Age= NR	Field GCS	Good Outcome Early Late	
Class III (high risk of bias)	Level of injury: Severe TBI	3–5	6%	12%
	<i>Methods:</i> NR <i>Hypothesis:</i> NR	6–15	67%	33%
using only the motor component of the GCS and a dichotomised outcome of good (moderate, no disability) vs. bad (dead, vegetative, or severely disabled), revealed that the GCS motor component alone was indicative of outcome				
Holmes, 2005	Prospective review <i>Country:</i> NR <i>Sample:</i> n=2043. Age= 0-18 years	Paediatric GCS Age < 2 years	Standard GCS 2 years and Older	
Class II (moderate risk of bias)	Level of injury: NR	Area Under the Curve and 90% Confidence Interval		
	<i>Methods:</i> NR	Eye opening		
	<i>Hypothesis:</i> NR	0.66 (0.53,0.79)	0.77(0.71,0.82)	
		Verbal		
		0.70 (0.55,0.85)	0.77 (0.71,0.82)	
		Motor		
		0.60 (0.48,0.72)	0.71 (0.65,0.77)	
		Total GCS		
		0.72 (0.65, 0.87)	0.82 (0.76, 0.87)	
The paediatric GCS accurately predicted 97% of infants needing acute intervention				
Johnson, 1997	Retrospective review <i>Country:</i> NR <i>Sample:</i> n=1320. Age= <14 years	GCS	EMS	Interfacility
Class III (high risk of bias)	Level of injury: 127-moderate, 94 severe	3–8	26.8%	1.7%
	<i>Methods:</i> compared mortality rate among 98 children with severe TBI; 56 children were transferred directly from the scene and 42 were transferred between facilities	9–12	50.0	2.3%
	<i>Hypothesis:</i> NR	13–15	0%	0%
		Mortality rates were significantly higher (50%) in children with a GCS between 3 and 8 when they were transferred from other facilities, compared to 27% for patients transported from the field.		
White, 2001	Retrospective review <i>Country:</i> NR <i>Sample:</i> n=136. Age= <14 years	GCS	Mortality	
Class III (high risk of bias)	Level of injury: 127-moderate, 94 severe	3	75%	
	<i>Methods:</i> Evaluated admission GCS and 6-hours GCS as predictors of outcome	4	18%	
	<i>Hypothesis:</i> NR	5	0%	
			6	6%
A higher GCS at 6 hours after admission to the paediatric intensive care unit was a better predictor of survival (odds				

ratio 4.6 and 95% CI 2.06, 11.9). All patients with a GCS > 8 at 6 hours survived

3. NICE 2007 Head injury: Triage, assessment, investigation and early management of head injury in infants, children and adults. National Institute of Health & Clinical Excellence

AGREE II score: 7/7

This UK guideline is the update of an earlier 2003 edition. 'This guideline addresses assessment, investigation and early management of head injury. Separate advice is provided for adults and children (including infants) where different practices are indicated' (p.4).

Recommendations relevant to assessment scales and scores:

- *Children under 10 years of age with a Glasgow Coma Score (GCS) of 8 or less should have CT imaging of the cervical spine within 1 hour of presentation or when they are sufficiently stable (p.7).*
- *The paediatric version of the Glasgow Coma Scale should include a 'grimace' alternative to the verbal score to facilitate scoring in pre-verbal children (p.9).*
- *Professionals should consider referral to an emergency department if any of the following factors are present depending on their own judgement of severity:*
 - Irritability or altered behaviour, particularly in infants and young children (that is, aged under 5 years)
 - Visible trauma to the head not covered above but still of concern to the professional
 - Adverse social factors (for example, no one able to supervise the injured person at home)
 - Continuing concern by the injured person or their carer about the diagnosis (p.16)

4. McCrory et al. Consensus Statement on Concussion in Sport – the 3rd International Conference on Concussion in Sport held in Zurich, Nov 2008. SAJSM; 2009; vol 21 No. 2.

AGREE II score: 4/7

This updated international consensus statement was 'developed for use by physicians, therapists, certified athletic trainers, health professionals, coaches and other people involved in the care of injured athletes, whether at the recreational, elite or professional level.' Recommendations apply to adults, adolescents and children. The guideline is based on a literature review, however details of its methodology are not provided.

The reference committee agreed that the following recommendations can apply to children and adolescents' ≥ 10 years; children below this age should be assessed with age appropriate checklists, as they report concussion symptoms differently to adults.

Recommendations relevant to assessment scales and scores:

- *The decision to use NP [neuropsychological] testing is broadly the same as the adult assessment paradigm. However, timing of testing may differ in order to assist planning in school and home management (and may be performed while the patient is still symptomatic).*
- *If cognitive testing is performed then it must be developmentally sensitive until late teen years due to the ongoing cognitive maturation that occurs during this period which, in turn, makes the utility of comparison to either the person's own baseline performance or to population norms limited.*
- *In this age group it is more important to consider the use of trained neuropsychologists to interpret assessment data, particularly in children with learning disorders and/or ADHD who may need more sophisticated assessment strategies.*
- *The panel strongly endorsed the view that children should not be returned to practice or play until clinically completely symptom free, which may require a longer time frame than for adults. In addition, the concept of 'cognitive rest' was highlighted with special reference to a child's need to limit exertion with activities of daily living and to limit scholastic and other cognitive stressors (eg. text messaging, videogames, etc.) while symptomatic. School attendance and activities may also need to be modified to avoid provocation of symptoms.*
- *Because of the different physiological response & longer recovery after concussion and specific risks (e.g. diffuse cerebral swelling) related to head impact during childhood and adolescence, a more conservative return to play approach is recommended. It is appropriate to extend the amount of time of asymptomatic rest and/ or the length of the graded exertion in children and adolescents. It is not appropriate for a child or adolescent athlete with concussion to RTP on the same day as the injury regardless of the level of athletic performance. Concussion modifiers apply even more to this population than adults and may mandate more cautious RTP advice (p.40-41).*

Key systematic review regarding assessment scales and scores

1. **Konigs, M., J. F. De Kieviet and J. Oosterlaan (2012). "Post-traumatic amnesia predicts intelligence impairment following traumatic brain injury: A meta-analysis." *Journal of Neurology, Neurosurgery and Psychiatry* 83(11): 1048-1055.**

CEBM score: 4/5

This review and meta-analysis examined the impact of TBI throughout the lifespan and the predictive value of post traumatic amnesia duration for impairment in intelligence. They

found four longitudinal studies (Knights et al. 1991; Chadwick et al. 1981; Catroppa & Anderson 2005; Cattelani et al. 1998) and 2 cross-sectional studies (Tremont et al. 1999; Catroppa & Anderson. 1999) on 147 children with TBI, of mixed quality scores.

Key findings from the review:

- Post traumatic amnesia duration strongly predicted depression of intelligence as measured by the Wechsler Full Scale IQ (FSIQ), Performance IQ (PIQ) and Verbal IQ (VIQ), the authors' state *"this is in line with previous studies reporting strong to moderate correlations between PTA duration and Wechsler scale FSIQ, PIQ and VIQ in children"* (p.1053).
- Post traumatic amnesia has shown to be of longer duration and impact in TBI as severity of the injury increases.
- Mild TBI is not associated with depression in intelligence scores.
- Age at time of injury has no significant effect on these outcomes.

The systematic review included the following studies in their review of this question:

Reference	Design	Results
Konigs 2012		
Knights et al. 1991	Longitudinal study <i>Country:</i> NR <i>Sample:</i> n=26. Ave Age=10.80	Moderate to strong relations between PTA duration and Welchsler scale FSIQ, PIQ and VIQ in children with TBI.
Newcastle-Ottawa Scale 1/9	Level of injury: mean GCS score= 5.50 <i>Methods:</i> performed intelligence testing at time of hospital discharge	Predictive value of PTA duration for intelligence is superior to that of GCS score, and LOC duration.
Tremont et al. 1999	Cross-sectional study <i>Country:</i> NR <i>Sample:</i> n=30. Ave Age=10.93	Moderate to strong relations between PTA duration and Welchsler scale FSIQ, PIQ and VIQ in children with TBI.
Newcastle-Ottawa Scale 6/9	Level of injury: mean GCS score= NR <i>Methods:</i> NR	Predictive value of PTA duration for intelligence is superior to that of GCS score, and LOC duration.
Chadwick et al. 1981	Longitudinal study <i>Country:</i> NR <i>Sample:</i> n=19. Ave Age=9.60	NR
Newcastle-Ottawa Scale 7/9	Level of injury: mean GCS score= NR <i>Methods:</i> NR	
Catroppa & Anderson 1999	Cross-sectional study <i>Country:</i> NR <i>Sample:</i> n=27. Ave Age=10.40 Level of injury: mean GCS score= 14.30	NR
Newcastle-Ottawa Scale 3/9	<i>Methods:</i> NR	

Catroppa & Anderson 2005	Longitudinal study <i>Country:</i> NR <i>Sample:</i> n=25. Ave Age=10.50 Level of injury: mean GCS score= 14.20 <i>Methods:</i> NR	NR
Newcastle-Ottawa Scale 3/9		
Cattelani et al. 1998	Longitudinal study <i>Country:</i> NR <i>Sample:</i> n=20. Ave Age=12.20 Level of injury: mean GCS score= 5 <i>Methods:</i> NR	NR
Newcastle-Ottawa Scale 3/9		

Assessment: Imaging and clinical decision rules

Executive summary

The evidence reviewed in this project for paediatric assessment imaging and clinical decision rules came from 3 systematic reviews (one excellent, one high, one moderate quality) and three guidelines (one excellent, one high, one moderate quality) and reported mixed findings. While the guidelines and systematic reviews agree on some markers for immediate CT scanning (abnormal drowsiness, three or more discrete episodes of vomiting, clinical suspicion of non-accidental injury, post-traumatic seizure but no history of epilepsy, suspicion of open or depressed skull injury or tense fontanelle, any sign of basal skull fracture, focal neurological deficit, or dangerous mechanism of injury (eg. high-speed road traffic accident either as pedestrian, cyclist or vehicle occupant, fall from a height of greater than 3 m, high-speed injury from a projectile or an object). Other markers received mixed reviews on reliability, namely GCS ranges from <15 to <13 on assessment in the emergency department and bruising or laceration.

The PECARN clinical decision rule was found to be the most sensitive and specific rule for discovering TBI in children and infants, however, the use of this rule could lead to an unacceptably high CT scan rate. The use of the CHALICE rule has been recommended instead, although in areas with no clinical decision rules in place this could still increase the rate of paediatric scanning.

Evidence statement

Key question	Rating	Notes
Evidence base	A	Information within high quality guidelines & reviews is based on data from observational studies and government agency reports, and expert consensus opinion
Consistency	C	Some recommendations were inconsistent across studies
Clinical impact	B	Substantial implications due difficulties related to assessing paediatric TBI population, and issues surrounding long term effects of radiation exposure

Key guidelines relevant to imaging and clinical decision rules

1. SIGN 2009 Early management of patients with a head injury. Scottish Intercollegiate Guidelines Network

AGREE II score 7/7

‘This guideline makes recommendations on the early management of patients with head injury, focusing on topics of importance throughout NHS Scotland.’ Recommendations are made for the management of adults and children.

The guideline discusses the implementation of the CHALICE criteria and the increase this would have on the present rates of CT scanning in Scotland. The guideline group did not feel this was a safe option as it would increase the number of children receiving a “*non-trivial radiation dose*” (p.21) from 1% to 14% of paediatric head injury cases.

Recommendations relevant to imaging and clinical decision rules:

- *Examination of children with a suspected head injury should be carried out by a clinician with experience in paediatric care.*
- *Immediate CT scanning should be done in a child (<16 years) who has any of the following features:*
 - GCS≤13 on assessment in emergency department
 - witnessed loss of consciousness >5 minutes
 - suspicion of open or depressed skull injury or tense fontanelle
 - focal neurological deficit (p.19)

(Grade B: A body of evidence including studies rated as high quality and directly applicable to the target population, and demonstrating overall consistency of results).

- *Any sign of basal skull fracture* (Grade C: A body of evidence including studies rated as low risk of bias and moderate probability that the relationship is causal, directly applicable to the target population and demonstrating overall consistency of results).

- *CT scanning should be considered within eight hours if any of the following features are present (excluding indications for an immediate scan):*
 - presence of any bruise/swelling/laceration >5 cm on the head
 - post-traumatic seizure, but no history of epilepsy nor history suggestive of reflex anoxic seizure
 - amnesia (anterograde or retrograde) lasting >5 minutes
 - clinical suspicion of non-accidental head injury
 - a significant fall
 - age under one year: GCS<15 in emergency department assessed by personnel experienced in paediatric GCS monitoring
 - three or more discrete episodes of vomiting
 - abnormal drowsiness (slowness to respond) (p.19)

(Grade C: A body of evidence including studies rated as low risk of bias and moderate probability that the relationship is causal, directly applicable to the target population and demonstrating overall consistency of results).

- *If a child meets head injury criteria for admission and was involved in a high speed road traffic accident, scanning should be done immediately.*
- *A child with a head injury who meets criteria for admission but not for an immediate CT scan should have active observation by experienced paediatric trained medical and nursing staff in an appropriate unit/ward. The decision to scan should be based on these observations.*
- *In any child where abuse is suspected a head CT scan should be performed as 'soon as the patient is stable' (within 24 hours of admission) for children:*
 - who present with evidence of encephalopathic features or focal neurological signs or haemorrhagic retinopathy, or
 - under the age of one (p.19)
- *Children under the age of 16 should not have a skull X-ray unless there is a specific clinical indication such as skeletal survey for non-accidental injury (p.20-21).*

(Recommended best practice based on the clinical experience of the guideline development group.)

2. Vos et al. Mild traumatic brain injury. *European Journal of Neurology* 2012, 19: 191–198

AGREE II score: 5/7

This European guideline provides recommendations for the acute management of adults and children presenting with mild TBI. It is aimed primarily at medical management.

Recommendations relevant to imaging and clinical decision rules:

- *In young patients with MTBI and a normal consciousness, prediction rules originally developed for adults may apply when they are 5 years of age or older (Grade C- established as possibly useful/predictive or not useful/predictive).*
- *In patients under 5 years of age, prediction rules for the need of CT to detect intracranial haematoma also apply but with a different set of risk factors, such as those applied in the Chalice study or the North American prospective cohort study (Grade A- established as useful/predictive or not useful/predictive).*
- *In young patients under 5 years of age, CT is a gold standard for the detection of life-threatening (and other intracranial) abnormalities after MTBI (Grade B- established as probably useful/predictive or not useful/predictive).*
- *In children under 2 years of age, a CT is not indicated if normal mental status, no scalp haematoma except frontal, no LOC or LOC for <5 s, non-severe injury mechanism, no palpable skull fracture and acting normally according to the parents (Grade A- established as useful/predictive or not useful/predictive).*
- *In children aged 2 years and older, a CT is not indicated if all apply: a normal mental status, no LOC, no vomiting, non-severe injury mechanism, no signs of basilar skull fracture and no severe headache (Grade A- established as useful/predictive or not useful/predictive) (p.194-195).*

3. NICE 2007 Head injury: Triage, assessment, investigation and early management of head injury in infants, children and adults. National Institute of Health & Clinical Excellence

AGREE II score: 7/7

This UK guideline is the update of an earlier 2003 edition. 'This guideline addresses assessment, investigation and early management of head injury. Separate advice is provided for adults and children (including infants) where different practices are indicated' (p.4).

Recommendations relevant to imaging and clinical decision rules:

- *Plain X-rays of the skull should not be used to diagnose significant brain injury without prior discussion with a neuroscience unit. However, they are useful as part of the skeletal survey in children presenting with suspected non-accidental injury (p.22).*
- *Children (under 16 years) who have sustained a head injury and present with any one of the risk factors in box 6 should have CT scanning of the head requested immediately (p.23).*

Criteria for immediate request for CT scan of the head (children)

Loss of consciousness lasting more than 5 minutes (witnessed).

Amnesia (antegrade or retrograde) lasting more than 5 minutes.

Abnormal drowsiness.

Three or more discrete episodes of vomiting.

Clinical suspicion of non-accidental injury.

Post-traumatic seizure but no history of epilepsy.

GCS less than 14, or for a baby under 1 year GCS (paediatric) less than 15, on assessment in the emergency department.

Suspicion of open or depressed skull injury or tense fontanelle.

Any sign of basal skull fracture (haemotympanum, 'panda' eyes, cerebrospinal fluid leakage from the ear or nose, Battle's sign).

Focal neurological deficit.

If under 1 year, presence of bruise, swelling or laceration of more than 5 cm on the head.

Dangerous mechanism of injury (high-speed road traffic accident either as pedestrian, cyclist or vehicle occupant, fall from a height of greater than 3 m, high-speed injury from a projectile or an object).

(p.24)

- *Children aged 10 years or more can be treated as adults for the purposes of cervical spine imaging (p.29).*
- *Children under 10 years should receive anterior/posterior and lateral plain films without an anterior/posterior peg view (p.29).*
- *In children under 10 years, because of the increased risks associated with irradiation, particularly to the thyroid gland, and the generally lower risk of significant spinal injury, CT of the cervical spine should be used only in cases where patients have a severe head injury (GCS \leq 8), or where there is a strong clinical suspicion of injury despite normal plain films (for example, focal neurological signs or paraesthesia in the extremities), or where plain films are technically difficult or inadequate (p.29).*
- *In line with good radiation exposure practice every effort should be made to minimise radiation dose during imaging of the head and cervical spine, while ensuring that image quality and coverage is sufficient to achieve an adequate diagnostic study (p.30).*

Systematic reviews regarding imaging and clinical decision rules

1. Pickering, A., S. Harnan, P. Fitzgerald, A. Pandor and S. Goodacre (2011). "Clinical decision rules for children with minor head injury: A systematic review." *Archives of Disease in Childhood* 96(5): 414-421.

CEBM score: 5/5

This review examined clinical decision rules for identifying mild TBI in children and compared the diagnostic accuracy for detection of intracranial injury and injury requiring neurosurgical intervention. This review found 16 cohort studies covering 14 cohort groups with a total of 79740 participants.

Key findings from the review:

- Four validated decision rules were found; children's head injury algorithm for the prediction of important clinical events (CHALICE); paediatric emergency care applied research network (PECARN); National Emergency X-Radiography Utilization Study II (NEXUS II); University of California–Davis rule (UCD).
- Of the current decision rules for minor head injury the PECARN rule appears the best for children and infants, with the largest cohort, highest sensitivity and acceptable specificity for clinically significant intracranial injury.
- Application of the PECARN rule in the UK would probably result in an unacceptably high rate of CT scans per injury, and continued use of the CHALICE based NICE guidelines represents an appropriate alternative.
- For identifying one clinically significant intracranial injury, using the positive predictive values from the data, use of PECARN would result in scans of approximately 50 children. Use of CHALICE would result in scans of only 18 children. For identifying one neurosurgical injury use of PECARN would result in scans of over 200 children while use of CHALICE would result in scans of 24 children. These figures demonstrate a more refined approach to risk management in the CHALICE group, and reduce the risk of excessive radiation exposure to this group.

2. **Pandor, A., S. Harnan, S. Goodacre, A. Pickering, P. Fitzgerald and A. Rees (2012). "Diagnostic accuracy of clinical characteristics for identifying CT abnormality after minor brain injury: a systematic review and meta-analysis." *Journal of Neurotrauma* 29(5): 707-718.**

CEBM score: 4/5

This review examined the diagnostic value of clinical characteristics that can be used to identify intracranial injury (including the need for neurosurgery). They found 71 studies, 26 of which provided data for brain injuries in children and infants. They did not present this information as individual studies, but rather summed the total of the 26 studies into two sections; children, and infants.

Most clinical decision rules for children use loss of consciousness, a GCS < 15, skull fracture, vomiting, headache, and visible injury as criteria. However, the meta-analysis conducted by Pandor et al (2012) indicates that individual characteristics of loss of consciousness, GCS < 15, skull fracture, vomiting, and headache (if severe or persistent), but that scalp laceration/hematoma or an undefined headache were of little diagnostic value. Pandor et al

(2012) goes on to state *“many rules do not use focal neurological deficit, amnesia, seizures, mechanism of injury, or coagulopathy as criteria. However, our meta-analysis suggested that these criteria were all potentially diagnostically useful. Overall the Children’s Head injury Algorithm for the prediction of Important Clinical Events (CHALICE) (Dunning et al., 2006) and National Emergency X-radiography Utilization Study II (NEXUS II) (Mower et al., 2005) rules appeared to be most consistent with the findings of our meta-analysis, in terms of including criteria that are diagnostically useful and excluding those that are not”* (p.716).

Key findings from the review:

Children:

- The most useful clinical characteristics were depressed or basal skull fracture and focal neurological deficit (Positive likelihood ratio (PLR) > 10).
- Coagulopathy, post-traumatic seizure, and previous neurosurgery all markedly increased the likelihood of intracranial injury (PLR 5–10).
- Visual symptoms, bicycle and pedestrian MVA, seizure, loss of consciousness, persistent vomiting, severe or persistent headache, anterograde or posttraumatic amnesia, GCS < 14, GCS < 15, intoxication, and radiological skull fracture all moderately increased the likelihood of intracranial injury (PLR 2–5).
- Headache (other than severe or persistent), scalp hematoma, and scalp laceration were not diagnostically useful.

Infants:

- Depressed skull fracture or focal neurological deficit indicated a substantially increased risk of intracranial injury (PLR > 10).
- Meta-analytical data suggested that radiological skull fracture, GCS < 15 and any loss of consciousness moderately increased the likelihood of intracranial injury (PLR 2–5).

3. **Keightley, M. L., J. K. Chen and A. Ptito (2012). "Examining the neural impact of pediatric concussion: A scoping review of multimodal and integrative approaches using functional and structural MRI techniques." *Current Opinion in Pediatrics* 24(6): 709-716.**

CEBM score: 3/5

This systematic review examined the use of functional and structural MRI scanning on the examination of the impact of concussion on the developing brain. They found only five studies, of unknown quality. They state that the literature is too scarce to formulate any definitive conclusions on neuroimaging and investigations, and the efficacy of MRI in revealing brain abnormalities after concussion.

Other earlier or lower quality evidence on the topic includes:

Barbosa, R. R., R. Jawa, J. M. Watters, J. C. Knight, A. J. Kerwin, E. S. Winston, R. D. Barraco, B. Tucker, J. M. Bardes, S. E. Rowell and T. Eastern Association for the Surgery of (2012). "Evaluation and management of mild traumatic brain injury: an Eastern Association for the Surgery of Trauma practice management guideline." The Journal of Trauma and Acute Care Surgery 73(5 Suppl 4): S307-314. (AGREE II score: 3/7)

Intracranial pressure

Executive summary

The evidence reviewed in this project for associations of paediatric intracranial pressure and poor outcomes included two good quality clinical guidelines and report consistent findings. Findings indicated that the treatment threshold of intracranial pressure levels in children is 20 mm Hg, and intracranial hypertension therapy supports the use of intracranial pressure monitoring in children with severe TBI.

Evidence statement

Key question	Rating	Notes
Evidence base	A	Information within high quality guidelines & reviews is based on data from observational studies and government agency reports
Consistency	A	Recommendations were consistent across studies
Clinical impact	B	Substantial implications due to severity of injuries and potential long term effects on both the child/children involved and their carers

Key guidelines regarding intracranial pressure

1. **Brain Trauma Foundation 2012. Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents - 2nd Ed.**

AGREE II score: 5/7

This US guideline updates an earlier 2003 edition. Recommendations for the management of infants, children and adolescents with severe TBI are aimed at acute care clinicians (primarily medical staff).

Although levels have been assigned to these recommendations, explanation of these levels was not supplied in the guideline.

- *Use of intracranial pressure monitoring may be considered in infants and children with severe traumatic brain injury (p.S11).*
 - Two moderate and 14 poor quality studies reported high incidence of intracranial pressure in paediatric head injury, widely reported association between intracranial pressure and poor outcomes, agreement between protocol-based intracranial hypertension therapy and best reported clinical outcomes, and improved outcomes associated with intracranial hypertension therapy support the use of intracranial pressure monitoring in children with severe TBI.
- *Treatment of intracranial pressure may be considered at a threshold of 20mm Hg (p.S18).*
 - Eleven poor quality studies indicated that sustained elevation of intracranial pressure (>20mm Hg) is associated with poor outcomes in children with a severe TBI.
- *A minimum cerebral perfusion pressure of 40 mm Hg may be considered in children with TBI. A cerebral perfusion pressure of 40-50mm Hg may be considered. There may be age-specified thresholds with infants at the lower end and adolescents at the upper end of this range (p.S24).*
 - Three moderate quality and eight poor quality studies indicate that survivors of severe TBI undergoing intracranial pressure monitoring had consistently higher cerebral perfusion pressure than non-survivors. However, no study showed a reduction in mortality/morbidity when active maintenance of cerebral perfusion pressure above any targeted threshold.
- *If brain oxygenation monitoring is used, maintenance of partial pressure of brain tissue oxygen ≥ 10 mm Hg may be considered (p.S30).*
 - One poor quality case series and one moderate quality cohort indicate that advanced neuromonitoring may provide useful information in regards to abnormalities in cerebral oxygenation, blood flow/metabolism, autoregulation and function after severe TBI.
- *In the absence of neurologic deterioration or increasing intracranial pressure, obtaining a routine repeat computed tomography scan >24 hours after the admission and initial follow up study may not be indicated for decisions about neurosurgical interventions (p.S33).*
 - The one poor quality case series found questions the use of repeated CT scans in the absence of increasing intracranial pressure or neurologic deterioration.

2. Liao K-H et al. Clinical practice guidelines in severe traumatic brain injury in Taiwan. *Surgical Neurology* 72 (2009) S2:66–S2:74

AGREE II score: 5/7

This Taiwanese guideline updates an earlier 2000 edition. Recommendations are made for the management of adults and children with severe TBI, and include ED, acute medical and surgical care.

- *The treatment threshold of intracranial pressure levels in children is 20 mm Hg.*
 - Three good-moderate quality studies (Adelson et al. 2003; Howells et al. 2005; Saul & Ducker 1982) informed this recommendation. No details of the individual studies were supplied by the guideline authors.

Pharmacological treatments

Executive summary

The evidence reviewed in this project for pharmacological management of paediatric TBI came from one systematic review and one guideline and reported consistent findings. Roberts and Sydenham (2012) found no evidence for harmful effects of barbiturate therapy in reducing mortality, disability and raised intracranial pressure, and the Brain Trauma Foundation (2012) found this an effective therapy, although they did not establish the efficacy of this treatment in terms of increase in survival. Further pharmacological measures are discussed in the Brain Trauma Foundation (2012) guideline.

Evidence statement

Key question	Rating	Notes
Evidence base	A	Information within high quality guidelines & reviews is based on data from observational studies and government agency reports
Consistency	A	Recommendations were consistent across studies
Clinical impact	B	Substantial implications regarding pharmacology in paediatric TBI

Key guideline relevant to pharmacological treatments:

1. **Brain Trauma Foundation 2012. Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents - 2nd Ed.**

AGREE II score: 5/7

This US guideline updates an earlier 2003 edition. Recommendations for the management of infants, children and adolescents with severe TBI are aimed at acute care clinicians (primarily medical staff). Although levels have been assigned to these recommendations, explanation of these levels was not supplied in the guideline.

Recommendations relevant to pharmacological treatments:

- *High dose barbiturate therapy may be considered in hemodynamically stable patients with refractory intracranial hypertension despite maximal medical and surgical management. When high-dose barbiturate therapy is used to treat refractory intracranial hypertension, continuous arterial blood pressure monitoring and cardiovascular support to maintain adequate cerebral perfusion pressure are required (p.S49).*
 - The evidence (two poor quality case series) suggests that barbiturates effectively lower intracranial pressure in a subset of children with intractable intracranial hypertension; however, beneficial outcomes in regards to survival or neurological aspects have not been established.
- *The use of corticosteroids is not recommended to improve outcome or reduce intracranial pressure for children with severe TBI (p.S61).* (The level of evidence for this recommendation was from one moderate quality RCT).
 - The included moderate quality study found significant suppression of endogenous cortisol levels and a trend towards pneumonia in children treated with corticosteroids. As there was a lack of benefit found in conjunction with this the use of corticosteroids is not recommended.
- *Etomidate may be considered to control severe intracranial hypertension; however, the risks resulting from adrenal suppression must be considered. Thiopental may be considered to control intracranial hypertension (p.S64).*
 - Two low quality studies informed this recommendation, and despite the common use of analgesics, sedatives and neuromuscular blockades in the management of severe TBI, there have been few studies to focus on paediatric patients.
- *Prophylactic treatment with phenytoin may be considered to reduce the incidence of early post traumatic seizures in paediatric patients with severe TBI (p.S72).*
 - One moderate quality cohort study found treatment with anticonvulsant therapy may reduce the incidence of early risk of seizures, however, there was no compelling data to suggest that this treatment would reduce long term risk of post traumatic seizures or improve neurological outcomes over the long term.

Key systematic reviews relevant to pharmacological treatments:

1. **Roberts, I. and E. Sydenham (2012) "Barbiturates for acute traumatic brain injury." Cochrane Database of Systematic Reviews DOI: 10.1002/14651858.CD000033.pub2.**

CEBM score: 5/5

This review examined the effects of barbiturates in reducing mortality, disability and raised intracranial pressure in people with acute traumatic brain injury, and the possible side effects associated with the use of barbiturates. Of the seven eligible trials two included children;

Ward 1985 combined the results of children and adults and as such was not considered in this report. Bohn 1989 included 82 children with severe head injury (GCS ≤ 7).

Key findings from the review:

- The intracranial pressure lowering effect of barbiturates is believed to be due to the coupling of cerebral blood flow to regional metabolic demands. By suppressing cerebral metabolism, barbiturates reduce cerebral metabolic demands, thus reducing cerebral blood volume and intracranial pressure.
- The authors conclude that there is no current evidence to support the use of barbiturate therapy in TBI.
- In one in four patients, barbiturates resulted in a lowering of blood pressure that would offset any gain from intracranial pressure lowering that may have resulted from barbiturate therapy.
- No significant risk factors for barbiturates were found in this paper.

The systematic review included the following studies in their review of this question:

Reference	Design	Results
Roberts & Sydenham		
Bohn 1989	RCT <i>Country:</i> NR <i>Sample:</i> n=82. Ave Age=? (1-18 years)	Death and Glasgow Outcome Score were measured at time of hospital discharge and at 6 months.
Cochrane risk of bias score 3/8	Level of injury: GCS score ≤ 7 <i>Methods:</i> High-dose phenobarbitone (loading dose 50 mg/kg followed by 20 mg/kg/day) or no phenobarbitone <i>Hypothesis:</i> NR	Allocation was according to ICU physician on duty Blinding was not described. Risk ratio of death at the end of the follow up was 1.00 [95% CI 0.49, 2.04]. Risk ratio of death or severe disability at end of the follow up period was 1.38 [95% CI 0.79, 2.44].

Surgical treatments

Executive summary

The evidence reviewed in this project for surgical management of paediatric TBI came from two good quality guidelines and reported consistent findings. Both reported craniotomy may be beneficial, although the Brain Trauma Foundation (2006) state there is not enough data to support one surgical method over another, the Brain Trauma Foundation (2012) recommends (based on poor quality evidence) decompressive craniotomy with duraplasty may be the most beneficial in cases of neurological deterioration.

Evidence statement

Key question	Rating	Notes
Evidence base	A	Information within guidelines is based on data from poor quality case series studies and expert opinion
Consistency	A	Recommendations were consistent across guidelines
Clinical impact	C	Moderate implications regarding surgical management of paediatric TBI

Key guidelines relevant to surgical treatments:

1. Brain Trauma Foundation 2006. Guidelines for surgical management of TBI.

AGREE II score: 6/7

The overall aim of these US guidelines is to provide rigorous literature-based recommendations for the surgical management of adults and children with post traumatic intracranial mass lesions. (Lesions that develop within 10 days of injury, not chronic subdural haematoma) (p.S2-2).

The incidence of associated epidural haematoma post trauma is lower in very young children and neonates than in older children (6-10 years), which is less again than the incidence in adults. Falls are the leading cause of associated epidural haematoma. This is closely followed by traffic accidents. All studies found in this review were of low level evidence (they carried a significant risk of bias) and as such, reflect unclear clinical certainty. Expert opinion has been used to derive recommendations from the literature.

Recommendations relevant to surgical treatment:

- *Epidural hematoma greater than 30 cm³ should be surgically evacuated regardless of the patient's GCS score. Hematomas less than this, with less than a 5mm midline shift in patients with a GCS score <8 without focal deficit can be managed nonoperatively with serial computed tomographic scanning and close neurological observation in a neurosurgical centre.*
- *It is strongly recommended that patients with an acute epidural haematoma in coma (GCS score <9) with anisocoria undergo surgical evacuation as soon as possible.*
- *There are insufficient data to support one surgical treatment method. However, craniotomy provides a more complete evacuation of hematoma (p.S3-7).*

2. Brain Trauma Foundation 2012. Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents- 2nd Ed.

AGREE II score: 5/7

This US guideline updates an earlier 2003 edition. Recommendations for the management of infants, children and adolescents with severe TBI are aimed at acute care clinicians (primarily medical staff).

Although levels have been assigned to these recommendations, explanation of these levels was not supplied in the guideline.

- *Decompressive craniectomy with duraplasty, leaving the bone flap out, may be considered for paediatric patients with TBI who are showing early signs of neurologic deterioration or herniation or are developing hypertension refractory to medical management during the early stages of their treatment (p.S53).*
 - Eight poor quality case series suggest the effects of decompressive surgery in reversing early signs of neurologic deterioration may be correlated with improved outcomes in critically ill paediatric patients. The evidence suggests this is only applicable to large duraplasties.

Pre-hospital management and treatment

Executive summary

The evidence reviewed in this project for pre-hospital treatment of paediatric TBI came from one good quality guideline, one moderate quality guideline and one excellent quality systematic review, and reported consistent findings around the pre-hospital assessment, transfer, treatment and monitoring of TBI. Inconsistent evidence was reported by von Elm et al. (2009) around pre-hospital tracheal intubation.

Evidence statement

Key question	Rating	Notes
Evidence base	A	Information within guidelines is based on data from poor quality case series studies, database reviews and expert opinion
Consistency	A	Recommendations were consistent across guidelines
Clinical impact	B	substantial implications regarding pre-hospital management of paediatric TBI

Key guidelines relevant to pre-hospital management and treatment

1. **Brain Trauma Foundation 2007. Guidelines for prehospital management of severe TBI**

AGREE II score: 6/7

This US guideline updates an earlier 2000 edition. Recommendations are aimed at the pre-hospital management of adults and children with severe TBI, by emergency medical service personnel.

The literature base for this recommendation was very limited, hospital based, and of the poorest quality accepted by this guideline committee (Kokoska et al. 1998; Pigula et al. 1993; Vavilala et al. 2003).

Recommendations relevant to pre-hospital management and treatment:

- *Paediatric patients with suspected severe TBI should be monitored in the pre-hospital setting for hypotension. Paediatric hypotension is defined as follows:*

Age	SBP
0 to 28 days	<60 mmHg
1–12 months	<70
1–10 years	< 70 + 2 × age in years
>10 years	<90

- *Percentage of blood oxygen saturation should be measured continuously in the field with a pulse oximeter using an appropriate paediatric sensor.*
- *Systolic blood pressure (SBP) and diastolic blood pressure (DBP) should be measured using an appropriately sized paediatric cuff. When a blood pressure is difficult to obtain because of the child's age or body habitus, documentation of mental status, quality of peripheral pulses, and capillary refill time can be used as surrogate measures.*
- *Oxygenation and blood pressure should be measured as often as possible, and should be monitored continuously if possible (p.S11.)*

The guideline included the following studies in their review of this question:

Reference	Design	Results
Brain trauma foundation 2007		
Kokoska et al., 1998	Retrospective review Country: NR Sample: n=72. Age= 3 months - 14 years) Level of injury: GCS= 6-8	Pre-hospital, ED and ICU hypotensive episodes were significantly associated with poor outcome.
Class III (high risk of bias)	Methods: NR Hypothesis: NR	
Pigula et al., 1993	Prospective review Country: NR Sample: n=58. Age <17years Level of injury: GSC<8	An episode of hypotension decreased survival fourfold.
Class III (high risk of bias)	Methods: NR Hypothesis: effect of hypotension (SBP<90 mmHg) on outcome.	

Vavilala <i>et al.</i> , 2003	Retrospective review <i>Country:</i> NR <i>Sample:</i> n=NR. Age= <14 years Level of injury: AIS [*] <2, GCS <9	Among children with SBP below the 75th percentile for age, 63% had poor outcome and 29% died. By comparison children with SBP > 75th percentile for age, 29% had poor outcome and 10% died.
Class III (high risk of bias)	<i>Methods:</i> NR <i>Hypothesis:</i> NR	A systolic blood pressure less than the 75 th percentile for age is associated with poor outcome and higher mortality rate.

*AIS = Abbreviated Injury Severity Scale

The recommendation for treatment of hypotension in paediatric TBI patients is underpinned by literature from a systematic review and literature recommended by experts in the field and found in reference lists. The literature was of the lowest quality accepted by the guideline committee. Seven studies which focused solely on children informed this section of the guideline.

- *For the paediatric TBI patient, hypotension should be treated with isotonic solutions (p.S32).*

Haemorrhage following trauma decreases cardiac preload. Fluid therapy is used to support cardiovascular function and peripheral oxygen delivery in the incidence of preload. In patients with TBI, decreased cerebral perfusion can increase the extent of the primary injury. Specifically, hypotension has been shown to produce significant secondary brain injury and substantially worsen outcome. In children, fluid resuscitation is indicated for clinical signs of decreased perfusion even when an adequate blood pressure reading is obtained. The goal of pre-hospital fluid resuscitation is to support oxygen delivery and optimise cerebral hemodynamics.

The guideline included the following studies in their review of this question:

Reference	Design	Results
Brain trauma foundation 2007		
Johnson, 1995	Retrospective medical record and imaging review <i>Country:</i> NR <i>Sample:</i> n=28. Age= NR Level of injury: confirmed child abuse with significant TBI	Apnea was present in majority of patients and 50% of children were also hypotensive. No patient with clinical evidence of cerebral hypoxia and/or ischemia had a good outcome.
Class III (high risk of bias)	<i>Methods:</i> NR <i>Hypothesis:</i> NR	
Kokoska, 1998	Retrospective chart review <i>Country:</i> NR <i>Sample:</i> n=NR. Age NR	Early hypotension linked to prolonged length of stay and worse 3 month GOS.

Class III (high risk of bias)	Level of injury: NR <i>Methods:</i> NR <i>Hypothesis:</i> NR	
Levin, 1992	Prospective data bank cohort study <i>Country:</i> NR <i>Sample:</i> n=103. Age= <16 years	Outcome was poorest in 0-4 year age group, which had an increased incidence of evacuated subdural hematomas (20%) and hypotension (32%). 14-21% in all age ranges were hypoxic.
Class III (high risk of bias)	Level of injury: GCS <9 <i>Methods:</i> NR <i>Hypothesis:</i> NR	
Luerssen, 1988	Prospective series <i>Country:</i> NR <i>Sample:</i> n=1906. Age= <15 years	Only hypotension was associated with higher mortality in children. Children with severe hypertension had the lowest mortality rate.
Class III (high risk of bias)	Level of injury: NR <i>Methods:</i> NR <i>Hypothesis:</i> NR	
Mayer, 1985	Prospective study <i>Country:</i> NR <i>Sample:</i> n=200. Age= 3 weeks -16 years	Mortality 55% with any hypotension, hypercarbia or hypoxia vs. 7.7% without.
Class III (high risk of bias)	Level of injury: GCS <8 <i>Methods:</i> NR <i>Hypothesis:</i> NR	
Michaud, 1992	Retrospective study <i>Country:</i> NR <i>Sample:</i> n=75. Age= <15 years	Mortality increased if hypotension or abnormal pupils noted in the field. ED pO ₂ > 350 better outcome; pO ₂ 105–350 same outcome as hypoxic group.
Class III (high risk of bias)	Level of injury: GCS ≤8 <i>Methods:</i> Assessed fatality rate in system with advanced EMS and regional trauma center (83% received EMS field care). Identified factors predictive of survival and/or disability. GOS at discharge from acute care hospital measured. <i>Hypothesis:</i> NR	
Ong, 1996	Prospective cohort study <i>Country:</i> Kuala Lumpur <i>Sample:</i> n=151. Age= <15 years	Hypoxia increased poor outcome by 2 to 4 fold in severe TBI.
Class III (high risk of bias)	Level of injury: GCS < 15 <i>Methods:</i> Follow-up GOS at discharge and 6 months <i>Hypothesis:</i> NR	

2. NICE 2007 Head injury: Triage, assessment, investigation and early management of head injury in infants, children and adults. National Institute of Health & Clinical Excellence

AGREE II score: 7/7

This UK guideline is the update of an earlier 2003 edition. 'This guideline addresses assessment, investigation and early management of head injury. Separate advice is provided for adults and children (including infants) where different practices are indicated' (p.4).

Recommendations relevant to pre-hospital management and treatment:

- *The following principles should be adhered to in the immediate care of patients who have sustained a head injury.*
 - Children...who have sustained a head injury should initially be assessed and their care managed according to clear principles and standard practice... clear principles are outlined in the Advanced Paediatric Life Support (APLS)/European Paediatric Life Support (EPLS) course, the Pre-hospital Paediatric Life Support (PHPLS) course and the Paediatric Education for Pre-hospital Professionals (PEPP) course (p.17).
- *Ambulance crews should be fully trained in the use of the adult and paediatric versions of the Glasgow Coma Scale.*
- *Ambulance crews should be trained in the detection of non-accidental injury and should pass information to emergency department personnel when the relevant signs and symptoms arise.*
- *The priority for those administering immediate care is to treat first the greatest threat to life and avoid further harm.*
- *Patients who have sustained a head injury should be transported directly to a facility that has been identified as having the resources necessary to resuscitate, investigate and initially manage any patient with multiple injuries. It is expected that all acute hospitals and all neuroscience units accepting patients directly from an incident will have these resources, and that these resources will be appropriate for a patient's age (p.17).*
- *Patients who have sustained a head injury and present with any of the following risk factors should have full cervical spine immobilisation attempted unless other factors prevent this:*
 - GCS less than 15 on initial assessment by the healthcare professional
 - neck pain or tenderness
 - focal neurological deficit
 - paraesthesia in the extremities
 - any other clinical suspicion of cervical spine injury
- *Cervical spine immobilisation should be maintained until full risk assessment including clinical assessment (and imaging if deemed necessary) indicates it is safe to remove the immobilisation device.*
- *Standby calls to the destination emergency department should be made for all patients with a GCS less than or equal to 8, to ensure appropriately experienced professionals are available for their treatment and to prepare for imaging.*

- *Pain should be managed effectively because it can lead to a rise in intracranial pressure. Reassurance and splintage of limb fractures are helpful; catheterisation of a full bladder will reduce irritability (p.18).*

Key systematic reviews regarding pre-hospital management and treatment

1. von Elm, E., P. Schoettker, I. Henzi, J. Osterwalder and B. Walder (2009) "Pre-hospital tracheal intubation in patients with traumatic brain injury: systematic review of current evidence." *British Journal of Anaesthesia* 103, 371-386.

CEBM score: 5/5

This review investigated the benefit/ harm of pre-hospital tracheal intubation and mechanical ventilation after TBI. Of the 13 studies found, five moderate to poor quality studies used paediatric groups (Souminen et al. 2000; Cooper et al. 2001; DiRusso et al. 2005; Stanic-Canji et al. 2006).

The overall evidence on the efficacy and harms associated with pre-hospital intubation was of low strength/quality and there were no consistency in harm/benefits between studies. Multiple and prolonged intubation attempts, inadequate oxygenation, or excessive ventilation can contribute to secondary brain insult, furthermore, if this invasive procedure and the ensuing mechanical ventilation are performed poorly, the negative effects may outweigh any potential benefits. Adequate training of staff is therefore crucial and should be the subject of future quality improvement studies. The authors consider the poor quality and inconsistent results of the included studies to be insufficient to underpin a recommendation of pre-hospital intubation.

Key findings from the review:

- The overall available evidence did not support any benefit for pre-hospital intubation and mechanical ventilation after TBI.
- Pre-hospital intubation was consistently associated with increased odds of pneumonia.
- The results were contradictory across the included studies.

The systematic review included the following studies in their review of this question:

Reference	Design	Results
von Elm et al.		
Suominen et al. 2000	Database study <i>Country:</i> Finland <i>Sample:</i> n=59. Ave Age=? (<16 years)	NR
3	Level of injury: AIS* score ≥ 4 <i>Methods:</i> Pre-hospital vs intubation in ED of regional hospital vs intubation in ED of trauma centre <i>Hypothesis:</i> NR	
Gausche et al. 2000	Controlled clinical trial with treatment allocation alternating by day <i>Country:</i> USA <i>Sample:</i> n=61. Age ≤ 12 years	Inconclusive evidence regarding benefits of pre-hospital intubation
2	Level of injury: closed/open head trauma with non-purposeful response or no response to pain <i>Methods:</i> Pre-hospital intubation vs bag-valve-mask <i>Hypothesis:</i> NR	
Cooper et al. 2001	Database study <i>Country:</i> USA <i>Sample:</i> n=578. Age 1-15	Pre-hospital intubation was superior in regards to functional outcome by score
3	Level of injury: AIS > 3 <i>Methods:</i> Pre-hospital intubation vs bag-valve-mask <i>Hypothesis:</i> NR	
DiRusso et al. 2005	Database study <i>Country:</i> USA <i>Sample:</i> n=1018. Age 1-15	Better outcomes were found in the control intervention
3	Level of injury: RHISS^ 3 <i>Methods:</i> Pre-hospital vs intubation in non-trauma centre vs intubation in trauma centre <i>Hypothesis:</i> NR	
Stanic-Canji et al. 2006	Cohort study <i>Country:</i> Serbia <i>Sample:</i> n=60. Age ≤ 17	NR
3	Level of injury: GCS < 8 <i>Methods:</i> NR <i>Hypothesis:</i> NR	

*AIS Abbreviated injury score, ^RHISS relative head injury severity scale

Other treatments

Executive summary

This evidence reviewed in this project for treatment of paediatric TBI, didn't clearly fall into one of the other categories. The evidence came from one good quality guideline, and reported findings around the different treatments of paediatric TBI.

Evidence statement

Key question	Rating	Notes
Evidence base	A	Information within guidelines is based on data from moderate to poor quality RCTs, case series and cohort studies, and chart reviews
Consistency	NA	Only one guideline
Clinical impact	C	Moderate implications regarding pre-hospital management of paediatric TBI

Key guidelines relevant to other forms of treatment:

1. **Brain Trauma Foundation 2012. Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents - 2nd Ed.**

AGREE II score: 5/7

This US guideline updates an earlier 2003 edition. Recommendations for the management of infants, children and adolescents with severe TBI are aimed at acute care clinicians (primarily medical staff).

Although levels have been assigned to these recommendations, explanation of these levels was not supplied in the guideline.

Recommendations relevant to other forms of treatment:

- *Hypertonic saline should be considered for the treatment of severe paediatric TBI associated with intracranial hypertension. Effective doses range between 6.5 and 10mL/kg (p.S36).*
 - Two moderate quality RCTs and one poor quality chart review provided evidence to support the use of hypertonic saline in the acute treatment of severe paediatric TBI, and to support the use of hypertonic saline as a continuous infusion during the intensive care unit course.
- *Moderate hypothermia (32-33°C) beginning early after severe TBI for only 24 hrs duration should be avoided. Moderate hypothermia (32-33°C) beginning within 8hrs after severe TBI for up to 48 hrs duration should be considered to reduce intracranial*

hypertension. If hypothermia is induced for any indication, rewarming at a rate of >0.5°C/hr should be avoided (p.S42).

- One poor quality case series and two moderate quality RCTs found the efficacy of hypothermia versus other types of therapy to treat refractory intracranial hypertension remains unclear at this point.
- *Cerebrospinal fluid drainage through an external ventricular drain may be considered in the management of increased intracranial pressure in children with severe TBI. The addition of a lumbar drain may be considered in the case of refractory intracranial hypertension with a functioning external ventricular drain, open basal cisterns, and no evidence of a mass lesion or shift on imaging studies (p.S46).*
 - Four poor-moderate quality case series suggest that overall control of refractory intracranial pressure may be the most important factor of severe paediatric TBI, and this may not depend on a single form of treatment.
- *Avoidance of prophylactic severe hyperventilation to a $Paco_2$ <30mm Hg may be considered in the initial 48hrs after injury. If hyperventilation is used in the management of refractory intracranial hypertension, advanced neuromonitoring for evaluation of cerebral ischemia may be considered (p.S58).*
 - There is limited evidence on this area (one poor quality case series and one moderate quality cohort); however, what is available indicates that the use of hyperventilation is associated with reductions in cerebral blood flow and poor outcomes in severe TBI patients.
- *The evidence does not support the use of an immune-modulating diet for the treatment of severe TBI to improve outcome (p.S68). In the absence of outcome data, the specific approach to glycaemic control on the management of severe TBI should be left to the treating physician (p.S68).*
 - One moderate quality RCT showed no difference in the outcomes for children given an immune enhancing diet versus those given regular formula. There is insufficient evidence to recommend the use of glycaemic control after severe TBI even though there is evidence to suggest that post traumatic hyperglycaemia is detrimental to children's outcomes.

Investigations of non-accidental injury in children

Executive summary

The evidence reviewed in this project for non-accidental paediatric TBI came from one moderate quality guideline, one moderate quality systematic review and two excellent quality systematic reviews, and reported consistent findings around the assessment, management and treatment of non-accidental paediatric TBI.

Evidence statement

Key question	Rating	Notes
Evidence base	A	Information within guideline and reviews is based on data from mixed quality case, cross sectional or cohort studies.
Consistency	A	Recommendations were consistent across guidelines
Clinical impact	B	substantial implications regarding assessment and labelling of abusive trauma in paediatric TBI

Key guidelines regarding non-accidental injury in children:

1. **NICE 2007 Head injury: Triage, assessment, investigation and early management of head injury in infants, children and adults. National Institute of Health & Clinical Excellence**

AGREE II score: 7/7

This UK guideline is the update of an earlier 2003 edition. 'This guideline addresses assessment, investigation and early management of head injury. Separate advice is provided for adults and children (including infants) where different practices are indicated' (p.4). **NB:** *the NICE development group ruled that they would no longer publish grades with their recommendations.*

Recommendations relevant to non-accidental injury in children:

- *A clinician with expertise in non-accidental injuries in children should be involved in any suspected case of non-accidental injury in a child. Examinations/investigations that should be considered include: skull X-ray as part of a skeletal survey, ophthalmoscopic examination for retinal haemorrhage, and examination for pallor, anaemia, and tense fontanelle or other suggestive features. Other imaging such as CT and MRI may be required to define injuries (p.30).*
- *The care of all patients with new, surgically significant abnormalities on imaging should be discussed with a neurosurgeon. The definition of 'surgically significant' should be developed by local neurosurgical centres and agreed with referring hospitals. An example of a neurosurgical referral letter is provided on the NICE website (www.nice.org.uk) (p.30).*
- *Regardless of imaging, other reasons for discussing a patient's care plan with a neurosurgeon include:*
 - *persisting coma (GCS \leq 8) after initial resuscitation*
 - *unexplained confusion which persists for more than 4 hours*
 - *deterioration in GCS after admission (greater attention should be paid to motor response deterioration)*

- progressive focal neurological signs
- a seizure without full recovery
- definite or suspected penetrating injury
- a cerebrospinal fluid leak (p.31)
- *No infants or children presenting with head injuries that require imaging of the head or cervical spine should be discharged until assessed by a clinician experienced in the detection of non-accidental injury (p.40).*
- *It is expected that all personnel involved in the assessment of infants and children with head injury should have training in the detection of non-accidental injury (p.40).*

Key systematic reviews regarding non-accidental injury in children

1. **Kemp, A. M., S. Rajaram, M. Mann, V. Tempest, D. Farewell, M. L. Gawne-Cain, T. Jaspan, S. Maguire and G. Welsh Child Protection Systematic Review (2009). "What neuroimaging should be performed in children in whom inflicted brain injury (iBI) is suspected? A systematic review." Clinical Radiology 64(5): 473-483.**

CEBM score: 5/5

This systematic review investigated the optimal neurological investigation strategies to best identify inflicted brain injury in children. They found 18 case series or cross sectional studies (quality not supplied), involving 367 children with a mean age of 8 months, and concluded that in the acutely ill child, the optimal imaging strategy was CT scanning, followed by early MRI and Diffusion-weighted imaging (DWI) if abnormalities appeared in the CT scans, or if there is ongoing clinical concern. DWI found additional and more extensive abnormalities than what could be found with MRI scanning, which were correlated with ischemic damage, and later poor outcomes.

These findings are further supported by Gardner, A., F. Kay-Lambkin, P. Stanwell, J. Donnelly, W. H. Williams, A. Hiles, P. Schofield, C. Levi and D. K. Jones (2012). "A Systematic Review of Diffusion Tensor Imaging Findings in Sports-Related Concussion." Journal of Neurotrauma 29(16): 2521-2538. (CEBM score 4/5)

2. **Kemp, A. M., T. Jaspan, J. Griffiths, N. Stoodley, M. K. Mann, V. Tempest and S. A. Maguire (2011). "Neuroimaging: what neuroradiological features distinguish abusive from non-abusive head trauma? A systematic review." Archives of Disease in Childhood 96(12): 1103-1112.**

CEBM score: 5/5

This systematic review and meta-analysis focused solely on the identification of the evidence base behind the neuroradiological features that differentiate between abusive head trauma (AHT) and non-abusive head trauma. They found 21 moderate to good quality studies (scores not supplied) of 2353 children diagnosed as suffering abusive or non-abusive TBI with CT or

MRI scanning. The authors concluded that there are features significantly associated with abusive head trauma, which included Subdural haemorrhages, that were frequently multiple, located within the interhemispheric fissure, over the convexity and in the posterior fossa. abusive head trauma was more likely in the context of a closed head injury, while subarachnoid haemorrhages were found to be non-discriminatory and EDH were significantly associated with non-abusive head trauma. This was based predominantly upon CT imaging, which remains the recommended first line investigation for suspected abusive head trauma (p.1110).

Key findings from the review:

- Subdural haemorrhage was significantly associated with abusive head trauma, while extradural haemorrhage was significantly associated with non-abusive head trauma.
- There was no significant association to abusive head trauma for subarachnoid haemorrhage.
- Interhemispheric haemorrhages were significantly associated with abusive head trauma, as were extra-axial.
- Infra-tentorial/posterior fossa haemorrhages were associated with abusive head trauma.
- Cerebral oedema was significantly associated with AHT however they suggest that focal parenchymal injury is not a discriminatory feature for AHT.

Other earlier or lower quality evidence on the topic

Davis, G. A., G. L. Iverson, K. M. Guskiewicz, A. Ptito and K. M. Johnston (2009). "Contributions of neuroimaging, balance testing, electrophysiology and blood markers to the assessment of sport-related concussion." *British Journal of Sports Medicine* 43(SUPPL. 1): i36-i45. (CEBM score 1/5)

Deitch, E. A. and S. D. Dayal (2006). "Intensive care unit management of the trauma patient." *Critical Care Medicine* 34(9): 2294-2301 (CEBM score 1/5)

DeWall, J. (2009). "Severe pediatric traumatic brain injury. Evidence-based guidelines for pediatric TBI care." *EMS magazine* 38(9): 53-57. (AGREE II score 1/7)

Esposito, D. P. and J. B. Walker (2009). "Contemporary Management of Penetrating Brain Injury." *Neurosurgery Quarterly* 19(4): 249-254. (CEBM score 0/5)

Filippidis, A. S., D. C. Papadopoulos, E. Z. Kapsalaki and K. N. Fountas (2010). "Role of the S100B serum biomarker in the treatment of children suffering from mild traumatic brain injury." *Neurosurgical Focus* 29(5): E2. (CEBM score 2/5)

Foster, K., C. Stocker and A. Schibler (2010). "Controversies of prophylactic hypothermia and the emerging use of brain tissue oxygen tension monitoring and decompressive craniectomy in traumatic brain-injured children." *Australian Critical Care* 23(1): 4-11. (CEBM score 1/5)

Greer, D. M., S. E. Funk, N. L. Reaven, M. Ouzounelli and G. C. Uman (2008). "Impact of fever on outcome in patients with stroke and neurologic injury: a comprehensive meta-analysis." *Stroke* 39(11): 3029-3035. (CEBM score 2/5)

Harhangi, B. S., E. J. O. Kompanje, F. W. G. Leebeek and A. I. R. Maas (2008). "Coagulation disorders after traumatic brain injury." *Acta Neurochirurgica* 150(2): 165-175. (CEBM score 2/5)

Harmon, K. G., J. A. Drezner, M. Gammons, K. M. Guskiewicz, M. Halstead, S. A. Herring, J. S. Kutcher, A. Pana, M. Putukian and W. O. Roberts (2013). "American Medical Society for Sports Medicine position statement: concussion in sport." *British Journal of Sports Medicine* 47(1): 15-26. (AGREE II score 2/7)

Purcell, LK, Canadian Paediatric Society, Healthy Active Living and Sports Medicine Committee 2012, 'Evaluation and management of children and adolescents with sports-related concussion, *Paediatr Child Health*, vol. 17, no. 1, pp. 31. (AGREE II score 1/7)

Hebb, M. O., D. B. Clarke and J. M. Tallon (2007). "Development of a provincial guideline for the acute assessment and management of adult and pediatric patients with head injuries." *Canadian Journal of Surgery* 50(3): 187-194. (AGREE II score 3/7)

Huynh, F., V. H. Mabasa and M. H. Ensom (2009). "A critical review: does thiopental continuous infusion warrant therapeutic drug monitoring in the critical care population?" *Therapeutic Drug Monitoring* 31(2): 153-169. (CEBM score 1/5)

Kochanek, P. M. and R. C. Tasker (2009). "Pediatric neurointensive care: 2008 update for the Rogers' Textbook of Pediatric Intensive Care." *Pediatric Critical Care Medicine* 10(4): 517-523. (CEBM score 1/5)

Kövesdi, E., J. Lückl, P. Bukovics, O. Farkas, J. Pál, E. Czeiter, D. Szellár, T. Dóczi, S. Komoly and A. Büki (2010). "Update on protein biomarkers in traumatic brain injury with emphasis on clinical use in adults and pediatrics." *Acta Neurochirurgica* 152(1): 1-17. (CEBM score 1/5)

Li, L. M., I. Timofeev, M. Czosnyka and P. J. A. Hutchinson (2010). "The Surgical Approach to the Management of Increased Intracranial Pressure After Traumatic Brain Injury." *Anesthesia and Analgesia* 111(3): 736-748. (CEBM score 2/5)

Papa, L., M. M. Ramia, J. M. Kelly, S. S. Burks, A. Pawlowicz and R. P. Berger (2013). "Systematic review of clinical research on biomarkers for pediatric traumatic brain injury." *Journal of Neurotrauma* 30(5): 324-338. (CEBM score 2/5)

Shigemori, M., T. Abe, T. Aruga, T. Ogawa, H. Okudera, J. Ono, T. Onuma, Y. Katayama, N. Kawai, T. Kawamata, E. Kohmura, T. Sakaki, T. Sakamoto, T. Sasaki, A. Sato, T. Shiogai, K. Shima, K. Sugiura, Y. Takasato, T. Tokutomi, H. Tomita, I. Toyoda, S. Nagao, H. Nakamura, Y. S. Park, M. Matsumae, T. Miki, Y. Miyake, H. Murai, S. Murakami, A. Yamaura, T. Yamaki, K. Yamada and T. Yoshimine (2012). "Guidelines for the Management of Severe Head Injury, 2nd Edition Guidelines from the Guidelines Committee on the Management of Severe Head Injury, the Japan Society of Neurotraumatology The guidelines are officially approved by the Japan Neurosurgical Society." *Neurologia Medico-Chirurgica* 52(1): 1-30. (AGREE II score 3/7)

Question 1.2 What is the evidence for in-patient and out-patient rehabilitation for children and adolescents (0-15 years) with traumatic brain injury?

Executive Summary

Three guidelines (one excellent, one high and one moderate quality) and two systematic reviews (one moderate and one high quality) were identified for in-patient and out-patient rehabilitation of children with TBI. The guidelines concern early management of head injury, concussion in sport, and general outpatient recommendations; the systematic reviews considers interventions for communication and cognitive and behavioural interventions.

Evidence statement

Key question	Rating	Notes
Evidence base	A	Evidence is provided in three guidelines and one systematic review. The underpinning evidence is varied, including a systematic review, RCTs, cohort studies, case-control studies, a guideline and expert consensus.
Consistency	C	The lack of findings from the included studies and paucity of literature relating to the topic meant that there was little consensus across studies on aspects of rehabilitation for the population. Each review or guideline focused on a different aspect of the area of rehabilitation therefore there was little opportunity for comparison of findings.
Clinical impact	D	Despite the potentially high clinical impact of rehabilitation for children and adolescents, there is a lack of evidence relating to this question.

Key guidelines

1. **Cincinnati Children's Best Evidence Statement (2012). "Coordination of Outpatient Rehabilitative Care for patients with Traumatic Brain Injury (TBI) and their Families."**

AGREE II score: 4/7

This US guideline provides recommendations on outpatient rehabilitation applicable to children (3yrs+), adolescents, and young adults (<21yrs), who have: sustained a TBI, been discharged from an inpatient rehabilitation unit and transitioned to the community for post-discharge rehabilitation services (p. 1).

The recommendations for this question were informed by a systematic review, an RCT, a retrospective cohort study and a guideline.

Recommendations regarding outpatient rehabilitation for children with TBI:

Note: inclusion criteria regarding age for underpinning evidence within the guideline was between 3 and 21 years of age.

- *It is recommended that children who have sustained a TBI and have been discharged from an inpatient rehabilitation setting, receive a coordinated multi-disciplinary approach to rehabilitative care to improve functional performance* (p.1, Kim & Colantonio 2010, Cicerone et al 2008, Altman et al 2010, Commission on Accreditation of Rehabilitation Facilities (CARF) 2012). Based on assortment of levels of evidence, one each of:
 - good quality systematic review, meta-analysis, or meta-synthesis of multiple studies (1a),
 - lesser quality best study design for domain (2b),
 - lesser quality weak study design for domain (4b),
 - good quality general review, expert opinion, case report, consensus report, or guideline (5a).
- *There is insufficient evidence and a lack of consensus to make a recommendation that the impact of a coordinated multi-disciplinary rehabilitation approach improves quality of life or caregiver satisfaction* (p.1, Cicerone et al 2008). (Level 2b: Lesser quality best study design for domain).

2. Scottish Intercollegiate Guidelines Network (2009). “Early management of patients with a head injury.”

AGREE II score: 7/7

‘This guideline makes recommendations on the early management of patients with head injury, focusing on topics of importance throughout NHS Scotland.’ Recommendations are made for the management of adults and children.

The recommendations for this question were informed by expert opinion of the panel forming the guideline development group.

Recommendations regarding rehabilitation for children with TBI:

- *Children suffering from moderate/severe head injury should be followed up by a specialist multidisciplinary team to assess rehabilitation needs* (p.36). (‘Good Practice Point’: recommended best practice based on the clinical experience of the guideline development group.)

- *Parents should be given information and advice about the possible short/longer term difficulties that their child may have (p.36). ('Good Practice Point': recommended best practice based on the clinical experience of the guideline development group.*
- *The primary healthcare team, school health team and teachers should be notified of all children with a head injury regardless of severity (p.36). ('Good Practice Point': recommended best practice based on the clinical experience of the guideline development group).*

3. McCrory, P., Meeuwisse, W., Johnston, K., Dvorak, J., Aubry, M., Molloy, M. and Cantu, R. (2009). "Consensus Statement on Concussion in Sport – the 3rd International Conference on Concussion in Sport held in Zurich, November 2008." SAJSM, vol 21, No. 2.

AGREE II score: 4/7

This updated international consensus statement was 'developed for use by physicians, therapists, certified athletic trainers, health professionals, coaches and other people involved in the care of injured athletes, whether at the recreational, elite or professional level. Recommendations apply to adults, adolescents and children. The guideline is based on a literature review, however details of its methodology are not provided.

The recommendations for this question were informed by consensus of the panel.

Recommendations regarding rehabilitation for children with TBI:

Note: guideline not paediatric-specific, but it is highlighted that recommendations can be applied to children aged 10 years and over.

- *A player with diagnosed concussion should not be allowed to return to play on the day of injury (p. 37).*
- *Children should not be returned to practice or play until clinically completely symptom free, which may require a longer time frame than for adults (p. 41).*
- *It is appropriate to extend the amount of time of asymptomatic rest and/or the length of the graded exertion in children and adolescents (p. 41).*
- *It is not appropriate for a child or adolescent athlete with concussion to RTP on the same day as the injury regardless of the level of athletic performance (p. 41).*
- *Concussion modifiers apply even more to this population than adults and may mandate more cautious RTP advice (p. 41).*

Rationale:

There is evidence that delayed neuropsychological deficits may present in young athletes allowed to return to play on the same day as injury, despite the fact that these symptoms may not be evident when assessed at the sideline (Lovell et al 2004, McCrea et al 2004, Collins et al 2003). The guideline recommends a more graduated and conservative approach to return

to play in the paediatric population following concussion. It is strongly suggested that the modifiers given in the table below are taken into account and weighted more heavily than when considering the adult population, and extra caution is applied when considering return to play for children and adolescents post-concussion. The healthcare professional involved in assessment of a paediatric sport-related concussion needs to consider patient, parent, teacher and school in terms of management (Purcell & Carson 2008, Lee 2007, Schnadower et al 2007).

Table: Concussion modifiers (p. 40)	
Factors	Modifier
Symptoms	Number Duration (> 10 days) Severity
Signs	Prolonged LOC (> 1min), amnesia
Sequelae	Concussive convulsions
Temporal	Frequency - repeated concussions over time Timing - injuries close together in time "Recency" - recent concussion or TBI
Threshold	Repeated concussions occurring with progressively less impact force or slower recovery after each successive concussion.
Age	Child and adolescent (< 18 years old)
Co- and Pre-morbidities	Migraine, depression or other mental health disorders, attention deficit hyperactivity disorder (ADHD), learning disabilities (LD), sleep disorders
Medication	Psychoactive drugs, anticoagulants
Behaviour	Dangerous style of play
Sport	High risk activity, contact and collision sport, high sporting level

Key systematic reviews

1. **Rispoli, M. J., W. Machalicek and R. Lang (2010). "Communication interventions for individuals with acquired brain injury." *Developmental neurorehabilitation* 13(2): 141-151.**

CEBM Score: 3/5

This systematic review aimed to systematically analyse studies on interventions for communication in people who have sustained an acquired brain injury (ABI). Of the 21 included studies, only one was relevant to this question (paediatric ABI population). This was an observational cohort study. Note this study drew on evidence for all forms of brain injury not just TBI.

Key findings from the review:

- The data available around this area of rehabilitation in children is minimal, and there were no conclusive findings surrounding any single intervention
- Further research regarding interventions to address communication issues in those with acquired brain injuries is required

The systematic review included the following study in their review of this question:

Reference	Design	Results
Rispoli et al (2010)		
Wiseman-Hakes et al 1998	Interventional, group training <i>Sample:</i> n=6; aged 14-17y; frontal lobe ABI	Inconclusive evidence that conversation skills improved (mean 44% on RICS-RSPCS*) via specific programme: 'Improving Pragmatic Skills in Persons with Head Injury'

*RICS-RSPCS: Rehabilitation Institute of Chicago Rating Scale of Pragmatic Communication Skills.

2. **Laatsch, L., D. Harrington, G. Hotz, J. Marcantuono, M. P. Mozzoni, V. Walsh and K. P. Hersey (2007). "An evidence-based review of cognitive and behavioral rehabilitation treatment studies in children with acquired brain injury." *Journal of Head Trauma Rehabilitation* 22(4): 248-256.**

CEBM score: 4/5

This systematic review is discussed in detail under Question 1.4.

Other earlier or lower quality evidence on the topic

Fehlings, D., I. Novak, S. Berweck, B. Hoare, N. S. Stott and R. N. Russo (2010). "Botulinum toxin assessment, intervention and follow-up for paediatric upper limb hypertonicity: international consensus statement." *European Journal of Neurology* 17: 38-56. (CEBM score 2/5)

Greenwald, B. D. and J. L. Rigg (2009). "Neurorehabilitation in traumatic brain injury: does it make a difference?" *Mount Sinai Journal of Medicine* 76(2): 182-189. (CEBM score 0/5)

Harmon, K. G., J. A. Drezner, M. Gammons, K. M. Guskiewicz, M. Halstead, S. A. Herring, J. S. Kutcher, A. Pana, M. Putukian and W. O. Roberts (2013). "American Medical Society for Sports Medicine position statement: concussion in sport." *British Journal of Sports Medicine* 47(1): 15-26. (AGREE II score 2/7)

Li, L. M., I. Timofeev, M. Czosnyka and P. J. A. Hutchinson (2010). "The Surgical Approach to the Management of Increased Intracranial Pressure After Traumatic Brain Injury." *Anesthesia and Analgesia* 111(3): 736-748. (CEBM score 2/5)

Morgan A T. and Vogel A (2008) "Intervention for dysarthria associated with acquired brain injury in children and adolescents." *Cochrane Database of Systematic Reviews* DOI: 10.1002/14651858.CD006279.pub2. (CEBM score 1/5)

Poole, N. A. and N. Agrawal (2008). "Cholinomimetic agents and neurocognitive impairment following head injury: a systematic review." *Brain Injury* 22(7-8): 519-534. (CEBM score 2/5)

Provvidenza, C. F. and K. M. Johnston (2009). "Knowledge transfer principles as applied to sport concussion education." *British Journal of Sports Medicine* 43: i68-i75. (CEBM score 1/5)

Putukian, M., M. Aubry and P. McCrory (2009). "Return to play after sports concussion in elite and non-elite athletes?" *British Journal of Sports Medicine* 43: i28-31. (CEBM score 1/5)

Tume, L. and A. Jinks (2008). "Endotracheal suctioning in children with severe traumatic brain injury: a literature review." *Nursing in Critical Care* 13(5): 232-240. (CEBM score 2/5)

Ylvisaker, M., L. Turkstra, et al. (2007). "Behavioural interventions for children and adults with behaviour disorders after TBI: A systematic review of the evidence." *Brain Injury* 21(8): 769-805. (CEBM score 2/5)

Question 1.3 What is the evidence for transitions of care for children and adolescents (0-15 years) with traumatic brain injury?

Executive Summary

Five guidelines (three high and two moderate quality) and one systematic review provided evidence for this question. The relevant literature found during this review is mainly concerned with transitions between the site of injury to hospital, between ED and other acute care services such as neurosurgery or from hospital to community services. Only one of the guidelines was paediatric-specific. A lack of data exists on transitions between acute care and rehabilitation, and on communication between services providing initial care and community services.

Evidence statement

Key question	Rating	Notes
Evidence base	A	Underpinning evidence for the guidelines comes from a mixture of RCTs, cohort studies, case-control studies, case series, databases and registries, observational, diagnostic and economic studies. The quality of these primary studies was often weak. One high level recommendation was made, alongside many 'good practice points' or equivalent, which were based on expert opinion.
Consistency	B	There are some differences between guidelines regarding specific criteria for the need for various levels of care, but there is agreement that signs and symptoms should be assessed to determine level of care required, and general consensus (low quality recommendations) regarding best care facilities and discharge advice and follow up.
Clinical impact	B	The recommendations made have large degree of potential impact for hospital services, in terms of response to and triage of paediatric patients presenting with head injury. However, it must be noted that all of the literature has been created based on evidence from American and European populations, and their specific healthcare systems.

Key guidelines regarding transitions of care

1. Vos et al. Mild traumatic brain injury. *European Journal of Neurology* 2012, 19: 191–198.

AGREE II score: 5/7

This European guideline provides recommendations for the acute management of adults and children presenting with mild TBI. It is aimed primarily at medical management.

Recommendations for this question were informed by evidence ranging from high level to expert opinion. There are few explicit references relating to transitions of care in the paediatric TBI population.

Recommendations relevant to transitions of care:

- *Patients with MTBI and a normal neurological examination (including a GCS = 15), no risk factors (in particular a normal coagulation status, no drug or alcohol intoxication, no other injuries, no suspected non-accidental injury, no cerebrospinal fluid leak) and a normal CT could be observed at home and the patient is admitted only if some extracerebral cause occurred (p.195). (Grade A recommendation: at least one convincing Class I study (high quality prospective diagnostic study) or two consistent, convincing Class II studies (eg. high quality retrospective diagnostic study).*
- *For children under 6 years of age who are discharged home from the ED, head injury warning instructions are recommended because of the likelihood of delayed cerebral swelling (p.195). (Good Practice Point: Lack of evidence but consensus clear.)*

Rationale:

Only one study containing data relevant to the question was mentioned in the guidelines. It is marked as being a level II study, although it is over 20 years old now, and the results are not clearly displayed within the guidelines. Teasdale and colleagues (1990) found that, after imaging children with mild TBI using CT, the absolute risk of haematoma in patients with GCS of 15 and no skull fracture was 1 in 12559. The authors of the review suggest this may be indicative of CT as a better instrument than x-ray for determining which patients can be discharged home.

2. Barbosa et al. Evaluation and management of mild TBI: An Eastern Association for the Surgery of Trauma practice management guideline. *J Trauma Acute Care Surg.* (2012) 73:S307-S314.

AGREE II score: 3/7

This US guideline updates an earlier 2001 edition. Recommendations for the management of mild TBI (mTBI) are aimed at clinicians (primarily medical staff) working in acute care.

The recommendations for this question were informed by one study (112 studies were included in the review in total).

Recommendations relevant to transitions of care:

- *Patients with an isolated mTBI and a negative brain CT scan may be discharged from the ED if they have no other injuries or issues requiring hospital admission (p.S308).*

(**Level 3 recommendation:** Supported by available data, but inadequate scientific data are available; or recommendation supported by retrospectively collected data)

Rationale:

The table below outlines the details of the only study involving an exclusively paediatric population within the guidelines. The results supported CT as a safe means of making decisions regarding the discharge of children from the emergency department, concluding that a GCS of 14-15 and a negative brain CT scan was indicative of the child being safe for discharge.

The following study was included in making recommendations relevant to this question:

Reference	Design	Results
Barbosa et al 2012		
Holmes et al 2011	Observational, prospective <i>Sample:</i> n=13,543, mean age=8.9y <i>Level of injury:</i> Blunt head injury, GCS 14-15, negative CT findings <i>Methods:</i> Multicentre study; hospital charts reviewed if admitted, telephone follow up if discharged, to ascertain reliability of CT in determining patients at risk of positive CT or MRI findings or need for neurosurgical intervention some time after initial event	Subsequent positive findings on CT or MRI: 0.16% No patients requiring surgical intervention

3. SIGN 2009 Early management of patients with a head injury. Scottish Intercollegiate Guidelines Network.

AGREE II score: 7/7

‘This guideline makes recommendations on the early management of patients with head injury, focusing on topics of importance throughout NHS Scotland.’ Recommendations are made for the management of adults and children.

The recommendations for this question were informed by evidence ranging from high quality systematic reviews to expert opinion of the panel forming the guideline development group.

Recommendations regarding transitions of care:

Referral to emergency department:

- *Children should be referred by telephone service to hospital emergency department if any of the following signs, symptoms or risk factors are present:*
 - High risk mechanism of injury
 - Initial GCS <15
 - Loss of consciousness
 - Post traumatic seizure
 - Focal neurological signs
 - Severe, persistent headache
 - Signs of skull fracture
 - Repeated vomiting
 - Post-traumatic amnesia >5mins
 - Retrograde amnesia >30mins
 - Coagulopathy
 - Suspicion of non-accidental injury

(Grade B recommendation: A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+. See table below for details on levels of evidence.)

- *Children should be referred by telephone service to hospital emergency department if any of the following are present:*
 - Full on-site assessment difficult
 - Significant comorbidities
 - Child not with a responsible adult
 - Social circumstances are deemed unsuitable

(Good Practice Point: best practice based on the clinical experience of the guideline development group.)

Admission:

- *Children who have sustained a head injury should be **admitted** to hospital if any of the following risk factors apply:*
 - Any indication for a CT scan
 - Suspicion of non-accidental injury
 - Significant medical comorbidity
 - Difficulty making a full assessment
 - Child not accompanied by a responsible adult
 - Social circumstances considered unsuitable.

(p.23) **(Good Practice Point:** Recommended best practice based on the clinical experience of the guideline development group.)

Referral/transfer to neurosurgical unit:

- *Children should be referred to a neurosurgical unit if any of the following are present:*
 - CT scan shows recent intracranial lesion
 - CT scan unavailable but child shows signs indicating one should be performed
 - Clinical features evident (regardless of CT result) indicating specialist management appropriate

(Grade D recommendation: Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+. See table below for details on levels of evidence.)

- *Transfer of a child to a specialist neurosurgical unit should be undertaken by staff experienced in the transfer of ill children, such as the Scottish Paediatric Retrieval Service.*

(p.33) **(Good Practice Point:** Recommended best practice based on the clinical experience of the guideline development group.)

- *Consultation on the best method of transfer for an individual patient should be with referring healthcare professionals, transfer clinicians and the receiving neurosurgeon. It should take into account the clinical circumstances, skill of available staff, imaging, mode of transfer and timing issues.*

(p.33) **(Good Practice Point:** Recommended best practice based on the clinical experience of the guideline development group.)

Discharge:

- *The following criteria must be met prior to discharge:*
 - A responsible adult is available and willing to observe the patient for at least 24 hours
 - Verbal and written instructions about observations to be made and action to be taken are given to and discussed with that adult
 - There is easy access to a telephone
 - The patient is within reasonable access of medical care transport home is available.

- *Children can be discharged from the ED if no additional risk factors are present.*

(p.24) **(Good Practice Point:** Recommended best practice based on the clinical experience of the guideline development group.)

- *Clear written instruction should be given to and discussed with parents or carers before a child is discharged.*

(p.25) **(Good Practice Point:** Recommended best practice based on the clinical experience of the guideline development group.)

Levels of Evidence (SIGN)	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies; high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg. case reports, case series
4	Expert opinion

ADVICE CARD FOR PATIENT ALLOWED HOME FROM EMERGENCY DEPARTMENT POST-HEAD INJURY (SIGN 2009, p. 68)

Do you feel well?

Often people can feel unwell after a head injury even when they are back home.

Common symptoms are:

- slight headache
- dizziness
- memory problems
- poor concentration
- irritability or being easily annoyed
- tiredness
- poor sleep.

If you have any of these symptoms, do not worry because they should clear up in time without any treatment.

If you still have any of the symptoms after two weeks you should see your own doctor.

Some extra advice to help you get well:

Following this advice will help you to recover from your head injury more quickly, and it may stop some of the symptoms from happening.

- DO have plenty of rest and avoid stressful and noisy situations.
- DO NOT take any alcohol or any non-prescribed drugs.
- DO NOT take sleeping pills, sedatives or tranquillisers. If in doubt contact your GP.
- DO NOT play any contact sport (eg. football or squash) for at least three weeks without talking to your doctor first.

4. **NICE 2007 Head injury: Triage, assessment, investigation and early management of head injury in infants, children and adults. National Institute of Health & Clinical Excellence.**

AGREE II score: 7/7

This UK guideline is the update of an earlier 2003 edition. 'This guideline addresses assessment, investigation and early management of head injury. Separate advice is provided for adults and children (including infants) where different practices are indicated' (p.4).

NB: the NICE development group ruled that they would no longer publish grades with their recommendations.

The recommendations for this question were informed by expert opinion without explicit critical appraisal, or based on physiology, bench research, "first principles" or inconclusive evidence. There is a small number of paediatric-specific points within the guidelines when compared to the adult-specific points, however, note is often made of the fact that a set of criteria/guidelines referring to an adult population is also applicable to the paediatric population.

Recommendations regarding transitions of care:

Referral to emergency ambulance services:

- *Telephone advice services should refer to emergency ambulance services in the case of the following:*
 - Unconsciousness
 - Focal neurological deficit
 - Suspected penetrating head injury or skull fracture
 - Seizure following injury
 - High-impact head injury
 - Difficulty transferring injured person to hospital without ambulance

(Grade D recommendation: Level 5 evidence or troublingly inconsistent or inconclusive studies of any level. **Level 5 evidence:** Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles")

Referral to emergency department:

- *Telephone advice services should refer to a **hospital emergency department** in the case of the following:*
 - Previous loss of consciousness (recovered)
 - Amnesia regarding pre- or post-injury events (should be assumed in children <5years)
 - Vomiting or persistent headache post-injury
 - Previous cranial neurosurgery

- Clotting or bleeding history, or current anti-coagulant therapy
- Current drug/alcohol intoxication
- Suspected non-accidental injury
- Altered/irritable behaviour, especially in children <5years
- Continued concern about the child's diagnosis

(Grade D recommendation: Level 5 evidence or troublingly inconsistent or inconclusive studies of any level. **Level 5 evidence:** Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles")

- ***Community health services should refer to hospital emergency department in the case of the following:***
 - GCS <15, or previous loss of consciousness post-injury
 - Focal neurological deficit
 - Suspected penetrating head injury or skull fracture
 - Amnesia regarding pre- or post-injury events (should be assumed in children <5years)
 - Vomiting or persistent headache post-injury
 - Seizure following injury
 - Previous cranial neurosurgery
 - High-impact head injury
 - Clotting or bleeding history, or current anti-coagulant therapy
 - Current drug/alcohol intoxication
 - Suspected non-accidental injury
 - Continued concern by professional regarding diagnosis

(Grade D recommendation: Level 5 evidence or troublingly inconsistent or inconclusive studies of any level. **Level 5 evidence:** Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles")

Admission:

- ***Admission to hospital should occur in the case of the following:***
 - New clinically significant irregularities on imaging
 - GCS remaining <15 after imaging
 - Patient suitable for but unable to have imaging (due to resources/cooperativeness)
 - Continued concern by professional regarding condition

(Grade D recommendation: Level 5 evidence or troublingly inconsistent or inconclusive studies of any level. **Level 5 evidence:** Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles")

Referral to community services:

- ***Telephone advice services should refer to community services in the case of the following:***
 - Poor social factors

- Continued concern by person/carer/guardian regarding diagnosis

(Grade D recommendation: Level 5 evidence or troublingly inconsistent or inconclusive studies of any level. **Level 5 evidence:** Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles")

Discharge:

- *Discharge should only occur in the case of the following:*
 - GCS ≥ 15 or normal consciousness as assessed by paediatric GCS
 - Provision of a head injury advice card, the details of which are discussed with the patient and parent/caregiver, given in a format suitable to the patient/carer (taking into account literacy levels, language, etc.), and include information about delayed-onset symptoms and contacting community health services should they occur
 - Children with head injury requiring imaging have been assessed by a clinician experienced in non-accidental injury detection
 - Those requiring imaging or admission have been referred to their GP for follow-up within a week
 - For those who have attended the emergency department with a head injury, a letter or email, detailing clinical history and findings, has been generated and provided to:
 - GP
 - School nurse
 - Health-visitor (in eg. pre-school institutions)

(Grade D recommendation: Level 5 evidence or troublingly inconsistent or inconclusive studies of any level. **Level 5 evidence:** Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles")

Transport:

- *Transfer to a neurospecialist facility is of benefit to all patients with severe (GCS ≤ 8) TBI.*
- *Transport from community services to emergency department should be accompanied by adult.*
- *Need for ambulance should be assessed and determined by health professional*
- *Hospital should be notified by referring professional of transfer, and given written summary of initial assessment if possible.*
- *Ambulance staff should be trained in use of age-specific GCS, and detection of non-accidental injury.*
- *Regardless of whether a patient is transferred to a specialist unit, communication between the hospital and specialist facility is important to optimise clinical management.*
- *Transfer of child to neurosurgical facility should be performed by specially-trained staff.*

- *Families should be informed and involved when it comes to transfer of a child.*

(**Grade D recommendations:** Level 5 evidence or troublingly inconsistent or inconclusive studies of any level. **Level 5 evidence:** Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles")

Regional Guidelines:

- *Regional guidelines should be drawn up to facilitate coordination between hospitals, specialist facilities and ambulance services*

(**No grade** noted for this recommendation)

5. Brain Trauma Foundation. Guidelines for prehospital management of traumatic brain injury, 2nd edition. *Prehospital Emergency Care* 2007; 12(SUPPL. 1): S1-S52.

AGREE II score: 6/7

This US guideline updates an earlier 2000 edition. Recommendations are aimed at the pre-hospital management of adults and children with severe TBI, by emergency medical service personnel.

The recommendations for this question were informed by low quality primary studies identified as having major flaws in their design or methodology.

Recommendations relevant to transitions of care:

- *In a metropolitan area, paediatric patients with severe TBI should be transported directly to a paediatric trauma center if available (p.S42).* (Potoka et al 2001, Johnson et al 1996) (**Weak recommendation:** from class III studies, contradictory findings, and indirect evidence. **Class III study:** has fatal flaw such as: uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; very small sample size of very narrow selected spectrum of patients.)
- *Paediatric patients with severe TBI should be treated in a paediatric trauma centre or in an adult trauma centre with added qualifications to treat children in preference to a level I or II adult trauma centre without added qualifications for paediatric treatment.* (**Weak recommendation:** from class III studies, contradictory findings, and indirect evidence. **Class III study:** has fatal flaw such as: uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; very small sample size of very narrow selected spectrum of patients.)

The following studies were included in making recommendations relevant to this question:

Reference	Design	Results
Brain Trauma Foundation guidelines 2007		
Potoka et al 2001 <i>Class III study: inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; and/or very small sample size of very narrow selected spectrum of patients.</i>	Observational, retrospective <i>Sample:</i> n=3056. Aged 0-16 years <i>Level of injury:</i> severe TBI (GCS 3-8) <i>Methods:</i> Organised paediatric severe TBI patients into groups according to facility at which they were treated, assessed mortality and neurosurgical procedures	Survival better when treated in paediatric trauma centres or adult trauma centres specially equipped to treat children also, than in level I or level II adult trauma centre. Chance of survival lower severe TBI in a level II adult trauma centre compared with the other facilities.
Johnson and Krishnamurthy 1996 <i>Class III study</i>	Observational, prospective <i>Sample:</i> aged 1-12 years <i>Level of injury:</i> mild-severe TBI <i>Methods:</i> Comparison of mortality between those transported directly to paediatric hospital with those transferred from another hospital	For those with severe TBI, survival greater for those transported directly to paediatric trauma centre compared with those with transferred from another hospital (4.7%) than direct transport (1.9%), although overall comparison also included patients with mild and moderate TBI. For those with moderate TBI, equal chance of survival for direct transport versus transfer. Overall mortality rates (mild/mod/severe combined): Direct transport: 1.9%; transfer: 4.7%

Key systematic reviews regarding transitions of care:

1. Hill, A. D., R. A. Fowler and A. B. Nathens (2011). "Impact of interhospital transfer on outcomes for trauma patients: A systematic review." *Journal of Trauma - Injury, Infection and Critical Care* 71(6): 1885-1900.

CEBM score: 4/5

This systematic review aimed to analyse the available evidence relating to the relationship between transfer status and patient outcomes.

Of the 36 observational studies included in the review, only one looked specifically at the paediatric, head-injured population (Johnson and Krishnamurthy 1996). With a sample of 1320 patients, it compared length of stay and mortality outcomes between patients admitted directly to a trauma centre with those transferred from another facility. The quality of the primary studies was not appraised.

Key finding from the review:

- Limited and out-dated paediatric data available, suggesting that direct transport to trauma centre produces better outcomes regarding ICU stay and mortality than transfer from another centre. Further research is needed to verify this.

The systematic review included the following studies in their review of this question:

Reference	Design	Results
Hill et al 2011		
Johnson and Krishnamurthy 1996	<p>Observational, prospective cohort</p> <p><i>Country:</i> USA</p> <p><i>Sample:</i> n= 1320</p> <ul style="list-style-type: none"> • 841 direct admissions to Level 1 paediatric trauma centre • 479 transfer from hospital <p><i>Level of injury:</i></p> <ul style="list-style-type: none"> • Direct: mean ISS*= 11.6 (SD 10.4) • Transfer: mean ISS= 10.2 (SD 9.9) <p><i>Methods:</i> collection of data on paediatric, head-injured patients admitted to a trauma centre and follow up regarding their length of stay and in-hospital mortality.</p>	<p>Mortality associated with direct admission to trauma centre lower (1.8%) than that associated with transfer to trauma centre from another hospital (4.7%)</p> <p>ICU length of stay shorter in those directly admitted to trauma centre (3.71 days) than those transferred from another hospital (4.48 days)</p>

*ISS= Injury Severity Score

Other earlier or lower quality evidence on the topic includes:

Shigemori, M., T. Abe, T. Aruga, T. Ogawa, H. Okudera, et al (2012). "Guidelines for the Management of Severe Head Injury, 2nd Edition Guidelines from the Guidelines Committee on the Management of Severe Head Injury, the Japan Society of Neurotraumatology." *Neurologia Medico-Chirurgica* 52(1): 1-30. (AGREE II score 3/7)

DeWall, J. (2009). "Severe pediatric traumatic brain injury. Evidence-based guidelines for pediatric TBI care." *EMS magazine* 38(9): 53-57. (AGREE II score 1/7)

Greer, D. M., S. E. Funk, N. L. Reaven, M. Ouzounelli and G. C. Uman (2008). "Impact of fever on outcome in patients with stroke and neurologic injury: a comprehensive meta-analysis." *Stroke* 39(11): 3029-3035. (CEBM score 2/5)

Hebb, M. O., D. B. Clarke and J. M. Tallon (2007). "Development of a provincial guideline for the acute assessment and management of adult and pediatric patients with head injuries." Canadian Journal of Surgery 50(3): 187-194. (AGREE II score 3/7)

Question 1.4 What is the evidence for cognitive, educational and training issues for children and adolescents (0-15 years) with traumatic brain injury?

Executive summary

Five high and three moderate quality systematic reviews were identified for cognitive, educational and training issues. These reviews cover a wide range of subtopics, including predicting the impact of TBI on intelligence, psychological interventions for psychosocial problems, prospective memory, sleep interventions, language and academic deficits and problem solving capabilities. There were no guidelines of adequate quality identified.

Evidence statement

Key question	Rating	Notes
Evidence base	A	Eight moderate to high level systematic reviews formed the literature base for this question. Two of the reviews carried out meta-analyses on their data. The level of underpinning evidence was generally low to moderate (level II to IV). A range of RCTs, cohort studies, case-control studies, case series, observational studies were included in the reviews.
Consistency	C	A number of the systematic reviews observed or trialled interventions for specific areas of neurocognitive or psychosocial dysfunction, and thus it is difficult to make generalisations about such outcomes and interventions. There is consensus on the need for more longitudinal data on neurocognitive and psychosocial outcomes for children who have suffered a TBI. There is also agreement that children with severe TBI have worse cognitive/social outcomes than those with mild or moderate TBI, and attention appears to be an area of specific concern.
Clinical impact	C	Systematic reviews involving training areas of cognition, planning and social factors were generally inconclusive, and specific clinical recommendations cannot be made. The observational data on neurocognitive and psychosocial outcomes relating to varying degrees of injury provides some clinically important considerations, but predominantly highlights the need for more longitudinal and severity-/intervention-specific research.

Key systematic reviews regarding cognitive, educational and training issues for children who have sustained a traumatic brain injury:

1. **Konigs, M., J. F. De Kieviet and J. Oosterlaan (2012). "Post-traumatic amnesia predicts intelligence impairment following traumatic brain injury: A meta-analysis." *Journal of Neurology, Neurosurgery and Psychiatry* 83(11): 1048-1055.**

CEBM score: 4/5

The aim of this systematic review was to determine the long term impact of TBI on intelligence, and whether the duration of post-traumatic amnesia has predictive value. Meta-analysis was performed on the data. Of the twenty-one studies included, six concerned the paediatric TBI population (Knights et al 1991; Tremont et al 1999; Catroppa & Anderson 1999, 2005; Chadwick et al 1981; Cattalani et al 1998). Only two provided details regarding their findings (Knights et al 1991; Tremont et al 1999). One of these was of moderate quality, whilst the other was low. They both concluded that the predictive value of the duration of post-traumatic amnesia is superior to GCS score and duration of loss of consciousness. These paediatric-focussed results were not discussed separately from the overall findings of the review.

Key finding from the review:

- Following a TBI, the duration of post traumatic amnesia is a strong predictor of intelligence impairment up until the chronic phase of recovery; however, it is difficult to apply these findings to the paediatric population with certainty.

The systematic review included the following studies in their review of this question:

Reference	Design	Results
Konigs 2012		
Knights et al 1991	Longitudinal cohort study <i>Sample:</i> n=26. Ave Age=10.80 <i>Level of injury:</i> mean GCS score= 5.50 <i>Outcomes:</i> performed intelligence testing at time of hospital discharge <i>Newcastle-Ottawa Scale: 1</i>	Moderate to strong relations between PTA duration and Welchsler scale FSIQ, PIQ and VIQ in children with TBI. Predictive value of PTA duration for intelligence is superior to that of GCS score, and LOC duration.
Tremont et al 1999	Cross-sectional study <i>Country:</i> NR <i>Sample:</i> n=30. Ave Age=10.93 <i>Level of injury:</i> mean GCS score= NR <i>Outcomes:</i> intelligence testing <i>Newcastle-Ottawa Scale: 6</i>	Moderate to strong relations between PTA duration and Welchsler scale FSIQ, PIQ and VIQ in children with TBI. Predictive value of PTA duration for intelligence is superior to that of GCS score, and LOC duration.

2. Ross, K. A., L. Dorris and T. McMillan (2011). "A systematic review of psychological interventions to alleviate cognitive and psychosocial problems in children with acquired brain injury." *Developmental Medicine and Child Neurology* 53(8): 692-701.

CEBM score: 4/5

The aim of this systematic review was to summarise the evidence for psychological interventions in improving cognitive and psychosocial outcomes after in children with acquired brain injury (ABI). Nine interventional studies were included in the review: five concerning cognitive outcomes and four concerning psychosocial outcomes. The authors appraised these with the CONSORT checklist (Schultz et al 2010), which identified two high, five moderate and two low quality studies. A number of the primary studies included participants outside of the 0-15 years age range (up to 19 years).

Key findings from the review:

- Interventions aimed at psychosocial outcomes may lessen internalising symptoms (Wade et al 2006a).
- Although individualisation of interventions is important, and should be patient-focussed, it is important to involve family members, particularly in cognitive outcome interventions (Braga et al 2005).
- Children from lower socio-economic families and children >11 years may have most benefits from online-based family interventions (Wade et al 2006a).
- If interventions for cognitive outcomes are to be effective, they need to be intensive.

3. Shum, D., H. Levin and R. C. K. Chan (2011). "Prospective memory in patients with closed head injury: A review." *Neuropsychologia* 49(8): 2156-2165.

CEBM score: 3/5

This systematic review aimed to review the evidence around prospective memory (PM) following closed head injury (CHI). Thirty articles in total were summarised, six of which related to children or adolescents. The paediatric data was explored separately to that relating to adults. Prospective memory is “the encoding, storage, and delayed retrieval of intended actions” (p. 2157), and is essential in performing everyday tasks such as keeping appointments or remembering routine duties. No mention is made of the methodological quality of the included studies.

Key findings from the review:

- Prospective memory performance is susceptible to damage in children and adolescents following closed head injury
- In some cases, increasing monetary incentive may be beneficial in improving PM performance
- Higher quality studies should examine the effects (especially long-term) of interventions aimed at improving PM

The systematic review included the following study in their review of this question:

Reference	Design	Results
Shum 2011		
Ward et al (2004)	Qualitative interview <i>Sample:</i> n=13 parents (11 mothers, 2 fathers) <i>Level of injury (of children):</i> mild to severe TBI	Prospective memory problems reported by all parents; cause of stress/concern. PM impairments reported to be affecting areas of daily functioning.
McCauley and Levin (2004)	Prospective, observational <i>Sample:</i> n=32 TBI, 15 orthopaedic controls <i>Level of injury:</i> mild and severe	Participants with mild and severe TBI impaired in terms of PM compared to controls. Those with severe TBI did not improve task performance following reminder.
Ward et al (2007)	Prospective, observational <i>Sample:</i> n=28 TBI, 48 controls <i>Level of injury:</i> mild/moderate and severe	Increase in cognitive demand had greater impact on older than younger children.
McCauley et al (2009)	Interventional <i>Sample:</i> n=42 TBI, 42 orthopaedic controls <i>Level of injury:</i> mild and severe <i>Method:</i> Offering increased monetary reward as incentive for performing tasks	Improved PM performance in subjects with mild and severe CHI ≥ 1 year post-injury.
McCauley, Pedroza et al (2010a)	Interventional <i>Sample:</i> n=58 TBI, 61 orthopaedic controls <i>Level of injury:</i> moderate and severe <i>Method:</i> Offering increased monetary reward as incentive for performing tasks	Improved PM performance in subjects with moderate CHI 1month post-injury. No effect on PM performance in subjects with severe CHI 1-2 months post-injury.
McCauley, Wilde et al (2010b)	Observational <i>Sample:</i> n=40 TBI, 41 orthopaedic controls <i>Level of injury:</i> moderate/severe <i>Method:</i> Use of MRI to assess relation of cortical thinning to PM	Dorsolateral prefrontal and temporal cortical thinning related to poor PM performance 3 months post-injury.

4. Vu, J. A., T. Babikian, et al. (2011). "Academic and Language Outcomes in Children After Traumatic Brain Injury: A Meta-Analysis." *Exceptional Children* 77(3): 263-281.

CEBM score: 3/5

This systematic review sought to collate and synthesise the evidence (via meta-analysis) pertaining to the following three areas for TBI in the paediatric population:

- The effect of injury severity on academic and language outcomes (at various time points)
- The degree of difference between levels of injury severity (at various time points)
- The amount of recovery over time

Eighteen studies reporting on language or academic outcomes of children with mild, moderate or severe TBI were identified. The authors followed a similar protocol to Babikian and Asarnow (2009) on neurocognitive outcomes (see below), but focused on academic and language outcomes only. Time points examined were 0-5 months, 6-23 months and 24+ months post-injury. The study looked at both longitudinal and cross-sectional studies. Analyses were performed based on the severity of injury and the time post-injury. The quality of the included studies was not noted.

Key findings from the review:

- Timely initial assessment and routine follow up of children who have experienced a TBI is important in order to track changes, monitor recovery, and target interventions as indicated.
- Testing of language and academic domains should be specific, multi-faceted, and have real-world application, to ensure that subcategories of the various domains are not 'lost' in a general, more gross test of these areas.
- Across all domains, children who have experienced mild TBI can be expected to recover along a similar trajectory to healthy controls, although deficit gap in the various domains that results from the injury is unlikely to be closed in the first 2 years following injury.
- Children with severe TBI can be expected to display deficits in all domains following injury, and have a slower rate of recovery in the domains of reading, expressive and receptive language.
- Children with severe TBI should be particularly closely monitored, and receive targeted intervention as indicated, beyond 2 years post-injury, as their improvement in language and academic domains can be expected to continue beyond this time period.
- Learning may be facilitated by modifications to activities aimed at intervention, for example task breakdown, or increased time allocated to task completion.

Rationale:

Mild TBI:

- No statistically significant differences in terms of language or academic abilities compared to controls at any time point

- No statistically significant changes over time in any of the language or academic domains

Mild compared to moderate TBI

- Small significant differences in overall language when compared to children with moderate TBI; those with mild TBI performing better in this domain up to 23 months post-injury, but difference no longer present 24+ months post-injury
- With regards to reading capabilities, there was no significant difference up to 23 months post-injury between those with mild and moderate TBI, but at 24+ months, there was a significant difference, indicating poorer outcomes for those with moderate TBI.

Moderate TBI:

- Small but significant difference in academic outcomes between children with moderate TBI and controls at all three time points
- No statistically significant changes over time in any of the language or academic domains
- Although the *rate* of development of academic skills is the same as controls, deficits that present acutely post-injury do not appear to resolve

Moderate compared to severe TBI

- Small significant differences in reading outcomes, moderate differences in receptive language outcomes when compared to children with severe TBI; those with moderate TBI performed better in this domain at all three time periods
- Looking at expressive language, no significant difference between moderate and severe TBI sufferers at 0-23 months post-injury, but moderate difference at 24+ months
- Looking at arithmetic, spelling and overall language capabilities, there were moderate-large significant difference at 0-5 months, although these reduced significantly by 24+ months post-injury

Severe TBI:

- Large statistically significant differences in reading and overall language outcomes between children with severe TBI and controls at all three time points
- Moderate statistically significant differences in expressive and receptive language outcomes compared to controls at all three time points
- Large statistically significant differences in arithmetic, spelling, language pragmatic domains; this difference as particularly large at 0-5 months post-injury, and decreased in its magnitude (although remained a large difference) by 24+ months post-injury
- No significant recovery over time in reading, receptive and overall language; other domains exhibited some level of recovery

Severe compared to mild or moderate TBI

- Larger differences in outcomes between children with severe and mild than moderate and mild TBI
- Large statistically significant differences in terms of reading and overall language between children with severe TBI compared with mild TBI; this persisted across the three time period studied

5. Babikian, T. and R. Asarnow (2009). "Neurocognitive outcomes and recovery after pediatric TBI: meta-analytic review of the literature." *Neuropsychology* 23(3): 283-296.

CEBM score: 3/5

This systematic review sought to collate and synthesise the evidence (via meta-analysis) pertaining to the following three areas in relation to TBI in the paediatric population:

- The effect of injury severity on academic and language outcomes (at various time points) (case-control studies)
- The degree of difference between levels of injury severity (at various time points) (case-case studies)
- The amount of recovery over time (longitudinal studies)

Twenty eight studies reporting on neurocognitive outcomes for paediatric subjects with mild, moderate or severe TBI were analysed. Time points examined were 0-5 months, 6-23 months and 24+ months post-injury. Analyses were performed based on the severity of injury and the time post-injury. Neurocognitive domains assessed included:

- General intellectual functioning (measures include FSIQ, VIQ and PIQ*)
- Attention/executive functions (working memory, processing, attention etc.)
- Memory (verbal, visual, immediate, delayed)
- Visual Perceptual/Motor Skills

* Full Scale Intelligence Quotient, Verbal Intelligence Quotient and Performance Intelligence Quotient

The quality of the included studies was not noted.

Key findings from the review:

- The visual perceptual functioning domain of neuro-cognition is most affected by injury.
- There is a lack of literature distinguishing between groups (in terms of severity) when reporting data on neurocognitive outcomes.
- There is a lack of studies looking at longitudinal neurocognitive outcomes.
- Children with mild TBI were found to experience mild to no neurocognitive impairments when looking across all time periods.
- Children with moderate TBI can be expected to exhibit deficits that persist beyond 2 years compared to their peers.

- Children with severe TBI can be expected to exhibit neurocognitive deficits that persist beyond 2 years, and over time the gap between them and unaffected peers widens in terms of their performance.

Rationale:

Mild TBI:

- Most neurocognitive outcomes unaffected or minimally affected at 0-5 months
- By 24+ months post-injury, small and often statistically insignificant changes present; gains shown in PIQ and processing speed
- Problem solving domain most positively affected by interventions
- Little to no difference compared with controls in nearly all neurocognitive-related measures at all time points (although inconsistencies in the outcomes used for reporting in this group are made note of)

Mild compared to moderate TBI

- Small to no effect size for attention, working memory, verbal delayed memory
- Small to moderate effect sizes for VIQ, PIQ, processing speed, visual perceptual functioning
- Similar pattern of recovery from deficits over time

Moderate TBI:

- In post-acute phase (0-5 months), significantly worse scores compared to controls in terms of general intellectual functioning, processing speed, attention, problem solving, visual immediate memory, verbal delayed memory; no differences in terms of verbal immediate memory and visual perceptual functioning
- Large significant difference from controls for processing speed and inhibition

Moderate compared to severe TBI

- Small to moderate differences at all time points for VIQ and processing speed
- Small to moderate differences at 24+ months for verbals and visual delayed memory
- Moderate to large differences in post-acute phase for FSIQ, PIQ, visual perceptual functioning, attention; differences decreased over time

Severe TBI:

- Small differences compared to controls in terms of fluency and problem solving in the post-acute phase; these differences became bigger towards the chronic phase
- Significant impairments in outcomes relating to general intellectual functioning, executive functioning and verbal memory when compare to controls
- Although some domains did not display significant impairment at 0-5 months, for almost all domains there was a significant difference between those with severe TBI and controls by 24+ months
- Areas most impacted appear be fluency, processing speed, attention, problems solving

- Significant recovery over time in terms of intellectual functioning, and to a lesser degree executive functioning, processing speed and working memory
- Rate of recovery is slower, however, compared to those with mild or moderate TBI

Severe TBI compared to mild or moderate TBI

- Moderate to large differences between severe TBI and those with either mild or moderate TBI for FSIQ, VIQ, attention, problems solving and visual delayed memory by the chronic phase (24+ months)

6. Kennedy, M. R., C. Coelho, L. Turkstra, M. Ylvisaker, M. Moore Sohlberg, K. Yorkston, H. H. Chiou and P. F. Kan (2008) "Intervention for executive functions after traumatic brain injury: a systematic review, meta-analysis and clinical recommendations (Structured abstract)." *Neuropsychological Rehabilitation* 18, 257-299.

CEBM score: 4/5

This systematic review aimed to collate and appraise the evidence for interventions for planning, organising, problem solving and multi-tasking in TBI-affected adults. Of the fifteen studies included in the review, one paediatric-focused study with a small sample size was included. This was of low quality, and provided limited evidence for the metacognitive strategy instruction (MSI) intervention trialled.

Key finding from the review:

- Although there was compelling evidence for MSI interventions, this was specific to the adult population focused on in this review, and there is insufficient evidence to make any clinical recommendations for the paediatric population

The systematic review included the following study in their review of this question:

Reference	Design	Results
Kennedy 2008		
Suzman et al 1997	Prospective, interventional <i>Sample: n=5, aged 6-11</i>	Children produced fewer errors during the problem solving tasks with implementation of the MSI.
<i>AAN level of evidence: Class III (low) (Case series, case reports or studies with historical controls; or expert opinion)</i>	<i>Level of injury: moderate to severe; 3-6 months post-injury</i> <i>Method: Use of MSI to affect performance in problem solving within a computer game</i>	Insufficient/anecdotal evidence that intervention improved organisational abilities when facing new tasks.

7. Laatsch, L., D. Harrington, G. Hotz, J. Marcantuono, M. P. Mozzoni, V. Walsh and K. P. Hersey (2007). "An evidence-based review of cognitive and behavioral rehabilitation treatment studies in children with acquired brain injury." *Journal of Head Trauma Rehabilitation* 22(4): 248-256.

CEBM score: 4/5

This systematic review aimed to summarise the evidence for cognitive and behavioural interventions for children and adolescents with acquired brain injuries (ABI). Twenty eight studies (n=366) were included in the review, not all of which included participants with TBI. The studies were analysed in four separate groupings of intervention studies:

- Comprehensive (ie. not exclusively focused on executive function)
- Attention/memory
- Speech/language/academic
- Behavioural

Age of participants in the included studies ranged from 0-19 years, and reporting of age for the primary studies was not done consistently throughout the review. Clinical recommendations were made based on the level of the underlying evidence supporting them, according to the Clinical Practice Guideline Process Manual (Edlund et al 2004).

Key findings from the review:

- *Providers of comprehensive rehabilitation serving children and adolescents with ABI should consider the involving family members as active treatment providers in the rehabilitation treatment plan* (p.252). (Braga et al 2005) (**Practice guideline:** Based on evidence from one good quality control trial).
- *Parents or guardians of children who are seen in an emergency department would most likely benefit from an information booklet concerning the effects and symptoms of traumatic brain injury* (p.252). (Ponsford et al 2001) (**Practice option:** Based on evidence from one prospective matched group cohort study).
- *Attention and memory: Service providers of children and adolescents with acquired brain injury (ABI) should consider providing attention remediation to assist recovery* (p.252). (Bulter and Copeland 2002; van't Hooft et al 2005) (**Practice guideline:** Based on evidence from one good quality control trial and one observational study not specific to TBI).

The systematic review included the following studies in their review of this question:

Reference	Design	Results
Laatsch et al (2007)		

Braga et al 2005 (Comprehensive) <i>Class I study: prospective RCT, masked outcome assessment, representative population, clearly defined primary outcome, exclusion/inclusion criteria, accounting of dropouts, matching of subjects</i>	<i>Country:</i> Brazil <i>Sample:</i> n=72, aged 5-12 years <i>Level of injury:</i> moderate to severe TBI, 6-30 months post-injury <i>Method:</i> 1 year of treatment provided; control group received rehabilitative interventions by clinicians, intervention group received family-led interventions (SARAH program)	Family-led program produced statistically significant results in cognitive (WISC-III) and function (SARAH scale) measures. Family's level of education made no impact on success.
Ponsford et al 2001 (Comprehensive) <i>Class II study: prospective, matched group cohort studies, but without "masked" outcome</i>	<i>Sample:</i> n=119, aged 6-15 years <i>Level of injury:</i> mild TBI <i>Method:</i> Control group received emergency department treatment, intervention group (specifically their family members) also received booklet explaining and suggesting strategies for dealing with common symptoms of mild TBI	Improvement seen in both intervention and control groups 3 months post-injury. Statistically significant impact of booklet on three measures of adaptive behaviour. Provision of booklet may help reduce stress for child and family, and reduce chance of TBI symptoms being wrongly credited to other causes.

8. Galland, B. C., D. E. Elder and B. J. Taylor (2012). "Interventions with a sleep outcome for children with cerebral palsy or a post-traumatic brain injury: a systematic review." *Sleep Medicine Reviews* 16(6): 561-573.

CEBM score: 4/5

The aim of this review was to identify interventions for sleep issues in children who had cerebral palsy or had sustained a TBI. Of the 20 studies included in the review, only one (a single case study) was relevant to this question.

Key finding from the review:

- There is no high quality evidence or conclusive findings from lower quality evidence regarding sleep issues in children with TBI. Sleep interventions for children with TBI should be developed, trialled and implemented.

The systematic review included the following study in their review of this question:

Reference	Design	Results
Galland et al (2012)		
Andersen et al 1999 <i>Grade III evidence: opinions of authorities, based on clinical experience; descriptive studies, case reports; or reports of expert committees</i>	Single case study <i>Country:</i> Denmark <i>Sample:</i> 6 year old boy with severe head injury, 3 weeks post-injury <i>Intervention:</i> Trial of once-daily Citalopram (2.5mg, increased to 5mg after three days) for pathological crying (and subsequent sleep disturbance) <i>Outcomes:</i> NR	Sleep pattern normalised within 2 days of starting medication. Drug perceived to have aided in reducing rehabilitation time and costs. Note made by authors that child's symptoms may have improved without drug.

Question 1.5 What is the evidence for community integration for children and adolescents (0-15 years) with traumatic brain injury?

Executive Summary

There were no guidelines relating to this topic. Two systematic reviews reported on areas associated with community integration (social function and quality of life). Greater severity of TBI in children and adolescents was generally found to be associated with a greater degree of impairment in terms of social integration and quality of life. One systematic review focused on the potential efficacy of drama-based interventions for community integration of children and adolescents with TBI (although the subjects in the underlying primary studies were not TBI sufferers). This study found no conclusive evidence.

Evidence statement

Key question	Rating	Notes
Evidence base	A	Three moderate to high quality SR comprised the evidence base found for this question. The underpinning evidence was a mix of RCTs, longitudinal and cross-sectional case control studies, and case series.
Consistency	C	There was consistency across the systematic reviews that greater severity of injury was associated with a greater degree of impairment when it comes to social function and quality of life, although not all primary studies within a review found evidence supporting this. There were no comparable studies relating to drama-based interventions, and the results of this review were inconclusive.
Clinical impact	B	Potential risk factors for quality of life and social function in children post-TBI have been highlighted, which are of clinical importance when looking at long term outcomes for this population. The need for further research has been identified.

Key systematic reviews regarding community integration

1. Di Battista, A., C. Soo, C. Catroppa and V. Anderson (2012). "Quality of Life in Children and Adolescents Post-TBI: A Systematic Review and Meta-Analysis." *Journal of Neurotrauma* 29(9): 1717-1727.

CEBM score: 3/5

This systematic review aimed to identify predictors of quality of life (QoL) for children and adolescents with TBI, and also clarify the nature in which QoL is reported. Included in the review were 11 studies (n= 968), comprising one RCT, seven cohort studies (mix of prospective

and retrospective, four observational), two case control studies and a case series study. A meta-analysis was carried out on nine of these. Participants ranged in age from 6 months to 18 years (two studies included participants up to 18 years), and were 3 months to 5 years post-injury.

Key findings from the review:

- Quality of life following TBI is linked with severity of injury: the odds of having poor QoL score increased by 5.8 times when level of severity was greater than mild.
- Good QoL outcomes are associated with milder injuries, report on QoL from family/physician (rather than child/adolescent), early assessment of QoL (≤ 6 months post-injury); poor outcomes are associated with late assessment of QoL (≥ 1 year post-injury).
- QoL reports carried out too early post-injury may not be an true indication of the impact of injury on the child and family; later assessments are likely more accurately reflect the impact of time, rehabilitation and community reintegration.
- QoL is often reported via family or physician reports; the likelihood of a poor QoL report is increased by 7.9 times when a parent or physician reports in place of the child.
- Quality of life is most often defined as an achievement, and alternative ways of defining and reporting it should be investigated.

2. **Rosema, S., L. Crowe and V. Anderson (2012). "Social function in children and adolescents after traumatic brain injury: A systematic review 1989–2011." *Journal of Neurotrauma* 29(7): 1277-1291.**

CEBM score: 3/5

The aim of this systematic review was to identify common findings relating to social outcome following TBI in children and adolescents. Twenty eight articles (20 cross-sectional and eight prospective longitudinal) are summarised. Participants in the primary studies range in age from 2 to 22 years, with 16 studies involving participants within the 0-15 years age bracket. Most of the underpinning evidence gathered by this systematic review was published within the five years prior to its publishing. Those studies included in the table below provide an overview of the literature published since 2006, and including participants in the 0-15 years age bracket.

Design	Methods	Results
Rosema et al 2012		
Chapman et al (2010)	Prospective, longitudinal case-control <i>Sample:</i> n=169 (orthopaedic controls=93), aged 3-7y <i>Level of injury:</i> moderate & severe <i>Measures:</i> CBCL, BRIEF, PKBS-2, HCSBS	Social competence: minimal difficulties present at 18 months post-injury for TBI group. Severe TBI: more externalising behaviours, executive dysfunction than moderate group at 18 months post-injury.
Ganesalingham et al (2006, 2007a, 2007b)	Cross-sectional case-control <i>Sample:</i> n=130 (controls=65); mean age=8.2y <i>Level of injury:</i> moderate & severe <i>Measures:</i> ECBI, SESBI-R, SSRS, ERC, DGT	Social skills and emotional regulation: poorer in TBI group than controls Significant association between TBI and behavioural/social problems
Ganesalingham et al (2011)	Cross-sectional case-control <i>Sample:</i> n=260 (controls=119); mean age=3.0-6.11y <i>Level of injury:</i> moderate & severe <i>Measures:</i> ABAS, PKBS-2/HCSBS	Social competence: significantly worse scores for severe than moderate group. Level of severity did not impact outcomes on PKBS-2/HCSBS. TBI: worse outcomes on PKBS-2/HCSBS than controls.
Pritagano and Gupta (2006)	Retrospective case-control <i>Sample:</i> n=76 (controls=14); aged=7-13y <i>Level of injury:</i> mild-severe <i>Measures:</i> CBCL	TBI: less close friendships than controls. Severe TBI: less close friendships than mild and moderate groups. Moderate TBI: less close friendships than mild group.
Ross et al (2011)	Cross-sectional case-control <i>Sample:</i> n=28 (controls=14); aged=7-13y <i>Level of injury:</i> not specified <i>Measures:</i> FFQ, LSDS, PIC-2, SDQ	Friendship: no difficulties reported by children in either group. Social interaction/adjustment: no difference in ratings given by parents of TBI and control groups.
Yeates et al (2010)	Retrospective case-control <i>Sample:</i> n=174 (controls=99); aged=3-6.11y <i>Level of injury:</i> mild-severe <i>Measures:</i> CBCL, ABAS, PKBS/HCSBS	Social competence: severe < moderate < control group in terms of scores.

CBCL= Child behaviour Checklist; BRIEF= behaviour Rating Inventory of Executive Function; PKBS-2= Preschool & Kindergarten behaviour Scales-2; HCSBS= Home and Community Social and behaviour Scales; ECBI= Eyberg Child behaviour Inventory; SESBI-R= Sutter-Eyberg Student behaviour Inventory-Revised; SSRS= Social Skill Rating System; ERC= Emotion Regulation Checklist; DGT= 10-Minute Delay of Gratification Task; ABAS= Adaptive behaviour Assessment System; FFQ= Friendship Quality Questionnaire; LSDS= Loneliness and Social Dissatisfaction Scale; PIC-2= Personality Inventory for Children 2; SDQ= Strengths and Difficulties

Key findings from the review:

- There is an increased risk of social impairments for children and adolescents with moderate and severe TBI.
- Younger age, poor social or family factors, and involvement of frontal and corpus callosum areas of the brain are likely contributors to worse social outcomes for children with TBI.
- There is little to no data available on the impact of injury severity and age of injury, and this has been highlighted as an area for further research.

Rationale:

Studies used a wide range of outcome measurement tools, calling on the children themselves, as well as parents and teachers. There was some discrepancy between studies examining outcomes related to social interactions. Ross et al (2011) found self-report of friendship networks to be similar by children with and without TBI. However, Prigatano and Gupta (2006), according to parent-report, found that children with TBI had fewer close friendships, and that those with severe TBI had less close friends than those with mild or moderate TBI. A number of studies (Chapman et al 2010, Ganesalingam et al 2011, Yeates et al 2010) found that greater severity of injury resulted was linked to poorer communication and social competence. Links between social outcomes and social incompetence, socio-economic status, family dysfunction, permissive parenting, and lack of family resources were suggested (Chapman et al 2010, Yeates et al 2010).

Question 1.6 What is the evidence for challenging behaviour in children (0-15) with TBI?

Executive summary

The evidence reviewed in this project for challenging behaviour following paediatric TBI reports, varied in its focus. Two guidelines, one of moderate and one high quality, provide minimal guidance on TBI-related behavioural issues, due to a lack of sound primary evidence (Brain Trauma Foundation 2012; NICE 2007).

Three recent systematic reviews add to the evidence of relationships between challenging behaviours and child/adolescent TBI. There is strong evidence from 50 non-experimental studies to support an association between TBI and subsequent behavioural problems and/or new onset psychiatric problems in children/adolescents. Behavioural problems may arise shortly or several years after injury and often persist (Li & Liu 2012). The home and family environment can moderate TBI-related behavioural problems (Li & Liu 2012; Rosema et al 2012). The impact of TBI on aspects childrens'/adolescents' social functioning is less clear (Rosema et al. 2012). Parent reporting of social adjustment in their children with TBI was inconclusive, however when measures were taken directly from children, those with TBI had significantly lower scores in areas of social cognition and social adjustment (Rosema et al. 2012). Despite a strong association between TBI and the onset of schizophrenia in adults, there is no current evidence of this in children/adolescents (Molloy et al. 2011). There is currently very little evidence for interventions to assist behavioural and psychosocial problems in young people with TBI (Ross et al. 2011). Ross et al. (2011) found only one RCT with evidence of effectiveness for using an online family intervention for the psychosocial problems in children/adolescents with TBI (Wade et al. 2006c).

Evidence statement

Key question	Rating	Notes
Evidence base	A	Information within two guidelines (one high & one mod quality) & four systematic reviews (two good & two moderate quality) is based on data from mostly observational studies
Consistency	A	Consistency in findings of a relationship between TBI & behavioural problems.
	C	Some inconsistency in the relationship of TBI & social functioning which is largely explained by the sources of data (parents/teachers/child with TBI), or by methodology.
Clinical impact	A	Substantial implications due to the significant proportion children/adolescents with TBI who experience behavioural & psychosocial problems

Key guidelines on challenging behaviour following paediatric TBI:

1. **Brain Trauma Foundation. Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents. *Paediatric Crit Care Med*; 2012; 31(1) Sup.**

AGREE II score: 5/7

This US guideline group searched for evidence on the use of analgesia, sedation and neuro-muscular blocks in the acute management of children with TBI, however only poor quality primary studies with high risk of bias were found.

Recommendations regarding behaviour in the acute phase of management (p.S64):

- In the absence of outcome data, the specific indications, choice and dosing of analgesics, sedatives and neuro-muscular blocking agents used in the management of infants and children with severe TBI should be left to the treating physician.(p S64)(Grade III: from poor quality RCTs or cohort studies; mod-poor quality case controls or case series).

2. **NICE 2007 Head injury: Triage, assessment, investigation and early management of head injury in infants, children and adults. National Institute of Health & Clinical Excellence.**

This UK guideline is the update of an earlier 2003 edition. 'This guideline addresses assessment, investigation and early management of head injury. Separate advice is provided for adults and children (including infants) where different practices are indicated.' (pg 4) **NB:** *the NICE development group ruled that they would no longer publish grades with their recommendations.*

AGREE II score: 7/7

Recommendation regarding behaviour in the acute pre-admission phase of management (p.13,16):

- Telephone advice services and other professionals should refer people who have sustained a head injury to a hospital emergency department if the history indicates ... irritability or altered behaviour ('easily distracted', 'not themselves', 'no concentration', 'no interest in things around them') particularly in infants and young children (that is, aged under 5 years).

Key systematic reviews on challenging behaviour following paediatric TBI:

1. Li, L. and J. Liu (2012). "The effect of pediatric traumatic brain injury on behavioral outcomes: a systematic review." *Developmental Medicine & Child Neurology* 55(1): 37-45.

CEBM Score: 4/5

This review examined the relationship between childhood TBI and subsequent behavioural problems. Included studies (n=50) considered children and adolescents 0 to 18yr. It was not possible to determine which of these studies met this report's criteria (0-15yr). Studies were assessed for quality and risk of bias using a modified Cappa test (Cappa et al. 2011) and were excluded from the review if they scored < 3/9. Details of the primary studies were not provided, however studies published post-2000 are referenced here.

Key findings of the review (p.37-39):

- Paediatric patients with TBI are at significantly increased risk of various behavioural and novel psychiatric problems, with prevalence rates of 10 – 50%.
- Behavioural problems may arise shortly or several years after injury and often persist or even worsen over time.
- The behavioural outcomes in older children with TBI include:
 - the emergence of general internalising & externalising problems after injury (Anderson et al 2005; Schwartz et al 2003; Taylor et al 2002)
 - increases in aggression (Cole et al. 2008; Dooley et al. 2008),
 - impulsivity and hyperactivity (Catale et al. 2009; Yeates et al. 2005),
 - withdrawal (Wetherington et al. 2010; Hawley 2004),
 - anxiety (Hawley 2004; Tonks et al. 2011), and
 - depression (Kirkwood et al. 2000; Tonks et al. 2011)
- These behavioural impairments appear to be moderated by the family environment (Chapman et al. 2010; Gerring et al. 2009).
- Caregivers should be encouraged to provide positive environments and parenting styles which may help reduce chronic behavioural problems after TBI (Wade et al. 2011a; Kurowski et al. 2011; Yeates et al. 2010).
- TBI has been linked to new-onset psychiatric disorders, including:
 - Personality change (Max et al. 2004; 2005a,2006)
 - Attention deficit hyperactivity disorder (ADHD) (Levin et al. 2007; Max et al. 2004; 2005b; Schachar et al. 2004)
 - Mood and depressive disorders (Luis et al. 2002; Max et al 2012)

2. Rosema, S., L. Crowe and V. Anderson (2012). "Social function in children and adolescents after traumatic brain injury: A systematic review 1989–2011." *Journal of Neurotrauma* 29(7): 1277-1291.

CEBM Score: 3/5

The review aimed to clarify the impact of TBI on social function in children and adolescents. Social function outcomes included social adjustment, social interaction and social cognition which were defined in the paper. This review identified 28 relevant studies, of these 14 fit the inclusion criteria (0-15yr) (Anderson et al. 2001; Asarnow et al. 1991; Chapman et al. 2010; Fletcher et al. 1990; Ganesalingam et al. 2006, 2007a, 2007b; Ganesalingam et al. 2011; Max et al. 1998; Papero et al. 1993; Poggi et al. 2005; Prigatano & Gupta 2006; Ross et al. 2011a; Warschausky et al. 1997; Yeates et al. 2004; Yeates et al. 2010). Another 14 studies included age ranges up to 0-22yr. The author report that all studies had significant methodological flaws. The results of the studies published after 2007 are presented in the table below.

Key findings from the review:

- Social adjustment outcomes, as rated by parents of children and adolescents with TBI, show mixed results, with some studies reporting poor social adjustment in TBI groups (Ganesalingam et al. 2011; Levin et al. 2009; Yeates et al. 2010) and others reporting no group differences (Chapman et al. 2010; Hanten et al. 2008; Ross et al. 2011a).
- In studies where social adjustment is measured using direct child measures as well as parent ratings, children with TBI scored significantly lower than uninjured children in adaptive behaviour, self-esteem and higher in maladaptive aggressive and anti-social behaviour (Ganesalingam et al. 2006, 2007a, 2007b).
- Studies considering the social interaction aspect of social function also report variable results. Ross and associates (2011a) found no differences in friendship networks and friendship quality between children with and without TBI. This differs from an earlier study that found a dose response, with parents reporting progressively fewer friendships for children as TBI severity increased (Prigatano & Gupta 2006).
- Studies on social cognition (the ability to perceive and process social cues) were more consistent in finding that children and adolescents with TBI have more difficulty than controls in social problem solving (Hanten et al. 2008, 2011). Similarly, TBI groups have increased difficulty with social information processing and conversation skills (Turkstra et al. 2004, 2008), and recognizing emotions (Tonks et al. 2007).

Reference	Design	Results
Rosema et al 2012		
Ganesalingam et al. 2006, 2007a, 2007b	Cross-sectional design <i>Sample:</i> 130 children (mean age 8.2y) <i>Level of injury:</i> Moderate (n=33), Severe (n=32), controls (n=65)	- Parents and teachers reported TBI had poorer social skills than control (CO)

	<p><i>Methods:</i> observational study. Informants parents, teachers, children</p> <p><i>Focus:</i> Social adjustment, social cognition</p>	<ul style="list-style-type: none"> - TBI had lower emotion regulation and higher liability/negativity than CO - TBI fewer distraction strategies and poorer behavioural self-regulation - Total effect of group membership was significant for each measure of social and behavioural function; TBI was associated with behaviour and social problems - TBI group used significantly more aggressive, avoidant, or irrelevant solutions, and less assertive responses compared to CO
Yeates et al. 2010	<p>Retrospective study</p> <p><i>Sample:</i> 174 children (age 3-6.11y)</p> <p><i>Level of injury:</i> complicated mild/moderate (n=56), severe (n=19), orthopaedic controls</p> <p><i>Methods:</i> observational</p> <p><i>Focus:</i> social adjustment</p>	<ul style="list-style-type: none"> - Severe TBI < Moderate TBI < controls on social competence measures
Levin et al. 2009	<p>Cross-sectional study</p> <p><i>Sample:</i> 93 children (age 6-16y)</p> <p><i>Level of injury:</i> moderate (n=24), severe (n=28), orthopaedic controls</p> <p><i>Methods:</i> observational, informants teachers, parents, psychiatrists, child adolescent</p> <p><i>Focus:</i> social adjustment</p>	<p>TBI poorer socialisation & communication than controls</p>
Chapman et al. 2010	<p>Prospective longitudinal cohort</p> <p><i>Sample:</i> 169 children (age 3-7y)</p> <p><i>Level of injury:</i> Moderate (n=55), severe (n=21), orthopaedic injury- control (n=93)</p> <p><i>Focus:</i> social adjustment, behaviour, executive function, environment</p> <p><i>Informants:</i> parents</p>	<p>Severe TBI: more externalizing behaviours and executive dysfunction at 18 months</p> <ul style="list-style-type: none"> - Minimal social competence difficulties at 18 months
Hanten et al. 2011	<p><i>Sample:</i> 28 adolescents (age 12-19y)</p> <p><i>Level of injury:</i> Moderate severe (n=15), control (n=13)</p> <p><i>Focus:</i> social cognition</p> <p><i>Informants:</i> adolescents</p>	<p>TBI group lower on social problem solving skills</p> <p>Relationship between brain structure (area of injury) and scores</p>

Ross et al. 2011a	<p>Cross sectional study</p> <p><i>Sample:</i> 28 children (age 7-13y)</p> <p><i>Level of injury:</i> TBI (n=14), control (n=14)</p> <p><i>Focus:</i> social adjustment, social interactions</p> <p><i>Informants:</i> parents & children</p>	<p>Children in both groups reported friendship difficulties.</p> <p>Parent in both groups did not differ in reports of social function</p>
Ganesalingam et al. 2011	<p>Cross-sectional design</p> <p><i>Sample:</i> 160 children (age 83.0-6.11yr)</p> <p><i>Level of injury:</i> Moderate (n=64), Severe (n=23), orthopaedic injury controls (n=119)</p> <p><i>Methods:</i> observational study.</p> <p>Informants parents,</p> <p><i>Focus:</i> Social adjustment</p>	<p>Severe TBI scored significantly lower on social competence than moderate TBI, who scored lower than the controls.</p> <p>No difference between severe & mod TBI in preschool and community behaviour scales' scores, but severe TBI significantly worse than controls.</p>
Prigatano & Gupta 2006	<p>Retrospective study</p> <p><i>Sample:</i> 76 children (age 7-14y)</p> <p><i>Level of injury:</i> Ortho injury controls (n=16), mild TBI (n=36), moderate (n=10), severe (n=14)</p> <p><i>Focus:</i> social interactions</p> <p><i>Informants:</i> parents</p>	<p>TBI had less close friends than controls.</p> <p>Severe TBI fewer close friends than mod TBI, and mod TBI fewer close friends than mild TBI</p>
Turkstra et al. 2008	<p>Cross sectional study</p> <p><i>Sample:</i> 18 adolescents (age 13 -22y)</p> <p><i>Level of injury:</i> controls (n=9), TBI (n=9),</p> <p><i>Focus:</i> social cognition</p> <p><i>Informants:</i> adolescents</p>	<p>TBI less able to generate appropriate response to everyday situations.</p> <p>No significant difference in theory of mind measures</p>

3. Molloy, C., R. M. Conroy, D. R. Cotter and M. Cannon (2011). "Is traumatic brain injury a risk factor for schizophrenia? A meta-analysis of case-controlled population-based studies." *Schizophrenia Bulletin* 37(6): 1104-1110.

CEBM Score: 3/5

This evidence is presented here as schizophrenia is a mental illness which may produce challenging behaviours. This meta-analysis and systematic review of the literature on TBI and psychosis aimed to identify population-based controlled studies which provide risk estimates for developing schizophrenia following TBI. This review reported on nine studies that reported estimates of risk, however only two of these sampled children with TBI (Timonen et al. 2002; Massagli et al. 2004).

Key findings from the review:

Pooled analysis of data from all studies (adults and children) found a significant association between TBI and schizophrenia (OR = 1.65; 95% CI = 1.17-2.32). There was no dose response relationship with severity of TBI. Neither of the studies on children reported a significant risk of psychosis following TBI.

The systematic review included the following study in their review of this question:

Reference	Design	Results
Molloy et al. 2011		
Timomen et al. 2002	Retrospective cohort study Country: Finland Sample: n= 10,934 TBI patients (age <15y)	Risk Estimate for psychosis following TBI = 1.1 (95% CI 0.41-2.96)
Massagli et al. 2004	Retrospective cohort study Sample: n= 1,960 mild TBI patients (age <14y)	Risk Estimate for psychosis following TBI = 3.01 (95% CI 0.9 – 10.2)

4. Ross, K. A., L. Dorris and T. McMillan (2011). "A systematic review of psychological interventions to alleviate cognitive and psychosocial problems in children with acquired brain injury." *Developmental Medicine and Child Neurology* 53(8): 692-701.

CEBM Score: 4/5

This review aimed to summarise the effectiveness of psychological interventions for cognitive and psychosocial effects of paediatric ABI. This systematic review summarises nine interventional studies: five concerning cognitive outcomes and four concerning psychosocial outcomes. These were scored using the CONSORT guidelines tool. Only one study on psychosocial functioning met our inclusion criteria (children 0-15) (Wade et al. 2006c), others included older participants.

Key findings from the review:

- There was evidence from one high quality RCT, that an online family problem-solving intervention is effective for the psychosocial internalising of symptoms (such as depression / anxiety and withdrawal) in children/adolescents with TBI (Wade et al 2006c).

The systematic review included the following study in their review of this question:

Reference	Design	Results
Ross et al. 2011b		
Wade et al 2006c CONSORT score = 77%	RCT <i>Sample:</i> 39 families with children with mod-severe TBI (age 8-13y) <i>Intervention:</i> 14 session online computer based training, family problem solving <i>Outcome:</i> Child Behaviour Check List (CBCL) <i>Focus:</i> child adjustment	CBCL: Internalising effect size $g=0.45$ (small-medium) An online family problem-solving intervention is effective for the psychosocial internalising of symptoms in children/adolescents with TBI.

Other earlier or lower quality evidence on the topic:

Ylvisaker, M., L. Turkstra, et al. (2007). "Behavioural interventions for children and adults with behaviour disorders after TBI: A systematic review of the evidence." *Brain Injury* 21(8): 769-805. (CEBM Score 2/5)

Question 1.7 What is the evidence for growth and developmental issues in children (0-15 years) with TBI?

Executive summary

No guidelines were found with information relating to this topic. Six systematic reviews were included, three of high quality and three of moderate quality. These reviews reported on a wide range of topics including the relationship between childhood TBI and behavioural problems (investigating potential contributing factors and when the behavioural issues may arise); impact of TBI on intelligence (additionally the impact of post traumatic amnesia following TBI on intelligence impairment); academic and language outcomes; the onset of perceptive visual dysfunctions (with regard to various aetiologies of brain damage) neurocognitive outcomes across a variety of domains and cognitive and behavioural treatments for children with TBI. Many of the included reviews examined these topics and accounted for changes through the lifespan (including time post-injury, and at various time points since injury), injury severity, and age at injury.

Evidence statement

Key question	Rating	Notes
Evidence base	A	Information within six systematic reviews (three of high quality and three of moderate quality) is based on data from observational studies, randomised controlled trials, and case series. Three of the reviews carried out meta-analyses on their data.
Consistency	B	There were a range of interventions and/or the range of domains reported in the reviews. However, most studies which have examined similar domains have reported consistent findings.
Clinical impact	B	Substantial implications due to the significant proportion children/adolescents with TBI who experience growth and developmental issues (in terms of a variety of domains).

Key guidelines regarding growth and developmental issues in children with traumatic brain injury (TBI):

There were no guidelines with a quality rating of $\geq 50\%$ using the AGREE II tool regarding growth and developmental issues in paediatrics (0-15 years) with TBI.

Key systematic reviews regarding growth and developmental issues in children with traumatic brain injury (TBI):

1. Li, L & Liu, J 2012, 'The effect of pediatric traumatic brain injury on behavioral outcomes: a systematic review', *Developmental Medicine & Child Neurology*, vol. 55, no. 1, pp. 37-45.

CEBM Score: 4/5

This review examined the relationship between childhood TBI and behavioural problems, additionally investigating potential contributing factors. Of the 50 studies included in the review only three studies applied to the development of children with TBI.

Key findings from the review:

- Behavioural problems and new-onset psychiatric disorders affect a significant proportion of children/adolescents with TBI
- These issues may arise shortly or several years after injury and often persist or even worsen over time (see further details of this review under Q 1.6).
- In young children, social or behavioural impairments may lay dormant for several years or may not be detectable in parent/teacher behavioural rating scales (Wetherington et al. 2010; Chapman et al 2010).
- Children with inflicted TBI perform significantly more poorly on cognitive measures than those sustaining accidental TBI (Keenan et al. 2007; Wetherington et al. 2010).

The systematic review included the following study in their review of this question:

Reference	Design	Results
Li & Liu (2012)		
Chapman et al. 2010	Prospective Longitudinal <i>Country:</i> USA <i>Sample:</i> n=169 <i>Level of injury:</i> Moderate (55); Severe (21); Control- orthopaedic injuries (93)	NR
Modified Scale (Cappa et al. 2011)	<i>Age (at injury) Range:</i> 3-7 <i>Methods:</i> NR <i>Hypothesis:</i> NR	
Score= 8/9		
Keenan et al. 2007	Case Study <i>Country:</i> USA <i>Sample:</i> n=79 <i>Level of injury:</i> Inflicted (25); Accidental (23); Control- orthopaedic injuries (31)	NR
Modified Scale (Cappa et al. 2011)	<i>Age (at injury) Range:</i> 0-2 <i>Methods:</i> NR <i>Hypothesis:</i> NR	
Score= 7/9		

Wetherington et al. 2010	Case Study <i>Country:</i> USA <i>Sample:</i> n=82 <i>Level of injury:</i> Mild (31); Moderate – Severe (20); Control- orthopaedic injuries (31) <i>Age (at injury) Range:</i> 0-2 <i>Methods:</i> NR <i>Hypothesis:</i> NR	NR
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Cappa, KA, Conger, JC & Conger, AJ 2011, 'Injury severity and outcome: a meta-analysis of prospective studies on TBI outcome', *Health Psychol*, vol. 30, pp.542–60.

2. **Königs, M, De Kieviet, JF, & Oosterlaan, J 2012, 'Post-traumatic amnesia predicts intelligence impairment following traumatic brain injury: A meta-analysis', *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 83, no. 11, pp. 1048-1055.**

CEBM Score: 4/5

This meta-analysis aimed to determine the impact of TBI on intelligence throughout the lifespan. Additionally the review investigated the predictive value of post-traumatic amnesia (PTA) duration for intelligence impairment. This review reported on 21 studies of mixed design and quality. Six of these studies reported on paediatric TBI (Catroppa & Anderson 1999; Catroppa & Anderson 2005; Cattalani et al. 1998; Chadwick et al. 1981; Knights et al. 1991; Tremont et al. 1999).

Key findings from the review:

- Results of the paediatric studies were provided, however not discussed separately from general findings; no separate analysis done on these studies.
- A longer period of post traumatic amnesia is a strong predictor of intelligence impairment.
- Routine assessment of PTA duration should occur in clinical settings.

The systematic review included the following study in their review of this question:

Reference	Design	Results
Konigs et al (2012)		
Catroppa & Anderson. 1999	Cross-sectional <i>Country:</i> NR <i>Sample:</i> n=27. Ave Age=10.40 Level of injury: mean GCS score= 14.30	NR
Newcastle-Ottawa Scale 3	<i>Methods:</i> NR <i>Hypothesis:</i> NR	
Catroppa & Anderson 2005	Longitudinal <i>Country:</i> NR <i>Sample:</i> n=25. Ave Age=10.50	NR

Newcastle- Ottawa Scale 3	Level of injury: mean GCS score= 14.20 <i>Methods:</i> NR <i>Hypothesis:</i> NR	
Cattelani et al. 1998	Longitudinal <i>Country:</i> NR <i>Sample:</i> n=20. Ave Age=12.20	NR
Newcastle- Ottawa Scale3	Level of injury: mean GCS score= 5 <i>Methods:</i> NR <i>Hypothesis:</i> NR	
Chadwick et al. 1981	Longitudinal <i>Country:</i> NR <i>Sample:</i> n=19. Ave Age=9.60	NR
Newcastle- Ottawa Scale 7	Level of injury: mean GCS score= NR <i>Methods:</i> NR <i>Hypothesis:</i> NR	
Knights et al. 1991	Longitudinal <i>Country:</i> NR <i>Sample:</i> n=26. Ave Age=10.80	Moderate to strong relations between PTA duration and Welchsler scale FSIQ, PIQ and VIQ in children with TBI.
Newcastle- Ottawa Scale score =1	Level of injury: mean GCS score= 5.50 <i>Methods:</i> performed intelligence testing at time of hospital discharge <i>Hypothesis:</i> NR	Predictive value of PTA duration for intelligence is superior to that of GCS score, and LOC duration.
Tremont et al. 1999	Cross-sectional <i>Country:</i> NR <i>Sample:</i> n=30. Ave Age=10.93	Moderate to strong relations between PTA duration and Welchsler scale FSIQ, PIQ and VIQ in children with TBI.
Newcastle- Ottawa Scale 6	Level of injury: mean GCS score= NR <i>Methods:</i> NR <i>Hypothesis:</i> NR	Predictive value of PTA duration for intelligence is superior to that of GCS score, and LOC duration.

Full scale IQ (FSIQ); Glasgow Coma Scale (GCS); loss of consciousness (LOC); not reported (NR); performance IQ (PIQ); post traumatic amnesia (PTA); traumatic brain injury (TBI); verbal IQ (VIQ).

3. **Vu, JA, Babikian, T, Asarnow, RF 2011, 'Academic and Language Outcomes in Children After Traumatic Brain Injury: A Meta-Analysis', *Exceptional Children*, vol. 77, no.3, pp. 263-281.**

CEBM Score: 3/5

This meta-analysis examined academic and language outcomes at different time points post-TBI* in children and adolescents. Eighteen studies were included that reported on language or academic outcomes of children with TBI (mild, moderate or severe). It looked at both longitudinal and cross-sectional studies. Analyses were performed based on the severity of injury and the time post-injury. Overall, minimal statistically significant results were found, this being attributed to the small number of studies eligible for inclusion in the review.

Key findings from the review:

- Across all domains, children who have experienced mild TBI can be expected to recover along a similar trajectory to healthy controls, although deficit gap in the various domains that results from the injury is unlikely to be closed in the first 2 years following injury
- Children with severe TBI can be expected to display deficits in all domains following injury, and have a slower rate of recovery in the domains of reading, expressive and receptive language
- Children with severe TBI should be particularly closely monitored, and receive targeted intervention as indicated, beyond 2 years post-injury, as their improvement in language and academic domains can be expected to continue beyond this time period
- Learning may be facilitated by modifications to activities aimed at intervention, for example task breakdown, or increased time allocated to task completion

Rationale:

Mild TBI:

- No statistically significant differences in terms of language or academic abilities compared to controls at any time point.
- No statistically significant changes over time in any of the language or academic domains.

Mild compared with moderate TBI

- Small significant differences in overall language when compared to children with moderate TBI; those with mild TBI performing better in this domain up to 23 months post-injury, but difference no longer present 24+ months post-injury.
- With regards to reading capabilities, there was no significant difference up to 23 months post-injury between those with mild and moderate TBI, but at 24+ months, there was a significant difference, indicating poorer outcomes for those with moderate TBI.

Moderate TBI:

- Small but significant difference in academic outcomes between children with moderate TBI and controls at all three time points.
- No statistically significant changes over time in any of the language or academic domains.
- Although the *rate* of development of academic skills is the same as controls, deficits that present acutely post-injury do not appear to resolve.

Moderate compared to severe TBI

- Small significant differences in reading outcomes, moderate differences in receptive language outcomes when compared to children with severe TBI; those with moderate TBI performed better in this domain at all three time periods
- Looking at expressive language, no significant difference between moderate and severe TBI sufferers at 0-23 months post-injury, but moderate difference at 24+ months
- Looking at arithmetic, spelling and overall language capabilities, there were moderate-large significant difference at 0-5 months, although these reduced significantly by 24+ months post-injury

Severe TBI:

- Large statistically significant differences in reading and overall language outcomes between children with severe TBI and controls at all three time points
- Moderate statistically significant differences in expressive and receptive language outcomes compared to controls at all three time points
- Large statistically significant differences in were reported between children with severe TBI and controls in arithmetic, spelling, language pragmatic domains; this difference as particularly large at 0-5 months post-injury, and decreased in its magnitude (although remained a large difference) by 24+ months post-injury
- No significant recovery over time in reading, receptive and overall language; other domains exhibited some level of recovery

Severe compared to mild or moderate TBI

- Larger differences in outcomes between children with severe and mild than moderate and mild TBI
- Large statistically significant differences in terms of reading and overall language between children with severe TBI compared with mild TBI; this persisted across the three time periods studied.

*Post injury time bands: Time 1 was zero to 5 months post injury. Time 2 was six to 23 months post injury, and Time 3 was 24 months or more post injury (p. 266)

4. **Boot, FH, Pel, JJM, van der Steen, J & Evenhuis, HM 2010, 'Cerebral Visual Impairment: Which perceptive visual dysfunctions can be expected in children with brain damage? A systematic review', *Research in Developmental Disabilities*, vol. 31, no. 6, pp. 1149-1159.**

CEBM score: 3/5

This review aimed to summarise which perceptive visual dysfunctions are to be expected based on various aetiologies of brain damage and brain development disorders (including TBI) with their onset in the pre-, peri- or postnatal period. This review reported on 19 different studies, 8 'key' studies and 11 'complementary' studies, in children under the age of 18 (0-18

inclusion criteria). However, only two of the included studies were based on children with TBI and the specific age range was not reported (Braga et al. 2007; Roberts et al. 1995). No details were provided of these two studies.

Key findings from the review:

The two studies relevant to TBI were categorised as 'complimentary' studies. No main conclusions were drawn from these studies for postnatal head trauma in children, however, it was reported that both studies did show a reduced visual memory.

5. Babikian, T & Asarnow, R 2009, 'Neurocognitive outcomes and recovery after pediatric TBI: meta-analytic review of the literature', *Neuropsychology*, vol. 23, no. 3, pp. 283-296.

CEBM score: 3/5

This meta-analysis aimed to quantitatively summarise the current literature on neurocognitive outcomes across domains, accounting for time post injury, injury severity, and age at injury, subsequent to paediatric TBI.

This review reported on 28 publications (1988 to 2007) on paediatric TBI and reported on the three distinct injury severity and time post injury* for key neurocognitive domains**. The age range of the included studies was not specified however all the included studies were paediatric and divided into two groups based on their age of injury (group 1: injury age 0-5 OR group 2: injury age 6-16 years). Both cross-sectional and longitudinal studies were included, yielding data from either defined points in time as well as the time course of recovery.

Key findings from the review:

Mild: The studies including children with mild TBI showed few, if any, impairments in the neurocognitive domains reviewed at any time point, including postacute outcomes. Although majority of the studies found no statistically significant effects of mild TBI on neurocognitive functioning, it was suggested in some studies that there may be a subset of children with mild TBI who show adverse outcomes in some domains.

Moderate: Those in the moderate group had results more similar to those in the severe rather than the mild group, especially on measures of intellectual functioning and processing speed. The deficits in children with moderate TBI persist even after 2 years post injury compared with controls, despite recovery in intellectual functioning and attention.

Severe: Studies of the neurocognitive outcomes and recovery after a severe TBI revealed significant impairments, with moderate to very large effects noted for intellectual functioning (primarily PIQ), executive functioning (processing speed and attention), as well as verbal immediate and delayed memory at Time 1. Similarly to the moderate TBI group, children with

severe TBI, despite recovery over the first 2 years post injury, across most neurocognitive domains, fail to catch up to its peers and appear to fall farther behind over time.

*Time post injury: Time 1: 0–5 months post injury; Time 2: 6–23 months post injury, and Time 3: 24 + months post injury. (p 284)

**Key neurocognitive domains included were: General Intellectual Functioning (FSIQ or its equivalent; Verbal IQ; and Performance IQ); Attention/Executive Function (working memory, processing speed/reaction time, attention, fluency, inhibition, and problem solving); Memory (verbal/visual immediate/delayed); and Visual Perceptual/Motor skills. (p 285)

6. **Laatsch, LD, Harrington, G, Hotz, J, Marcantuono, MP, Mozzoni, V, Walsh & KP, Hersey 2007, 'An evidence-based review of cognitive and behavioral rehabilitation treatment studies in children with acquired brain injury', *Journal of Head Trauma Rehabilitation*, vol. 22, no. 4, pp.248-256.**

CEBM Score: 4/5

This review aimed to produce a systematic evidence based evaluation on published cognitive and behavioural treatment studies with paediatric subjects who have a history of an acquired brain injury (ABI). Twenty-eight publications (1980- 2006), totalling 366 children (including ages 0-19) with ABI were reported in this review. This included one prospective randomised controlled trial, five prospective cohort studies, a grouping of six retrospective case controls and matched case control studies and a grouping of 16 studies reporting individual case studies and clinical case series. Specific age ranges of only three studies (Braga et al. 2005; Ponsford et al. 2001; Silver et al. 1994) fit within our inclusion criteria (age 0-15) with other studies including children older than 15 or the inclusion age not reported in the review.

Key findings from the review (p. 252):

Studies were classified as Class I to Class IV*. Recommendations (practice guideline) were made based on evidence from at least 1 Class I or 2 Class II studies. The use of evidence from studies by the same author with the same intervention and using a similar population was used to support the practice option in 1 Class II study, due to the limited number of paediatric studies available.

Practice Guideline: *Attention and memory:* Service providers should consider providing attention remediation to assist recovery in children and adolescents with ABI (Bulter and Copeland, 2002; van't Hooft et al. 2005) [the age range of children in these studies were not reported, however the mean age of those included in the study by Butler and Copeland (2002) mean 4.0 years]. *Comprehensive:* Service providers of comprehensive rehabilitation should consider involving family members in the rehabilitation treatment plan for children and adolescents with ABI (Braga et al. 2005).

Practice Option: Comprehensive treatment: An information booklet regarding the effects and symptoms of traumatic brain injury may be of useful to give to parents or guardians of children seen in an emergency department (Ponsford et al. 2001; Ponsford et al. 2002). [The age range of children in these studies: Ponsford et al. 2001 6-15 years; Ponsford et al. 2002 adults with TBI].

*Studies were classified as Class I to Class IV, utilizing the following criteria. Class I, II, and III studies were controlled trials, while Class IV studies involved no control group and utilised individual case studies or clinical case series (p.249).

The systematic review included the following study in their review of this question:

Reference	Design	Results
Laatsch et al. 2007		
Braga et al. 2005	Randomised Controlled Trial <i>Country:</i> NR <i>Sample:</i> n=72. Age Range 5-12. <i>Level of injury:</i> Moderate to Severe <i>Methods:</i> children were randomised into either a control group that rehabilitation interventions were delivered by clinicians or into a second group that rehabilitative interventions were delivered by family members (under supervision). Both groups received this for one year and cognitive outcomes were assessed by the WISC-III and functional outcomes assessed by the SARAH scale. <i>Hypothesis:</i> NR	Both groups benefited from intervention, however, only children receiving the family-based SARAH model experienced statistically significant gains on both the cognitive and functional measures.
Class I		
Ponsford et al. 2001	Cohort Study <i>Country:</i> NR <i>Sample:</i> n=119. Age Range 6-15. <i>Level of injury:</i> Mild (MTBI) <i>Methods:</i> One MTBI group (n = 61) (assessed at one week and three months) was provided an informational booklet describing symptoms common to MTBI and suggestions and strategies for coping with them while the other MTBI group (n = 58) (assessed at three months only) received only emergency department treatment. These two groups were compared with two control groups consisting of children	At three months post injury, behavioural symptoms and cognitive difficulties had significantly improved in both MTBI groups overall. The information booklet had a statistically significant impact on 3 adaptive behaviour inventories when compared to the non-treated MTBI group at 3 months post injury. It was concluded that an information booklet early in treatment can help reduce both the parental and child stress and the frequency with which they misattributed MTBI-related symptoms to other causes.
Class II		

	with other minor injuries (not MTBI), one of the control groups was assessed at one week and three months and the other control group at three months only.	
	Hypothesis: NR	
Silver et al. 1994	Case Study Country: NR Sample: 1 Female Age 12. Level of injury: Severe Methods: NR	NR
Class IV	Hypothesis: NR	

Other earlier or lower quality evidence on the topic:

Greer, D. M., S. E. Funk, N. L. Reaven, M. Ouzounelli and G. C. Uman (2008). "Impact of fever on outcome in patients with stroke and neurologic injury: a comprehensive meta-analysis." *Stroke* 39(11): 3029-3035. (CEBM Score 2/5)

Question 1.8 What is the evidence for ongoing follow-up care and monitoring of children (0-15 years) with TBI?

Executive summary

Two clinical guidelines (one excellent and one high quality) and one high quality systematic review were identified for the ongoing follow-up care and monitoring of children with TBI. The review reports the impact of anticonvulsant on post-traumatic seizure disorder, and the guidelines provide recommendations on follow-up care after discharge.

Evidence statement

Key question	Rating	Notes
Evidence base	A	Information within the high quality systematic review is based on data from a randomised controlled trial; information within the guidelines is based on consensus of experts
Consistency	A	Evidence around ongoing follow up care and monitoring is consistent
Clinical impact	B	Substantial impact due to significant proportion of children post-TBI requiring follow-up care

Key guidelines regarding ongoing follow-up care and monitoring

1. **SIGN 2009 Early management of patients with a head injury. Scottish Intercollegiate Guideline Network.**

AGREE II Score: 7/7

This guideline makes recommendations on the early management of patients with head injury, focusing on topics of importance throughout NHS Scotland. Recommendations are made for the management of adults and children.

The majority of recommendations relevant to this question are informed by the clinical experience of the guideline development group.

Recommendations regarding ongoing follow-up care and monitoring:

Note: Age range of children not reported

- *There is some evidence to show that following mild traumatic brain injury a proportion of children will have moderate disability at follow up and that this group of patients would benefit from telephone/postal follow up (p. 36, Hawley et al 2004). Follow up is of benefit in patients with moderate/severe traumatic brain injury in terms of reducing reporting of symptoms, anxiety and behavioural changes (p. 36, Ponsford et al 2001).*

(Level 2+ : Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal)

- *Children suffering from moderate/severe head injury should be followed up by a specialist multidisciplinary team to assess rehabilitation needs* (p. 36). (Good practice point: Recommended best practice based on the clinical experience of the guideline development group.)
- *Parents should be given information and advice about the possible short/longer term difficulties that their child may have* (p. 36). (Good practice point: Recommended best practice based on the clinical experience of the guideline development group.)
- *The primary healthcare team, school health team and teachers should be notified of all children with a head injury regardless of severity* (p. 36). (Good practice point: Recommended best practice based on the clinical experience of the guideline development group.)

2. Vos PE, Alekseenko Y, Battistin L, Ehler E, Gerstenbrand F, Muresanu DF, et al. Mild traumatic brain injury. *European Journal of Neurology* 2012, 19: 191-198.

AGREE II score: 5/7

This European guideline provides recommendations for the acute management of adults and children presenting with mild TBI. It is aimed primarily at medical management.

The recommendation relevant to this question is based on consensus from the expert panel.

Recommendation regarding ongoing follow-up care and monitoring:

For children under 6 years of age who are discharged home from the emergency department, head injury warning instructions are recommended because of the likelihood of delayed cerebral swelling (p.195). (Good practice point: Recommendation based on consensus of experts.)

Key systematic review regarding ongoing follow-up care and monitoring

1. Teasell R, Bayona N, Lippert C, et al (2007). Post-traumatic seizure disorder following acquired brain injury. *Brain Injury*; 21(2):201-214.

CEBM score: 4/5

This review examined the effectiveness of prophylactic anticonvulsant pharmacological approaches for the prevention of seizure disorder following acquired brain injury in adults and children. Fifteen studies were identified for this review; of these 10 were randomised controlled trials, two retrospective studies, one prospective controlled trial, one single group study and one case series. The anticonvulsants varied between studies and included phenytoin, carbamazepine, valproate, and midazolam.

Out of the fifteen studies, only one (i.e. randomised controlled trial) was relevant to the question and involved children.

Key finding from the review:

In children (age range not reported), there is moderate evidence (i.e. supported by a single randomised controlled trial of fair quality) that prophylactic phenytoin does not reduce the incidence of late onset seizures (Young et al 1983). Late onset seizure was defined as a seizure which occurs later than one week after injury (Teasell 2007).

The systematic review included the following study in their review of this question:

Reference	Design	Results
Teasell et al (2007)		
Young et al (1983)	Randomised controlled trial <i>Country:</i> USA <i>Sample:</i> n=46. Patients with either a penetrating missile wound or a blunt head injury within 24 hours of hospital admission following a severe head injury; level of injury – not reported	There was no significant difference between groups regarding the percentage of children having late seizures.
Downs & Black score=23 PEDro=6	<i>Intervention:</i> Phenytoin group: initial dose of 18mg/kg of body weight infused over 20 minutes; then maintenance dose of 2mg/kg of body weight of phenytoin every 8 hours for 48 hours for a total of 5 additional doses; Placebo group: equivalent volume of the placebo solution <i>Outcome:</i> Percentage of children having late seizures	

Other earlier or lower quality evidence on the topic

Fehlings, D., I. Novak, S. Berweck, B. Hoare, N. S. Stott and R. N. Russo (2010). "Botulinum toxin assessment, intervention and follow-up for paediatric upper limb hypertonicity: international consensus statement." *European Journal of Neurology* 17: 38-56. (CEBM score 2/5)

Harmon, K. G., J. A. Drezner, M. Gammons, K. M. Guskiewicz, M. Halstead, S. A. Herring, J. S. Kutcher, A. Pana, M. Putukian and W. O. Roberts (2013). "American Medical Society for Sports Medicine position statement: concussion in sport." *British Journal of Sports Medicine* 47(1): 15-26. (AGREE II score 2/7)

Purcell, LK, Canadian Paediatric Society, Healthy Active Living and Sports Medicine Committee 2012, 'Evaluation and management of children and adolescents with sports-related concussion, *Paediatr Child Health*, vol. 17, no. 1, pp. 31. (AGREE II score 1/7)

Providence, C. F. and K. M. Johnston (2009). "Knowledge transfer principles as applied to sport concussion education." *British Journal of Sports Medicine* 43: i68-i75. (CEBM score 1/5)

Purcell, L. (2009). "What are the most appropriate return-to-play guidelines for concussed child athletes?" *British Journal of Sports Medicine* 43(SUPPL. 1): i51-i55. (CEBM score 1/5)

Putukian, M., M. Aubry and P. McCrory (2009). "Return to play after sports concussion in elite and non-elite athletes?" *British Journal of Sports Medicine* 43: i28-31. (CEBM score 1/5)

Torrence, C. B., C. DeCristofaro, et al. (2011). "Empowering the primary care provider to optimally manage mild traumatic brain injury." *Journal of the American Academy of Nurse Practitioners* 23(12): 638-647. (CEBM score 1/5)

Williams, S. E. (2007). "Amantadine treatment following traumatic brain injury in children." *Brain Injury* 21(9): 885-889. (CEBM score 2/5)

Question 1.9 What is the evidence for the needs of carers of children (0-15 years) with TBI?

Executive summary

Two good quality systematic reviews (one excellent quality and one high quality) report evidence for the effectiveness of interventions aimed at providing support and training to family members. Problem solving therapy for parents and telehealth programs delivered to family members were reported to improve psychological and mental outcomes.

Evidence statement

Key question	Rating	Notes
Evidence base	A	Information within the high quality systematic reviews is based on data from randomised controlled trials, non-randomised controlled trials and case series
Consistency	A	Evidence around the needs of carers is consistent
Clinical impact	B	Substantial implications due to the significant proportion of carers/family members experiencing difficulties caring for children with TBI

Key systematic reviews regarding needs of carers:

1. Eccleston C, Palermo T, Fisher E, et al (2012). Psychosocial interventions for parents of children and adolescents with chronic illness. *Cochrane Database of Systematic Reviews; Issue 8. Art. No.:CD009660.*

CEBM Score: 5/5

This review evaluated the effectiveness of psychological therapies including coping strategies for parents of children/adolescents (under the age of 19) with chronic illnesses (painful conditions, cancer, diabetes mellitus, asthma, traumatic brain injury, inflammatory bowel diseases, skin diseases or gynaecological disorders). Of the 35 randomised controlled trials that were included in the review, only three trials (Wade 2006a; Wade 2006b; Wade et al 2011b) investigated children with TBI.

Key finding from the review:

Across all conditions, there is good evidence to show that problem solving therapy delivered to parents is effective in improving parent problem solving skills and parent mental health immediately post-treatment.

The systematic review included the following study in their review of this question:

Reference	Design	Results
Eccleston et al (2012)		
Wade et al (a) (2006)	Randomised controlled trial <i>Country:</i> USA <i>Sample:</i> n=32 Children with traumatic brain injury (mean age 10.83±2.94); level of injury – not reported; mean years of illness – 8.78	Parents in the Family Problem Solving group reported significantly greater improvements in their children in internalizing symptoms, anxiety/depression, and withdrawal than did parents in the usual care comparison group.
Yates Quality Scale (22/35=high quality)	<i>Intervention:</i> Family-centred problem-solving intervention (delivered face-to-face for individual families by clinical psychology graduate student; the length of treatment varied between 8 hours x 45 minutes to 11 hours 40 minutes, up to four individualised sessions) compared with usual care <i>Outcomes:</i> parent measures, child measures (behaviour, symptom measures), treatment satisfaction	

2. **Rietdijk R, Togher L, Power E (2012). Supporting family members of people with traumatic brain injury using telehealth: a systematic review. *J Rehabil Med*; 44: 00-00 (epub ahead of print).**

CEBM score: 4/5

This review described the effectiveness of telehealth programs for providing training or support to family members of people with traumatic brain injury. Studies which reported an intervention involving family members of adults or children with traumatic brain injury, delivered at a distance through use of technology (including telephone, websites, or video-conferencing) were considered. The review identified seven randomised controlled trials, four non-randomised controlled trials and five case-series. Of these, only eight were relevant to children aged 0-15 (Wade et al 2006a; Wade et al 2006b; Carey et al 2008; Wade et al 2004; Wade et al 2005a; Wade et al 2005b; Wade et al 2009; Wade et al 2011b).

Key findings from the review:

- Review of all studies showed evidence of efficacy of telehealth in training and supporting family members of people with traumatic brain injury. Improved psychological well-being, support skills and fewer burdens on family members were reported.
- An interactive skills-based program was found to be more effective than providing caregivers with general information (Wade 2006b; Wade 2006c; Wade 2011b).

The systematic review included the following studies in their review of this question:

Reference	Design	Results
Rietdijk et al (2012)		
Wade et al (c) (2006)	Randomised controlled trial <i>Country:</i> USA <i>Sample:</i> n=45 Children with traumatic brain injury (mean age 10.96±3.16); level of injury moderate to severe;	An online cognitive– behavioural approach can improve child adjustment after TBI, particularly in older children and children of lower SES.
PEDro 6/10	<i>Intervention:</i> Family problem-solving (FPS) group or to the Internet resources comparison (IRC) group <i>Outcomes:</i> child behaviour problems, social competence, self-management/compliance	
Wade et al (b) (2006)	Randomised controlled trial <i>Country:</i> USA <i>Sample:</i> n=40 Children with traumatic brain injury (mean age 11± 3.27); level of injury – not reported; mean years of illness – 13.73	The Family Problem Solving (FPS) group (i.e. parents) reported significantly less global distress, depressive symptoms, and anxiety at follow-up than did the control group after controlling for baseline symptoms. The FPS group also reported significant improvements in problem-solving skills, although the groups did not differ significantly at follow-up.
PEDro 7/10	<i>Intervention:</i> Family problem solving (delivered individually, online and through videoconferencing by clinical psychology graduate student, using 8 core modules, 6 supplementary modules) compared with a control (internet resources) <i>Outcomes:</i> parent outcomes, family outcomes, child behaviour and symptoms	
Carey et al (2008)	Randomised controlled trial <i>Country:</i> USA <i>Sample:</i> n=40 families of children with traumatic brain injury (mean age 10.96±3.1); level of injury – moderate to severe;	Although an online family problem-solving intervention was effective in improving caregiver functioning, individuals with limited computer experience benefit less from an online intervention due to increased non-adherence
PEDro 4/10	<i>Intervention:</i> family problem solving intervention compared with an internet resource intervention <i>Outcomes:</i> parental depression and anxiety and computer usage	
Wade et al (2004)	Randomised controlled trial <i>Country:</i> USA <i>Sample:</i> n=19 participants in six families of children with traumatic brain injury (age range 6-15); level of injury – moderate to severe;	All families demonstrated improved outcomes on one or more target behaviours, including increased understanding of the injury and improved parent–child relationships.
PEDro 3/10		

	Intervention: training in stress management, problem solving, planning, and organisation, communication, and self-regulation Outcomes: children's behaviour, family relationship	
Wade et al (a) (2005)	Non-randomised controlled trial Country: USA Sample: 6 families comprising 8 parents, 5 siblings and 6 children with traumatic brain injury (mean age 10.5 ± 3.62); level of injury – moderate to severe; Intervention: Families received computers, Web cameras, and Internet access. Participants completed 7–11 online sessions and accompanying weekly videoconferences with the therapist. Outcomes: child behaviour problems, social competence, executive function skills, and parent– child conflict.	Parents reported improvements in antisocial behaviours, and children with traumatic brain injury reported reductions in conflict with parents regarding school.
PEDro 3/10		
Wade et al (b) (2005)	Non-randomised controlled trial Country: USA Sample: Eight parents and six children with moderate to severe traumatic brain injury (age range 6-15) Intervention: Families provided with computers, Web cameras, and high-speed Internet access. Weekly videoconferences with the therapist were conducted after completion of self-guided Web exercises on problem-solving, communication, and antecedent behaviour management strategies. Outcomes: parental burden, depression, anxiety, and distress; child behaviour problems, social outcomes and metacognitive or executive skills	A computer-based intervention may successfully be used to improve both parent and child outcomes following TBI in children.
No quality score reported		
Wade et al (2009)	Case series Country: USA Sample: families of 9 children with moderate TBI (age range 4-9) Intervention: Web-based parenting skills program: consisted of 10 core sessions and up to 4 supplemental	This study reported preliminary evidence of the potential feasibility and efficacy of an online parenting skills intervention for improving positive parenting skills and for reducing child behaviour problems following early TBI.

No quality score reported	<p>sessions; each session consisted of self-guided didactic information, video modelling skills, and exercises; online sessions were followed by synchronous sessions providing in vivo coaching of target skills.</p> <p>Outcomes: children's behaviour, parenting behaviour</p>	
Wade et al (2011b)	<p>Case series</p> <p>Country: USA</p> <p>Sample: 13 parents of children who were between the ages of 3 and 9 and who had sustained a moderate to severe traumatic brain injury</p> <p>Intervention: Web-based parenting skills program: consisted of 10 core sessions and up to 4 supplemental sessions; each session consisted of self-guided didactic information, video modelling skills, and exercises; online sessions were followed by synchronous sessions providing in vivo coaching of target skills.</p> <p>Outcomes: process measures, narratives of the authors' experiences with implementing the intervention</p>	<p>Therapists uniformly liked coaching over the web despite the need to address boundaries and troubleshoot technological difficulties. Therapeutic alliance was comparable to traditional therapy with nearly all families expressing a strong connection to the therapist. Individuals with less computer experience particularly liked the program because it gave them access to the web and a sense of empowerment.</p>

Other earlier or lower quality evidence on the topic

AANN and ARN clinical practice guidelines series- care of patient with mild traumatic brain injury 2011 (AGREE II score 4/7)

Sambuco, M., N. Brookes and S. Lah (2008). "Paediatric traumatic brain injury: a review of siblings' outcome." *Brain Injury* 22(1): 7-17. (CEBM score 1/5)

3.3.2 Question 2 Mild TBI: Consider the specific issues relevant to mild TBI in adult's

Question 2.1 What is the evidence for screening and early identification of mild TBI?

2.1.1 Recommendations for initial screening

Executive summary

Four guidelines (two of excellent quality, one of high quality & one of moderate quality) and two systematic reviews (one of high & one of moderate quality) were used to inform the recommendations for this question. The evidence reviewed for initial screening and early assessment of mTBI including post sports concussion reports consistent findings. Recommendations are made to guide the recognition of mTBI symptoms, 'return to play' decisions for sports related concussion, and the need for further assessment. Recommendations are made for screening and initial assessment tools including the Sport Concussion Assessment Tool (SCAT and SCAT2), Rivermead Post Concussion Symptoms Questionnaire, and the Glasgow Coma Scale.

Evidence statement

Key question	Rating	Justification
Evidence base	A	Information within high quality guidelines & reviews is based on data from a large body of evidence, some of which is Level I & II
Consistency	A	Scales & assessment tools recommended for screening post mTBI are consistent.
Clinical impact	A	Large implications as early diagnosis of MTBI following closed head injury will positively impact on health outcomes for patients.

Key guidelines regarding initial screening (*mainly in sports concussion*):

1. **Scottish Intercollegiate Guidelines Network (SIGN) *Early management of patients with a head injury: A national clinical guideline*; 2009.**

AGREE II score: 7/7

‘This guideline makes recommendations on the early management of patients with head injury, focusing on topics of importance throughout NHS Scotland.’ Recommendations are made for the management of adults and children.

The recommendations for this sub section were informed by one earlier guideline which is based on a systematic review of literature and consensus opinion (McCrory et al 2005).

Recommendations relevant to initial screening for mTBI:

- *The Sport Concussion Assessment Tool (SCAT) is a widely used standardised tool developed for physician assessment of sports concussion (pg. 15) (McCrory et al. 2005) (Good practice point: Recommended best practice based on the clinical experience of the guideline development group.).*
- *It can be used for patient education as well as for physician assessment of sports concussion. SCAT can also be used to compile a baseline evaluation prior to the beginning of a competitive sport season which allows more meaningful interpretation of post-concussive symptoms (pg. 15) (McCrory et al. 2005) (Good practice point: Recommended best practice based on the clinical experience of the guideline development group.).*
- *People with a sport-related head injury should be referred to hospital if the indications for referral are present (refer section 2.1.2) (pg. 15) (McCrory et al. 2005) (Good practice point: Recommended best practice based on the clinical experience of the guideline development group.)*

2. Marshall et al (Ontario Neurotrauma Foundation). Clinical practice guidelines for mild traumatic brain injury and persistent symptoms. Canadian Family Physician 2012; 58(3): 257.

AGREE II score: 6/7

The objective of this Canadian group was ‘to create a set of guidelines that can be used by healthcare professionals to implement evidence-based, best practice care of individuals who incur a mild traumatic brain injury and experience persistent symptoms’ (pg 1) Recommendations are made for the management of adults >18years.

The recommendations for this sub section were informed by two earlier guidelines NZGG (2006) & McCrory et al. (2009).

Recommendations relevant to initial screening for mTBI:

- *Patients with sport-related mTBI may present acutely or sub-acutely. If any one of the following signs/symptoms is observed at any point following a blow to or jarring of the*

head, mTBI should be suspected and appropriate management instituted (pg 17) (NZGG 2006) (Grade C: Expert opinion, experience of a consensus panel.):

- Loss of/impaired consciousness*
 - Any seizure*
 - Amnesia: unaware of period, opposition, score of game; or unaware of time, date, place*
 - Headache*
 - Nausea/vomiting*
 - Unsteadiness/loss of balance and/or poor coordination*
 - Dizziness*
 - Feeling stunned or ‘dazed’*
 - Seeing stars or flashing lights*
 - Ringing in the ears*
 - Double vision*
 - Vacant stare/glassy eyed*
 - Slurred speech*
 - Inappropriate playing behaviour - for example, running in the wrong direction*
 - Appreciably decreased play ability*
 - Confusion, such as being slow to answer questions or follow directions*
 - Easily distracted, poor concentration*
 - Other symptoms, such as sleepiness, sleep disturbance and a subjective feeling of slowness and fatigue in the setting of an impact*
 - Displaying unusual or inappropriate emotions, such as laughing or crying*
 - Personality changes*
- *When a player shows any symptoms or signs of mTBI (pg 18) (McCrory et al. 2009) (Grade C: Expert opinion, experience of a consensus panel.):*
 - the player should not be allowed to return to play in the current game or practice*
 - the player should not be left alone and should be regularly monitored for deterioration*
 - the player should receive a medical evaluation including evaluation of reported complaints [e.g., somatic symptoms (Rivermead Post Concussion Symptoms Questionnaire, balance, and cognition)]*
 - return to play must follow a medically supervised stepwise process*
 - a player should not be returned to play until asymptomatic at rest and with exertion.*

3. Motor Accidents Authority of NSW (MAA NSW). 2008 Guidelines for Mild Traumatic Brain Injury Following a Closed Head Injury.

AGREE II score: 7/7

These Australian guidelines make recommendations for the early identification and management of adults with mild traumatic brain injury. They are aimed at clinicians working pre-hospital, emergency departments and general practice settings.

The recommendations for this sub section were informed by guidelines and systematic reviews which includes several primary studies.

Recommendations relevant to initial screening for mTBI:

- *The initial (prehospital) assessment with the Glasgow Coma Scale should be used as a risk classification or indicator of risk* (pg 22) (Borg et al 2004a & Brain Trauma Foundation 2002) (Grade B: Body of evidence can be trusted to guide practice in most situations One or two Level II studies with low risk of bias or a systematic review/ multiple Level II studies with low risk of bias with most studies consistent or inconsistencies can be explained.)
- *Subsequent Glasgow Coma Scale scores taken 30 minutes or more after the time of injury should be considered reliable indicators of severity and therefore should be used for classification of the severity of traumatic brain injury.* (pg 22) (Brain Trauma Foundation 2002 & Borg et al. 2004b)(Grade B: Body of evidence can be trusted to guide practice in most situations One or two Level II studies with low risk of bias or a systematic review/ multiple Level II studies with low risk of bias with most studies consistent or inconsistencies can be explained.).
- *Clinicians should assess and monitor somatic, cognitive and emotional post-concussion symptoms* (pg 21) (Bryant 2008; Inverson et al. 2005; inversion & McCracken 1997; Kashluba et al. 2006a; McCrory et al. 2005 & Meares et al. 2006)(Grade A: Body of evidence can be trusted to guide practice Several Level I or II studies with low risk of bias and all studies consistent, or inconsistency can be explained.)
- *Clinicians should use the Rivermead Post Concussion Symptoms Questionnaire as part of their assessment and monitoring post concussive symptoms* (pg 21) (King et al. 1995; Ingebrigtsen et al. 1998; Eyres et al. 2005 & potter et al. 2006)(Consensus).
- *Clinicians should assess and interpret the symptoms in the light of other potentially contributing biopsychosocial factors and conditions (personal factors, injury related variables and environmental influences)* (pg 21) (Grade A: Body of evidence can be trusted to guide practice Several Level I or II studies with low risk of bias and all studies consistent, or inconsistency can be explained.).

4. McCrory et al. Consensus Statement on Concussion in Sport – the 3rd International Conference on Concussion in Sport held in Zurich, Nov 2008. SAJSM; 2009; vol 21 No. 2.

AGREE II score: 4/7

This updated international consensus statement was 'developed for use by physicians, therapists, certified athletic trainers, health professionals, coaches and other people involved in the care of injured athletes, whether at the recreational, elite or professional level.

Recommendations apply to adults, adolescents and children. The guideline is based on a literature review, however details of its methodology are not provided.

The recommendations for this sub section were informed by a consensus of expert opinion.

Recommendations relevant to initial screening for mTBI:

- *The player should be medically evaluated onsite using standard emergency management principles and particular attention should be given to excluding a cervical spine injury (pg 37) (Consensus).*
- *The appropriate disposition of the player must be determined by the treating healthcare provider in a timely manner. If no healthcare provider is available, the player should be safely removed from practice or play and urgent referral to a physician arranged (pg 37) (Consensus).*
- *Once the first aid issues are addressed, then an assessment of the concussive injury should be made using the SCAT2 or other similar tool (pg 37) (Consensus).*
- *The player should not be left alone following the injury and serial monitoring for deterioration is essential over the initial few hours following injury (pg 37) (Consensus).*
- *A player with diagnosed concussion should not be allowed to return to play on the day of injury. Occasionally in adult athletes, there may be return to play on the same day as the injury (pg 37) (Consensus).*

Other lower quality evidence on the topic includes:

Alla, S., S. J. Sullivan, L. Hale and P. McCrory. Self-report scales/checklists for the measurement of concussion symptoms: a systematic review. *British Journal of Sports Medicine* 2009; 43: i3-12. (CEBM Score 3/5)

Broglio, S. P. and T. W. Puetz (2008). "The effect of sport concussion on neurocognitive function, self-report symptoms and postural control: a meta-analysis." *Sports Medicine* 38(1): 53-67. (CEBM Score 4/5)

2.1.2 Indications for referral to hospital

Executive summary

Two excellent quality guidelines were used to inform this sub section. The evidence reviewed for indications for referral to the hospital post mTBI reports consistent findings. A patient should be referred to the hospital for further assessment and investigations if they demonstrate any of the specified high risk signs and symptoms.

Evidence statement

Key question	Rating	Justification
Evidence base	A	Information within high quality guidelines & reviews is based on data from a large body of evidence, some of which is Level I & II
Consistency	A	Signs and symptoms to look out for are consistent across guidelines
Clinical impact	A	Large implications as early diagnosis of MTBI following closed head injury will positively impact on health outcomes for patients.

Key guidelines regarding indications for referral to hospital:

1. Scottish Intercollegiate Guidelines Network (SIGN) Early management of patients with a head injury: A national clinical guideline; 2009.

AGREE II score: 7/7

‘This guideline makes recommendations on the early management of patients with head injury, focusing on topics of importance throughout NHS Scotland.’ Recommendations are made for the management of adults and children.

The recommendations for this sub section were informed by meta -analysis, systematic reviews, primary randomised controlled trials and diagnostic studies.

Recommendations relevant to indications for referral to hospital:

- *Indications for referral to hospital after a sport-related head injury are as for any head injury. Adult patients with any of the following signs and symptoms should be referred to an appropriate hospital for further assessment of potential brain injury (pg. 4) (Grade B: Includes good quality SRs of case control & cohort studies, or evidence extrapolated from SRs of RCTs, or RCTs at low risk of bias)*
 - *GCS<15 at initial assessment (if this is thought to be alcohol related observe for two hours and refer if GCS score remains<15 after this time)*
 - *post-traumatic seizure (generalised or focal)*
 - *focal neurological signs of a skull fracture (including cerebrospinal fluid from nose or ears, haemotympanum, boggy haematoma, post auricular or periorbital bruising) loss of consciousness*
 - *severe and persistent headache*
 - *repeated vomiting (two or more occasions)*
 - *post-traumatic amnesia >5 minutes*

- *retrograde amnesia >30 minutes*
- *high risk mechanism of injury (road traffic accident, significant fall)*
- *Coagulopathy, whether drug-induced or otherwise.*

2. Motor Accidents Authority of NSW (MAA NSW). 2008 Guidelines for Mild Traumatic Brain Injury Following a Closed Head Injury.

AGREE II score: 7/7

These Australian guidelines make recommendations for the early identification and management of adults with mild traumatic brain injury. They are aimed at clinicians working pre-hospital, emergency departments and general practice settings.

The recommendations for this sub section were informed by guidelines and systematic reviews which include several primary studies.

Recommendations relevant to indications for referral to hospital:

- *When the patient's GCS is 14/15 and "high risk mild head injury" features are present, the patient should be transported to hospital for further assessment. (features are similar to the SIGN 2009 guideline above) (pg 24) (Grade B: Body of evidence can be trusted to guide practice in most situations One or two Level II studies with low risk of bias or a systematic review/ multiple Level II studies with low risk of bias with most studies consistent or inconsistencies can be explained)*
- *If the patient's GCS on presentation is ≤ 13 , immediate transport to hospital should be arranged. (pg 24) (consensus)*

2.1.3 Indications for referral for Imaging (CT, MRI and X-rays)

Executive summary

A large body of secondary evidence informs this question including six clinical guidelines (three of excellent and three high quality) and four systematic reviews (two of high & two of moderate quality). The evidence reviewed for referral to head CT scan post mTBI reports consistent recommendations, with decision guides or algorithms available to assist clinical decision making. There is less clarity from emerging evidence for the about the use of MRI to investigate mTBI. One SR provides evidence for the use of levels of serum protein S100B levels to reducing the number of excessive referrals to CT post mTBI.

Evidence statement

Key question	Rating	Justification
Evidence base	A	Information within high quality guidelines & reviews is based on data from a large body of evidence, some of which is Level I & II
Consistency	B	Recommendations for when CT scan is indicated and its accuracy at detecting brain injury are mostly consistent. Less consistency for MRI.
Clinical impact	B	Substantial implications for the correct diagnosis and management of TBI, and also for the judicious use of CTs and MRI

Key guidelines regarding Indications for Imaging:

1. Scottish Intercollegiate Guidelines Network (SIGN) Early management of patients with a head injury: A national clinical guideline; 2009.

AGREE II score: 7/7

‘This guideline makes recommendations on the early management of patients with head injury, focusing on topics of importance throughout NHS Scotland.’ Recommendations are made for the management of adults and children.

The recommendations for this sub section were informed by meta -analysis, systematic reviews, primary randomised controlled trials and diagnostic studies.

This high quality guideline provides the following key points with regard to indications for referral to head CT (pg. 4-5):

- *Immediate CT scanning should be done in an adult patient who has any of the following features (pg 4) (Mower et al. 2005; Smits et al. 2005; Stiell et al. 2005 & Steill et al 2001)(Grade B: Includes good quality SRs of case control & cohort studies, or evidence extrapolated from SRs of RCTs, or RCTs at low risk of bias)*
 - *eye opening only to pain or not conversing (GCS 12/15 or less)*
 - *confusion or drowsiness (GCS 13/15 or 14/15) followed by failure to improve within at most one hour of clinical observation or within two hours of injury (whether or not intoxication from drugs or alcohol is a possible contributory factor)*
 - *base of skull or depressed skull fracture and/or suspected penetrating injuries*
 - *a deteriorating level of consciousness or new focal neurological signs*
 - *full consciousness (GCS 15/15) with no fracture but other features, eg.*
 - *severe and persistent headache*
 - *two distinct episodes of vomiting*
 - *a history of coagulopathy (eg warfarin use) and loss of consciousness, amnesia or any neurological*

- *CT scanning should be performed within eight hours in an adult patient who is otherwise well but has any of the following feature (pg 5) (Mower et al. 2005; Smits et al. 2005; Stiell et al. 2005 & Steill et al 2001) (Grade B: Includes good quality SRs of case control & cohort studies, or evidence extrapolated from SRs of RCTs, or RCTs at low risk of bias)*
 - *age>65 (with loss of consciousness or amnesia)*
 - *clinical evidence of a skull fracture (eg boggy scalp haematoma) but no clinical features indicative of an immediate CT scan*
 - *any seizure activity*
 - *significant retrograde amnesia (>30 minutes)*
 - *dangerous mechanism of injury (pedestrian struck by motor vehicle, occupant ejected from motor vehicle, significant fall from height) or significant assault (eg blunt trauma with a weapon).*
- *In adult patients who are GCS<15 with indications for a CT head scan, scanning should include the cervical spine (pg 5) (Holmes & Akkinepalli 2005b; Mann et al. 2003)(Grade B: Includes good quality SRs of case control & cohort studies, or evidence extrapolated from SRs of RCTs, or RCTs at low risk of bias)*

2. Vos et al. Mild traumatic brain injury. European Journal of Neurology 2012, 19: 191–198.

AGREE II score: 5/7

This European guideline provides recommendations for the acute management of adults and children presenting with mild TBI. It is aimed primarily at medical management.

Recommendations relevant to referral to imaging:

- *Protocols for initial management in mTBI should include a decision scheme or prediction rule algorithm for the use of CT after mTBI (pg. 193)(Stiell et al. 2001; Haydel et al. 2000; Vos et al 2002; Ibanez et al. 2004 & Smits et al. 2005) (Grade A: informed by systematic reviews and diagnostic studies).*

3. McCrory et al. Consensus Statement on Concussion in Sport – the 3rd International Conference on Concussion in Sport held in Zurich, Nov 2008. SAJSM; 2009; vol 21 No. 2.

AGREE II score: 4/7

This updated international consensus statement was 'developed for use by physicians, therapists, certified athletic trainers, health professionals, coaches and other people involved in the care of injured athletes, whether at the recreational, elite or professional level. Recommendations apply to adults, adolescents and children. The guideline is based on a literature review, however details of its methodology are not provided.

Recommendations relevant to referral to imaging:

- *Brain CT (or where available MR brain scan) contributes little to concussion evaluation but should be employed whenever suspicion of an intra-cerebral structural lesion exists. Examples of such situations may include prolonged disturbance of conscious state, focal neurological deficit or worsening symptoms (pg 38) (Consensus).*
- *Newer structural MRI modalities including gradient echo, perfusion and diffusion imaging have greater sensitivity for structural abnormalities. However, the lack of published studies as well as absent pre-injury neuroimaging data limits the usefulness of this approach in clinical management at the present time (pg 38) (Consensus).*

4. Scottish Intercollegiate Guidelines Network (SIGN).Guidelines for traumatic brain injury rehabilitation. Edinburgh: SIGN; 2013.

AGREE II score: 7/7

This Scottish guideline provides recommendations, for adults over 16 years of age about post-acute assessment and rehabilitation following mTBI. Interventions for cognitive, communicative, emotional, behavioural and physical rehabilitation are discussed and the evidence for each is presented.

The recommendation for this sub section is informed by one primary study from the WHO task force reporting on mild traumatic brain injury.

Recommendations relevant to referral to imaging post mTBI:

- *Cranial imaging is not routinely recommended for the assessment of post-acute mild brain injury, but should be considered in an atypical case (pg 11) (Borg et al. 2004a) (Grade B: Includes good quality SRs of case control & cohort studies, or evidence extrapolated from SRs of RCTs, or RCTs at low risk of bias)*

5. Jagoda et al (ACEP/CDC) Clinical Policy: Neuroimaging and decision making in adult mild traumatic brain injury in the acute setting. Ann Emerg Med. 2008;52:714-748.

AGREE II Score: 4/7

This US clinical policy provides recommendations on the management of adults with mild TBI in acute care settings and is primarily aimed at medical staff.

The recommendations for this sub section are informed by systematic reviews and primary studies.

Recommendations relevant to indications for Imaging after mTBI are:

- *Skull film radiographs are not recommended in the evaluation of mild TBI. Although the presence of a skull fracture increases the likelihood of an intracranial lesion, its sensitivity is not sufficient to be a useful screening test. Indeed, negative findings on skull films may mislead the clinician.* (pg 717) (Level B: Recommendations that reflect moderate clinical certainty i.e., based on evidence from nonrandomised trials or retrospective observational diagnostic studies or retrospective prognostic case control or cohort studies)
 - *A non-contrast head CT is indicated in head trauma patients with loss of consciousness or posttraumatic amnesia only if one or more of the following is present: headache, vomiting, age greater than 60 years, drug or alcohol intoxication, deficits in short-term memory, physical evidence of trauma above the clavicle, posttraumatic seizure, GCS score less than 15, focal neurologic deficit, or coagulopathy.* (pg 718) (Level A: Recommendations that reflect high degree of clinical certainty i.e., based on evidence from randomised intervention trials, or prospective cohort diagnostic and prognostic studies)
 - *A non-contrast head CT should be considered in head trauma patients with no loss of consciousness or posttraumatic amnesia if there is a focal neurologic deficit, vomiting, severe headache, age 65 years or greater, physical signs of a basilar skull fracture, GCS score less than 15, coagulopathy, or a dangerous mechanism of injury*.* (pg 718) (Level B: Recommendations that reflect moderate clinical certainty i.e., based on evidence from nonrandomised intervention trials or retrospective observational diagnostic studies or retrospective prognostic case control or cohort studies)
- * *Dangerous mechanism of injury includes ejection from a motor vehicle, a pedestrian struck, and a fall from a height of more than 3 feet or 5 stairs.*
- *No recommendations are provided for whether there is a role for head MRI over non-contrast CT in the ED evaluation of a patient with acute mild TBI* (pg 721).
 - *In mild TBI patients without significant extracranial injuries and a serum S-100B level less than 0.1 microg/L measured within 4 hours of injury, consideration can be given to not performing a CT.** (pg 722)(Townend et al. 2006; Bazarian et al. 2006a; Biberthaler et al. 2006) (Level C: Other strategies for patient management that are

based on preliminary, inconclusive, or conflicting evidence, or in the absence of any published literature, based on panel consensus.)

**This test has not yet received Food and Drug Administration approval for clinical use in the United States.*

- *Patients with an isolated mild TBI who have a negative head CT scan result are at minimal risk for developing an intracranial lesion and therefore may be safely discharged from the ED. *(pg 723) (Level B: Recommendations that reflect moderate clinical certainty i.e., based on evidence from nonrandomised intervention trials or retrospective observational diagnostic studies or retrospective prognostic case control or cohort studies)*

**There are inadequate data to include patients with a bleeding disorder; who are receiving anticoagulation therapy or antiplatelet therapy; or who have had a previous neurosurgical procedure in this population.*

- *Mild TBI patients discharged from the ED should be informed about post concussive symptoms (pg 724) (Level C: Other strategies for patient management that are based on preliminary, inconclusive, or conflicting evidence, or in the absence of any published literature, based on panel consensus.)*

6. NICE 2007 Head injury: Triage, assessment, investigation and early management of head injury in infants, children and adults. National Institute of Health & Clinical Excellence

AGREE II Score: 7/7

This UK guideline is the update of an earlier 2003 edition. 'This guideline addresses assessment, investigation and early management of head injury. Separate advice is provided for adults and children (including infants) where different practices are indicated.' (pg 4) *NB: the NICE development group ruled that they would no longer publish grades with their recommendations.*

The underpinning evidence for the recommendations from this guideline has not been explicitly outlined and hence has not been listed here.

The recommendations relevant to Imaging are:

- *Plain X-rays of the skull should not be used to diagnose significant brain injury without prior discussion with a neuroscience unit (pg 62).*
- *Unless the CT result is required within 1 hour, it is acceptable to admit a patient for effective overnight observation and delay the CT scan until the next morning if the*

patient presents out of hours and any of the following risk factors are present in addition to a period of loss of consciousness or amnesia (pg 62):

- Age > 65 years*
 - amnesia for events more than 30 minutes before impact*
 - dangerous mechanism of injury (a pedestrian or cyclist struck by a motor vehicle, an occupant ejected from a motor vehicle or a fall from a height of greater than 1 metre or five stairs).*
- *If CT imaging is unavailable because of equipment failure, patients with GCS 15 may be admitted for observation. Arrangements should be in place for urgent transfer to a centre with CT scanning available should there be a clinical deterioration that indicates immediate CT scanning is necessary (pg 62).*

Key systematic reviews regarding indications for CT scan or alternative imaging/testing:

1. Gardner et al. (2012). A Systematic Review of Diffusion Tensor Imaging (DTI) Findings in Sports-Related Concussion. *Journal of Neurotrauma* 29: 2521-2538.

CEBM score: 4/5

This review examined the utility of DTI as a clinical tool for diagnosing and managing Sports Related Concussion (SRC). It aimed to provide a focus and overview of research findings using this MRI technique in SRC.

Eight studies, observational, cohort, correlation, cross-sectional and longitudinal studies were all included in the current review and provide variable evidence on this topic. There was considerable methodological variations exist across the included studies.

Key findings from the review:

- The current review suggests that DTI may possess adequate diagnostic sensitivity to detect SRC in affected athletes.

2. Pandor et al. (2012). Diagnostic Accuracy of Clinical Characteristics for Identifying CT Abnormality after Minor Brain Injury: A Systematic Review and Meta-Analysis. *Journal of Neurotrauma* 29: 707-718.

CEBM score: 4/5

This review aimed to identify clinical features which can be used to identify which patients with mTBI require CT scanning. Seventy one cohort studies of patients with minor brain injury were included in the current review.

Key findings from the review:

- Depressed or basal skull fractures were the most useful clinical characteristics for the prediction of intracranial injury in adults.
- Other useful characteristics included focal neurological deficit, post-traumatic seizure, persistent vomiting, and coagulopathy.

3. Unden, J. and B. Romner. (2010). Can Low Serum Levels of S100B Predict Normal CT Findings After Minor Head Injury in Adults? An Evidence-Based Review and Meta-Analysis. *Journal of Head Trauma Rehabilitation* 25(4): 228-240.

CEBM score: 3/5

This review aimed to determine whether low levels of protein S100B in serum can predict normal CT findings after a minor head injury. Twelve studies that studied a total of 2466 patients in the acute phase after minor head injury were included in this review.

Key findings from the review:

- Low serum levels of S100B accurately predict normal CT findings after mild head injury in adults.
- S100B sampling should be considered in mTBI patients with no focal neurological deficit, an absence of significant cerebral injury and should be taken within 3 hrs of the injury.
- The cut off for omitting CT should be set at <0.10microgm/litre.
- It is important to note that S100B levels can be affected by alcohol intoxication.

4. Stippler, M., C. Smith, A. R. McLean, A. Carlson, S. Morley, C. Murray-Krezan, J. Kraynik and G. Kennedy (2012). "Utility of routine follow-up head CT scanning after mild traumatic brain injury: a systematic review of the literature." *Emergency Medicine Journal* 29(7): 528-532.

CEBM score: 3/5

This review aimed to evaluate the efficacy of routine follow up CT scans of the head after complicated mild traumatic brain injury.

The total number of included studies was nineteen of which the study design was retrospective in seven, prospective in six and unclear in two.

Key findings from the review:

- Routine follow up CT scans rarely alter treatment for patients with complicated mTBI. Follow up Ct scans based on neurological decline alter treatment five times more often than routine follow up CT scans.

Other earlier or lower quality evidence:

Barbosa, R. R., R. Jawa, J. M. Watters, J. C. Knight, A. J. Kerwin, E. S. Winston, R. D. Barraco, B. Tucker, J. M. Bardes, S. E. Rowell and T. Eastern Association for the Surgery of (2012). "Evaluation and management of mild traumatic brain injury: an Eastern Association for the Surgery of Trauma practice management guideline." *The Journal of Trauma and Acute Care Surgery* 73(5 Suppl 4): S307-314. (AGREE Score 3/7)

Harnan, S. E., A. Pickering, A. Pandor and S. W. Goodacre. Clinical decision rules for adults with minor head injury: a systematic review. *Journal of Trauma* 71(1): 245-251.(CEBM score 4/5.)

2.1.4 Recommendations to emergency department clinicians

Executive summary

Two guidelines (one of excellent & one of high quality) were extracted to inform this question. The available evidence is consistent in recommending that the emergency department clinician should assess a patient presenting post mTBI with detailed history and clinical assessment using scales such as Glasgow Coma Scale and the Westmead Post Traumatic Amnesia Scale. If CT scan is not indicated, then the patient should be observed and then discharge with verbal and written brain injury advice which should be discussed with the patient and their care provider.

Evidence statement

Key question	Rating	Justification
Evidence base	A	Information within high quality guidelines & reviews is based largely on the consensus of experts.
Consistency	A	Recommendations for when referral is indicated are consistent.
Clinical impact	B	Substantial implications as medical personnel and resources can be focused on patients that require help the most. In addition appropriate early diagnosis and management results in better prognosis for mTBI patients.

Key guidelines for recommendations to emergency department clinicians:

1. Marshall et al (Ontario Neurotrauma Foundation). Clinical practice guidelines for mild traumatic brain injury and persistent symptoms. Canadian Family Physician 2012; 58(3): 257.

AGREE II score: 6/7

The objective of this Canadian group was 'to create a set of guidelines that can be used by healthcare professionals to implement evidence-based, best practice care of individuals who incur a mild traumatic brain injury and experience persistent symptoms' (pg 1) Recommendations are made for the management of adults >18years.

The recommendations for this sub section were informed by two earlier guidelines NZGG (2006) & McCrory et al. (2009).

This high quality guideline provides the following key points (pg.12):

- *Hourly clinical observation should occur until at least four hours post injury. If the patient meets recommended discharge criteria at four hours post time of injury, they should be considered for discharge (pg 12) (Grade C: Expert opinion, experience of a consensus panel.).*
- *At four hours post injury, if the patient has a Glasgow Coma Scale score of 15, is clinically improving and has a normal CT scan or there is no indication for CT based on the Canadian CT Head Rule but their A-WPTAS score is < 18, then clinical judgment is required to determine whether the patient should be discharged home before a normal score for this measure is obtained (pg 12) (Grade C: Expert opinion, experience of a consensus panel.).*
- *If CT is not indicated on the basis of history and examination the clinician may conclude that the risk to the patient is low enough to warrant discharge to own care or to home, as long as no other factors that would warrant a hospital admission are present (for example, drug or alcohol intoxication, other injuries, shock, suspected non accidental injury, meningism, cerebrospinal fluid leak) and there are appropriate support structures for safe discharge and for subsequent care (for example, competent supervision at home) (pg 12) (Grade C: Expert opinion, experience of a consensus panel.).*
- *All patients with any degree of brain injury who are deemed safe for appropriate discharge from an emergency department or the observation ward should receive verbal advice and a written brain injury advice card. The details of the card should be discussed with the patient and their care providers. When necessary, communication*

in languages other than English or by other means should be used to communicate the information (pg 12) (Grade C: Expert opinion, experience of a consensus panel.).

- *If the patient re-presents to the emergency department with symptoms related to the initial injury, the following should be conducted (pg 12) (Grade C: Expert opinion, experience of a consensus panel.).*
 - *Full re-assessment*
 - *A-WPTAS assessment*
 - *CT scan, if indicated,*
 - *Emphasis and encouragement to the patients to attend their family physician for follow-up after discharge.*

2. NICE 2007 Head injury: Triage, assessment, investigation and early management of head injury in infants, children and adults. National Institute of Health & Clinical Excellence

AGREE II Score: 7/7

This UK guideline is the update of an earlier 2003 edition. 'This guideline addresses assessment, investigation and early management of head injury. Separate advice is provided for adults and children (including infants) where different practices are indicated.' (pg 4) *NB: the NICE development group ruled that they would no longer publish grades with their recommendations.*

The recommendations for this subsection were informed by the recommendations provided by the guideline. The underpinning evidence however has not been explicitly outlined and hence has not been listed here.

The recommendations relevant to emergency department clinicians are:

- *All patients presenting to an emergency department with a head injury should be assessed by a trained member of staff within a maximum of 15 minutes of arrival at hospital. Part of this assessment should establish whether they are high risk or low risk for clinically important brain injury and/or cervical spine injury, using the guidance on patient selection and urgency for imaging (head and cervical spine) (pg 52).*
- *The main focus of emergency department assessment for patients who have sustained a head injury should be the risk of clinically important brain injuries and injuries to the cervical spine and the consequent need for imaging (pg 60).*

- *Due attention should also be paid to co-existing injuries and to other concerns the clinician may have (for example, non-accidental injury, possible non-traumatic aetiology such as seizure) (pg 60).*
- *Early imaging, rather than admission and observation for neurological deterioration, will reduce the time to detection of life-threatening complications and is associated with better outcomes (pg 60).*
- *Depressed conscious level should be ascribed to intoxication only after a significant brain injury has been excluded (pg 60).*
- *All emergency department clinicians involved in the assessment of patients with a head injury should be capable of assessing the presence or absence of the risk factors in the guidance on patient selection and urgency for imaging (head and cervical spine). Training should be available as required to ensure that this is the case (pg 60-61).*
- *Patients who, on initial assessment, are considered to be at low risk for clinically important brain injury and/or cervical spine injury should be re-examined within a further hour by an emergency department clinician. Part of this assessment should fully establish the need to request CT imaging of the head and/or imaging of the cervical spine. The guidance on patient selection and urgency for imaging (head and cervical spine) should again form the basis for the final decision on imaging after discussion with the radiology department (pg 61).*

2.1.5 Indications for admission to hospital

Executive summary

Two guidelines (both excellent quality) have been extracted to inform this question. The evidence reviewed for recommendations for admission to hospital consistently report that it should be based on the need for detailed assessment, imaging (CT scan) or if levels of consciousness are impaired.

Evidence statement

Key question	Rating	Justification
Evidence base	A	Information within high quality guidelines & reviews is based largely on data from observational studies and government agency reports.
Consistency	A	Recommendations for when admission to hospital is indicated are consistent.

Clinical impact	B	Substantial implications as medical personnel and resources can be focused on patients that require help the most.
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Key guidelines regarding indications for admission to hospital:

1. Scottish Intercollegiate Guidelines Network (SIGN) *Early management of patients with a head injury: A national clinical guideline; 2009.*

AGREE II score: 7/7

‘This guideline makes recommendations on the early management of patients with head injury, focusing on topics of importance throughout NHS Scotland.’ Recommendations are made for the management of adults and children.

The recommendations for this sub section were informed by primary observational studies.

Recommendations relevant to indications for admission to hospital:

- *An adult patient should be admitted to hospital if (pg. 5)(Roy et al 1986) (Grade D: Evidence from nonanalytic studies (eg case series/case studies); or Extrapolated evidence from well conducted case control or cohort studies):*
 - *the level of consciousness is impaired (GCS<15/15)*
 - *the patient is fully conscious (GCS 15/15) but has any indication for a CT scan (if the scan is normal and there are no other reasons for admission, then the patient may be considered for discharge)*
 - *the patient has significant medical problems, eg anticoagulant use*
 - *the patient has social problems or cannot be supervised by a responsible adult.*

2. NICE 2007 Head injury: Triage, assessment, investigation and early management of head injury in infants, children and adults. National Institute of Health & Clinical Excellence

AGREE II score: 7/7

This UK guideline is the update of an earlier 2003 edition. ‘This guideline addresses assessment, investigation and early management of head injury. Separate advice is provided for adults and children (including infants) where different practices are indicated.’ (pg 4) *NB: the NICE development group ruled that they would no longer publish grades with their recommendations.*

The recommendations for this subsection were informed by the recommendations provided by the guideline. The underpinning evidence however has not been explicitly outlined and hence has not been listed here.

Recommendations relevant to indications for admission to hospital are:

- *In circumstances where a patient with a head injury requires hospital admission, it is recommended that the patient be admitted only under the care of a team led by a consultant who has been trained in the management of this condition during his/her higher specialist training. The consultant and his/her team should have competence (defined by local agreement with the neuroscience unit) in assessment, observation and indications for imaging; inpatient management; indications for transfer to a neuroscience unit; and hospital discharge and follow-up (pg 68).*
- *Community health services (general practice, ambulance crews, NHS walk-in centres, dental practitioners) and NHS minor injury clinics should refer patients who have sustained a head injury to a hospital emergency department, using the ambulance service if deemed necessary, if any of the following are present (pg 68):*
 - *GCS less than 15 on initial assessment.*
 - *Any loss of consciousness as a result of the injury.*
 - *Any focal neurological deficit since the injury (examples include problems understanding, speaking, reading or writing; decreased sensation; loss of balance; general weakness; visual changes; abnormal reflexes; and problems walking).*
 - *Any suspicion of a skull fracture or penetrating head injury since the injury (for example, clear fluid running from the ears or nose, black eye with no associated damage around the eyes, bleeding from one or both ears, new deafness in one or both ears, bruising behind one or both ears, penetrating injury signs, visible trauma to the scalp or skull of concern to the professional).*
 - *Amnesia for events before or after the injury. The assessment of amnesia will not be possible in pre-verbal children and is unlikely to be possible in any child aged under 5 years.*
 - *Persistent headache since the injury. - Any vomiting episodes since the injury.*
 - *Any seizure since the injury.*
 - *Any previous cranial neurosurgical interventions*
 - *A high-energy head injury (for example, pedestrian struck by motor vehicle, occupant ejected from motor vehicle, fall from a height of greater than 1 metre or more than five stairs, diving accident, high-speed motor vehicle collision, rollover motor accident, accident involving motorized recreational vehicles, bicycle collision, or any other potentially high-energy mechanism).*
 - *History of bleeding or clotting disorder.*
 - *Current anticoagulant therapy such as warfarin.*
 - *Current drug or alcohol intoxication.*
 - *Age 65 years or older.*
 - *Suspicion of non-accidental injury.*
 - *Continuing concern by the professional about the diagnosis*

2.1.6 Recommendations for initial assessment

Executive summary

Six guidelines (four of excellent, one high & one moderate quality) were extracted to inform this question. The evidence reviewed for recommendations for initial assessment post mTBI reports consistent findings. Diagnosis of mTBI should be based on a combination of clinical factors and symptoms. Recommendations are made to the use of appropriate assessment tools including the Glasgow Coma Scale and its score and The Abbreviated Westmead Post Traumatic Amnesia Scale.

Evidence statement

Key question	Rating	Justification
Evidence base	A	Information within high quality guidelines & reviews is based on a body of evidence that included Level I & II studies. Some recommendations based on consensus only.
Consistency	A	Recommended scales and clinical assessment pathway to be followed is consistent.
Clinical impact	B	Substantial implications as early diagnosis of MTBI following closed head injury will positively impact on health outcomes for patients.

Key guidelines regarding initial assessment:

- 1. Scottish Intercollegiate Guidelines Network (SIGN) *Early management of patients with a head injury: A national clinical guideline*; 2009.**

AGREE II score: 7/7

‘This guideline makes recommendations on the early management of patients with head injury, focusing on topics of importance throughout NHS Scotland.’ Recommendations are made for the management of adults and children.

The recommendations for this sub section were informed by case reports, case series and expert opinion.

Recommendations relevant to initial assessment post mTBI:

- The management of patients with a head injury should be guided by clinical assessments and protocols based on the Glasgow Coma Scale and its score (pg.4) (Gentleman et al. 1981; Ingersoll & Leyden 1987; Winkler et al. 1984) (Grade D: Evidence from nonanalytic studies (eg case series/case studies); or Extrapolated evidence from well conducted case control or cohort studies);*

- 2. Marshall et al (Ontario Neurotrauma Foundation). Clinical practice guidelines for mild traumatic brain injury and persistent symptoms. Canadian Family Physician 2012; 58(3): 257.**

AGREE II score: 6/7

The objective of this Canadian group was 'to create a set of guidelines that can be used by healthcare professionals to implement evidence-based, best practice care of individuals who incur a mild traumatic brain injury and experience persistent symptoms' (pg 1) Recommendations are made for the management of adults >18years.

Recommendations relevant to initial assessment for mTBI:

- *mTBI in the setting of closed head injury should be diagnosed early as early recognition will positively impact on health outcomes for patients* (pg 12) (Grade A: At least one randomized controlled trial, meta-analysis, or systematic review).
- *Diagnosis of mTBI should be performed through a combined assessment of clinical factors and symptoms* (pg 12) (Grade A: At least one randomized controlled trial, meta-analysis, or systematic review).
- *Standardized measurement of post traumatic amnesia should be routinely performed to assist with the monitoring, diagnosis, early management and prognosis of patients who have experienced mTBI. The Abbreviated Westmead Post Traumatic Amnesia Scale (A-WPTAS) is a standardized tool that can be used to monitor post traumatic amnesia* (pg 12) (Grade A: At least one randomized controlled trial, meta-analysis, or systematic review).
- *Medical assessment should include screening for health and contextual factors (flags) to identify patients for increased risk of persistent symptoms and urgent complications, such as subdural hematoma* (pg 12) (Grade B: At least one cohort comparison, case studies or other type of experimental study)

- 3. Motor Accidents Authority of NSW (MAA NSW). 2008 Guidelines for Mild Traumatic Brain Injury Following a Closed Head Injury.**

AGREE II score: 7/7

These Australian guidelines make recommendations for the early identification and management of adults with mild traumatic brain injury. They are aimed at clinicians working pre-hospital, emergency departments and general practice settings.

The recommendations for this sub section were informed by guidelines and systematic reviews which includes several primary studies.

Recommendations relevant to initial assessment for mTBI:

- *mTBI following closed head injury should be diagnosed early as it will positively impact on health outcomes for patients* (pg 19) (Grade A: Body of evidence can be trusted to guide practice Several Level I or II studies with low risk of bias and all studies consistent, or inconsistency can be explained.)
- *Diagnosis of mTBI should be performed through a combined assessment of clinical factors and symptoms* (pg 20) (Grade A: Body of evidence can be trusted to guide practice Several Level I or II studies with low risk of bias and all studies consistent, or inconsistency can be explained.)
- *The standardised prospective measurement of post traumatic amnesia should be routinely performed to assist with the monitoring, diagnosis, early management and prognosis of patients with mTBI* (pg 20) (Grade A: Body of evidence can be trusted to guide practice Several Level I or II studies with low risk of bias and all studies consistent, or inconsistency can be explained.)
- *Clinicians should use the recent version of the revised WPTAS – the Abbreviated Westmead Post Traumatic Amnesia Scale (A-WPTAS) for assessment of cognition to identify patients with mTBI.* (pg 21)(Consensus).

4. McCrory et al. Consensus Statement on Concussion in Sport – the 3rd International Conference on Concussion in Sport held in Zurich, Nov 2008. SAJSM; 2009; vol 21 No. 2.

AGREE II score: 4/7

This updated international consensus statement was ‘developed for use by physicians, therapists, certified athletic trainers, health professionals, coaches and other people involved in the care of injured athletes, whether at the recreational, elite or professional level. Recommendations apply to adults, adolescents and children. The guideline is based on a literature review, however details of its methodology are not provided.

The recommendations for this sub section were informed by a consensus of expert opinion.

Recommendations relevant to initial assessment:

- *A medical assessment including a comprehensive history and detailed neurological examination including a thorough assessment of mental status, cognitive functioning and gait and balance (pg.38) (Consensus).*
- *A determination of the clinical status of the patient including whether there has been improvement or deterioration since the time of injury. This may involve seeking additional information from parents, coaches, teammates and eyewitness to the injury (pg.38) (Consensus).*
- *A determination of the need for emergent neuroimaging in order to exclude a more severe brain injury involving a structural abnormality (pg.38) (Consensus).*

5. Scottish Intercollegiate Guidelines Network (SIGN).Guidelines for traumatic brain injury rehabilitation. Edinburgh: SIGN; 2013.

AGREE II score: 7/7

‘This guideline makes recommendations on the early management of patients with head injury, focusing on topics of importance throughout NHS Scotland.’ Recommendations are made for the management of adults and children.

The recommendations for this sub section were informed by the WHO task force investigating mild traumatic brain injury.

Recommendations relevant to initial assessment:

- *The diagnosis of mild traumatic brain injury should be made according to WHO task force operational criteria, subject to clinical judgement when complicating factors are present, e.g. skull fracture, seizures, or a haematoma (pg. 9) (Carroll et al. 2004a) (Grade B: Includes good quality SRs of case control & cohort studies, or evidence extrapolated from SRs of RCTs, or RCTs at low risk of bias)*

6. NICE 2007 Head injury: Triage, assessment, investigation and early management of head injury in infants, children and adults. National Institute of Health & Clinical Excellence.

AGREE II Score: 7/7

This UK guideline is the update of an earlier 2003 edition. ‘This guideline addresses assessment, investigation and early management of head injury. Separate advice is provided for adults and children (including infants) where different practices are indicated.’ (pg 4) *NB: the NICE development group ruled that they would no longer publish grades with their recommendations.*

The recommendations for this subsection were informed by the recommendations provided by the guideline. The underpinning evidence however has not been explicitly outlined and hence has not been listed here.

The recommendations relevant to initial assessment are:

- *The assessment and classification of patients who have sustained a head injury should be guided primarily by the adult and paediatric versions of the Glasgow Coma Scale and its derivative the Glasgow Coma Score (GCS) (pg 90).*
- *Monitoring and exchange of information about individual patients should be based on the three separate responses on the Glasgow Coma Score (for example, a patient scoring 13 based on scores of 4 on eye-opening, 4 on verbal response and 5 on motor response should be communicated as E4, V4, M5) (pg 90).*
- *If a total score is recorded or communicated, it should be based on a sum of 15, and to avoid confusion this denominator should be specified (for example, 13/15) (pg 90).*
- *The individual components of the GCS should be described in all communications and every note and should always accompany the total score (pg 90).*

Other earlier or lower quality evidence:

Brain Trauma Foundation 2007. Guidelines for prehospital management of severe TBI.
(AGREE Score 6/7)

2.1.7 Indications for referral to neurosurgical unit

Executive summary

Two clinical guidelines, both of excellent quality, provided evidence for this section. Recommendations for referral to the neurosurgical unit post mTBI are provided here, to cover instances where patients initially deemed to have a mild injury, subsequently deteriorate. Recommendations are made to assist clinical decision making for referral to neurosurgery.

Evidence statement

Key question	Rating	Justification
Evidence base	A	Information within high quality guidelines & reviews is based on data from lower level studies at risk of bias, or from expert consensus.
Consistency	A	Recommendations for when referral is indicated are consistent.

Clinical impact	B	Substantial implications as medical personnel and resources can be focused on patients that require help the most.
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Key guidelines regarding indications referral to neurosurgical unit:

1. Scottish Intercollegiate Guidelines Network (SIGN) *Early management of patients with a head injury: A national clinical guideline; 2009.*

AGREE II score: 7/7

‘This guideline makes recommendations on the early management of patients with head injury, focusing on topics of importance throughout NHS Scotland.’ Recommendations are made for the management of adults and children.

The recommendations for this sub section were informed by case reports, case series and expert opinion.

Recommendations relevant to referral to neurosurgical unit:

- *A patient with a head injury should be discussed with a neurosurgeon* (pg. 5) (Wester 1999; Gennarelli et al. 1989) (Grade D: Evidence from nonanalytic studies (eg case series/case studies); or Extrapolated evidence from well conducted case control or cohort studies):
 - *when a CT scan in a general hospital shows a recent intracranial lesion*
 - *when a patient fulfils the criteria for CT scanning but facilities are unavailable*
 - *when the patient has clinical features that suggest that specialist neuroscience assessment, monitoring, or management are appropriate, irrespective of the result of any CT scan.*

2. NICE 2007 Head injury: Triage, assessment, investigation and early management of head injury in infants, children and adults. National Institute of Health & Clinical Excellence.

AGREE II Score: 7/7

This UK guideline is the update of an earlier 2003 edition. ‘This guideline addresses assessment, investigation and early management of head injury. Separate advice is provided for adults and children (including infants) where different practices are indicated.’ (pg 4) *NB: the NICE development group ruled that they would no longer publish grades with their recommendations.*

The recommendations for this subsection were informed by the recommendations provided by the guideline. The underpinning evidence however has not been explicitly outlined and hence has not been listed here.

The recommendations relevant to referral to neurosurgical unit:

- *Organisation of transfer of patients between referring hospital and neuroscience unit*
-Local guidelines on the transfer of patients with head injuries should be drawn up between the referring hospital trusts, the neuroscience unit and the local ambulance service, and should recognise that (pg 54):
 - *Transfer would benefit all patients with serious head injuries (GCS ≤ 8), irrespective of the need for neurosurgery*
 - *If transfer of those who do not require neurosurgery is not possible, ongoing liaison with the neuroscience unit over clinical management is essential.*

Question 2.2 What is the evidence for the initial acute care of those with a mild TBI?

Q 2.2.1 –Initial acute care of those with mild TBI: Monitoring & observation

Executive summary

Recommendations on this topic are made by two guidelines of excellent quality. Recommendations are made for the monitoring and observation of individuals with mTBI, and the training required for clinical staff undertaking the care of mTBI. Observation post mTBI should focus on early detection of deterioration in neurological status and Glasgow Coma Scale should be applied repeatedly until it reaches a score of 15.

Evidence statement

Key question	Rating	Justification
Evidence base	A	Information within high quality guidelines comes from (mostly) expert opinion, non-analytical studies or extrapolated from observational studies with high risk of bias.
Consistency	A	The literature is consistent on the need to perform repeat measures of the GCS and on monitoring routinely for deterioration in neurological signs.
Clinical impact	B	Substantial implications due early appropriate management of mTBI can improve prognosis.

Key guidelines regarding initial acute care- Monitoring & observation:

1. **Scottish Intercollegiate Guidelines Network (SIGN).Early management of a patient with head injury. Edinburgh: SIGN; 2009.**

AGREE II Score: 7/7

‘This guideline makes recommendations on the early management of patients with head injury, focusing on topics of importance throughout NHS Scotland.’ Recommendations are made for the management of adults and children.

The recommendations for this sub section were informed by best practice based on the clinical experience of the guideline development group.

Recommendations relevant to monitoring are:

- *Emergency department medical and nursing staff should communicate details of the mechanism and type of injury and maintain a written record of the neurological progress since arrival in the ED (pg 26) (Good practice point).*
- *Nursing staff should carry out a neurological assessment (including limb movements, pupil reactions and GCS) on arrival in the ward and compare it with that obtained in the ED. Any discrepancy between these assessments, suggesting deterioration, or other concerns about the patient’s condition should be discussed immediately with the relevant medical staff (pg 26) (Good practice point).*
- *All medical and nursing staff involved in the care of patients with a head injury should be trained and competent in the use and recording of the Glasgow Coma Scale (pg 27) (Good practice point).*
- *The GCS should not be used in isolation and other parameters should be considered along with it, such as (pg 27) (Good practice point):*
 - *pupil size and reactivity*
 - *limb movements*
 - *respiratory rate and oxygen saturation*
 - *heart rate*
 - *blood pressure*
 - *temperature*
 - *unusual behaviour or temperament or speech impairment.*
- *Family members and friends should be used as a source of information (pg 27) (Good practice point).*
- *Observations should be recorded on a chart of a design common to Scottish hospitals, a copy of which must go with the patient throughout the different departments during the patient’s hospital stay (pg 27) (Good practice point).*

- *Patients with a head injury, who warrant admission, should have neurological observations carried out at least in the following frequency starting after initial assessment in the ED (pg 28) (Good practice point):*
 - *half hourly for two hours*
 - *hourly for four hours*
 - *two hourly for six hours*
 - *four hourly thereafter until agreed to be no longer necessary .*
- *It is necessary for medical staff to know the patient's condition on admission and to review progress. Medical staff should assess the patient on admission to the ward and should re-assess the patient at least once within the next 24 hours. Assessment should include examination for the GCS, neck movement, limb power, pupil reactions, all cranial nerves and signs of basal skull fracture (pg 28) (Good practice point).*
- *Any of the following examples of neurological deterioration should prompt urgent re-appraisal by a doctor (pg 28) (Miller & Becker 1982; Swann & Teasdale 1999) (Grade D: Evidence from nonanalytic studies (eg case series/case studies); or Extrapolated evidence from well conducted case control or cohort studies):*
 - *the development of agitation or abnormal behaviour*
 - *a sustained decrease in conscious level of at least one point in the motor or verbal response or two points in the eye opening response of the GCS score*
 - *the development of severe or increasing headache or persisting vomiting*
 - *new or evolving neurological symptoms or signs, such as pupil inequality or asymmetry of limb or facial movement.*
 - *Clinical signs of shock in a patient with a head injury should be assumed, until proven otherwise, to be due to hypovolaemia caused by associated injuries (pg 28) (Good practice point).*
 - *Whilst an intoxicating agent may confuse the clinical picture, the assumption that deterioration or failure to improve is due to drugs or alcohol must be resisted (pg 28) (Good practice point).*
 - *If systemic causes of deterioration such as hypoxia, fluid and electrolyte imbalance, or hypoglycaemia can be excluded, then resuscitation should continue according to Advanced Trauma Life Support principles while anaesthetic help and neurosurgical advice are sought (pg 28) (Good practice point).*

2. NICE 2007 Head injury: Triage, assessment, investigation and early management of head injury in infants, children and adults. National Institute of Health & Clinical Excellence.
AGREE II Score: 7/7

This UK guideline is the update of an earlier 2003 edition. 'This guideline addresses assessment, investigation and early management of head injury. Separate advice is provided for adults and children (including infants) where different practices are indicated.' (pg 4) *NB: the NICE development group ruled that they would no longer publish grades with their recommendations.*

The recommendations for this subsection were informed by the recommendations provided by the guideline. The underpinning evidence however has not been explicitly outlined and hence has not been listed here.

The recommendations relevant to monitoring and observation are:

- *Training in observation(pg 71):*
 - *For patients admitted for head injury observation the minimum acceptable documented neurological observations are: GCS; pupil size and reactivity; limb movements; respiratory rate; heart rate; blood pressure; temperature; blood oxygen saturation.*
 - *Medical, nursing and other staff caring for patients with head injury admitted for observation should all be capable of performing the above observations.*
 - *The acquisition and maintenance of observation and recording skills require dedicated training and this should be available to all relevant staff.*
- *Frequency of observations(pg 71):*

Observations should be performed and recorded on a half-hourly basis until GCS equal to 15 has been achieved. The minimum frequency of observations for patients with GCS equal to 15 should be as follows, starting after the initial assessment in the emergency department:

 - *Half-hourly for 2 hours*
 - *Then 1-hourly for 4 hours*
 - *Then 2-hourly thereafter.*
- *Should a patient with GCS equal to 15 deteriorate at any time after the initial 2-hour period, observations should revert to half-hourly and follow the original frequency schedule (pg 71).*

Q 2.2.2 Initial acute care: Clinical decision making about return to play (RTP)

Executive summary

Recommendations that apply to clinical decision making about return to play post mTBI have been informed by one high quality and one moderate quality guideline. There is agreement

that return to play post mTBI should follow a step by step protocol and is only safe to return to play if the athlete shows full clinical and cognitive recovery.

Evidence statement

Key question	Rating	Justification
Evidence base	A	Recommendations from one high and one moderate quality guideline are underpinned by expert consensus.
Consistency	A	The recommendations are consistent for return to play post mTBI.
Clinical impact	B	A substantial impact by providing step by step outline for safe return to play for an athlete after sustaining an injury.

Key guidelines regarding Initial acute care- Clinical decision making about return to play (RTP)

1. McCrory et al. Consensus Statement on Concussion in Sport – the 3rd International Conference on Concussion in Sport held in Zurich, Nov 2008. SAJSM; 2009; vol 21 No. 2. AGREE II Score: 4/7.

This updated international consensus statement was ‘developed for use by physicians, therapists, certified athletic trainers, health professionals, coaches and other people involved in the care of injured athletes, whether at the recreational, elite or professional level. Recommendations apply to adults, adolescents and children. The guideline is based on a literature review, however details of its methodology are not provided.

Recommendations relevant to return to play are:

- *Same day return to play strategy must follow the basic management principles namely, full clinical and cognitive recovery before consideration of return to play (pg 39) (Consensus).*
- *With adult athletes, in some settings, where there are team physicians experienced in concussion management and sufficient resources (e.g. access to neuropsychologists, consultants, neuroimaging etc) as well as access to immediate (i.e. sideline) neuro-cognitive assessment, return to play management is may be more rapid (pg 39) (Consensus).*
- *Return to play protocol following a concussion follows a stepwise process as outlined in the table below (pg 39) (Consensus).*

- *With this stepwise progression, the athlete should continue to proceed to the next level if asymptomatic at the current level. Generally each step should take 24 hours so that an athlete would take approximately one week to proceed through the full rehabilitation protocol once they are asymptomatic at rest and with provocative exercise (pg 39) (Consensus).*
- *If any post-concussion symptoms occur while in the stepwise program then the patient should drop back to the previous asymptomatic level and try to progress again after a further 24-hour period of rest has passed (pg 39) (Consensus).*

Graduated Return to Play Protocol (pg 39)			
No.	Rehabilitation Stage	Functional exercise at each stage of rehabilitation	Objective stage
1.	No activity	Complete physical and cognitive rest	Recovery
2.	Light aerobic exercises	Walking, swimming or stationary cycling keeping intensity < 70% MPHR No resistance training.	Increase HR
3.	Sport specific exercise	Skating drills in ice hockey, running drills in soccer. No head impact activities.	Add movement
4.	Non-contact training drills	Progression to more complex training drills e.g. passing drills in football and ice hockey. (May start load progressive resistance training)	Exercise co-ordination and cognitive
5.	Full contact practice	Following medical clearance participate in normal training activities.	Restore confidence and assess functional skills by coaching staff
6.	Return to play	Normal game play	

2. Marshall et al (Ontario Neurotrauma Foundation). Clinical practice guidelines for mild traumatic brain injury and persistent symptoms. *Canadian Family Physician* 2012; 58(3): 257.

AGREE II Score: 6/7

The objective of this Canadian group was 'to create a set of guidelines that can be used by healthcare professionals to implement evidence-based, best practice care of individuals who incur a mild traumatic brain injury and experience persistent symptoms' (pg1.) Recommendations are made for the management of adults >18years.

The recommendations for this sub section were informed by two guidelines McCrory et al. (2009) and NZGG (2006).

Recommendations relevant to return to play decision making are:

- *A player should never return to play while symptomatic. "If in doubt, sit them out"* (pg 18) (McCrory et al. 2009) (Grade C: Expert opinion, experience of a consensus panel.).
- *Return to play after mTBI should follow a stepwise process, proceeding to the next level only if asymptomatic. If any symptoms occur after mTBI, the person should revert to the previous asymptomatic level and try to progress again after 24 hours* (pg 18) (McCrory et al. 2009; NZGG 2006) (Grade C: Expert opinion, experience of a consensus panel.).
 1. *No activity. When asymptomatic, proceed to level 2.*
 2. *Light aerobic exercise such as walking or stationary cycling, no resistance training.*
 3. *Sport-specific training (e.g., skating in hockey, running in soccer).*
 4. *Non-contact training drills.*
 5. *Full contact training after medical clearance.*
 6. *Game play.*
- *An additional consideration on return to play is that athletes who have experienced mTBI should not only be symptom free but also should not be taking any pharmacological agents/medications that may affect or modify the symptoms of concussion* (pg 18) (McCrory et al. 2009) (Grade C: Expert opinion, experience of a consensus panel.).

Q 2.2.3 Initial acute care: Pharmacology

Executive summary

Recommendations that apply to the use of pharmacology post mTBI have been informed by one excellent quality guideline. The use of pharmacology is not widespread in the acute

phase post mTBI, however symptom relief for headaches, depressive symptoms and cognitive dysfunction can be found by use of antidepressants.

Evidence statement

Key question	Rating	Notes
Evidence Base	A	Recommendations from a high quality guideline are underpinned by Systematic reviews, experimental and observational studies.
Consistency	A	There are consistent recommendations for coordinated, inter-disciplinary management of mTBI.
Clinical impact	B	A potentially substantial impact by providing symptom relief to patients post mTBI.

Key guidelines regarding initial acute care: Pharmacology

1. **Scottish Intercollegiate Guidelines Network (SIGN). Brain injury rehabilitation in adults. Edinburgh: SIGN; 2013.**
AGREE II Score: 7/7

This Scottish guideline aims to provide recommendations about the management of adults (16+yrs) with brain injuries of all severities. Recommendations are made for post-acute assessment, interventions for cognitive, communicative, emotional, behavioural and physical rehabilitation, optimal models and settings of care.

The recommendation for this sub section was informed by one systematic review Comper et al. (2005).

Recommendations relevant to pharmacology post mTBI are:

- *Antidepressants (amitriptyline & sertraline) may be considered for symptom relief after MTBI* (pg. 12)(Comper et al. 2005) (Grade C: Includes well conducted case control or cohort studies with a low risk of bias, or extrapolated from good quality SRs of case control or cohort studies)

Other earlier or lower quality evidence relevant to this topic:

Reed D (2007). Adult Trauma Clinical Practice Guidelines, Initial Management of Closed Head Injury in Adults, NSW Institute of Trauma and Injury Management. (AGREE II Score 4/7)

Question 2.3 What is the evidence for the initial advice and outpatient rehabilitation those with mild TBI?

Q 2.3.1 Initial advice for adults with mild TBI

Executive summary

Three high quality guidelines make recommendations on this topic. Individuals with mild TBI and their carers should be given information (face-to-face and written) on post-concussion symptoms, symptom management, expectations for normal recovery, warning signs of complications, recommendations for rest and return to usual activities. Information should be provided in culturally appropriate formats. Several RCTs and systematic reviews underpin recommendations for the provision of evidence-based information. Other recommendations, such as the use of culturally specific written information, are backed by expert consensus only.

Evidence statement

Key question	Rating	Justification
Evidence base	A	Information within high quality guidelines comes from systematic reviews of (mostly) observational studies, scant primary experimental studies, and several primary observational studies. Some expert consensus recommendations.
Consistency	A	The literature is consistent on the need to provide advice and information to individuals with mTBI and their carers. There is also agreement on the type of information required.
Clinical impact	B	Substantial implications due to the significant proportion of mTBI population who experience persistent symptoms. The recommendations facilitate effective self-management

Background to initial advice required: (taken directly from MAA NSW 2008, pg 37)

'The literature (with control or comparison groups) suggests that 22–86% of adult patients who have sustained a MTBI may experience a range of post-concussion symptoms in the first day after injury or in the first weeks of the acute stage (Eyres et al 2005; Ingebrigtsen et al 1998; Savola & Hillbom 2003).

The symptoms usually resolve within a few weeks to three months in the majority of patients (Chambers et al 1996; Sheedy et al 2006).

At three months, research indicates that about 25% of patients will have ongoing symptoms (Bazarian et al 2006b; Chambers et al 1996; Lundin et al 2006; Ponsford et al 2000), with others recovering within 12 months (Carroll et al 2004b; Eyres et al 2005; Nolin & Heroux 2006; Iverson 2005a) and about 10–15% continuing to experience symptoms beyond 12 months post injury (Nolin & Heroux 2006).

A minority of patients with MTBI will have persistent symptoms beyond 12 months (Stalnacke 2007; Turner-Stokes et al 2005).’

Key guidelines regarding initial advice:

1. **Marshall et al (Ontario Neurotrauma Foundation). Clinical practice guidelines for mild traumatic brain injury and persistent symptoms. *Canadian Family Physician* 2012; 58(3): 257.**

AGREE II score: 6/7

The objective of this Canadian group was ‘to create a set of guidelines that can be used by healthcare professionals to implement evidence-based, best practice care of individuals who incur a mild traumatic brain injury and experience persistent symptoms’ (pg 1) Recommendations are made for the management of adults ≥ 18 years.

This comprehensive guideline addresses the topic of initial advice in some detail. An exemplar patient information sheet is provided in the guideline appendices, and covers expectations for normal recovery, warning signs of complications, advice for the first 48hrs and the first 4 weeks separately including regarding rest, driving, sport, pain relief, alcohol/drug consumption, return to work and other activities, post-concussion symptoms.

Recommendations of the guideline regarding initial advice (pp 14-15):

- *Minor problems should be managed symptomatically and the person should be offered reassurance and information on symptom management strategies. (Consensus point).*
- *All people who have sustained a possible or definite mTBI should receive information about common symptoms and reassurance that recovery over a short period of time (days to a few weeks) is anticipated (Mittenberg et al 2001). (Grade A evidence: At least one randomized controlled trial, meta-analysis, or SR)*
- *Management of patients who have had mTBI by primary care providers should involve guidance on strategies to minimize the impact of symptoms and to gradually resume activity and participation in life roles (Borg et al 2004; Mittenberg et al 2001; Ponsforth et al 2002). (Grade A evidence: At least one randomized controlled trial, meta-analysis, or SR)*
- *Education about symptoms, including an advice card, and reassurance should be provided to all patients who have experienced mTBI. Education should ideally be delivered at the time of initial assessment or minimally within one week of injury/first assessment (Mittenberg et al 2001; Ponsforth et al 2002; Turner-Stokes et al 2005; British Columbia 2003; Iverson 2005a). (Grade A evidence: At least one randomized controlled trial, meta-analysis, or SR)*

- *Elements that can be included in the education session are (Grade C evidence: Expert opinion, consensus of panel)*
 - *information about common symptoms,*
 - *reassurance that it is normal to experience some symptoms and that a positive outcome is expected,*
 - *typical time (allowing for individual differences) and course of recovery,*
 - *advice about how to manage or cope with symptoms,*
 - *advice about gradual reintegration to regular activities,*
 - *information on how to access further support if needed,*
 - *advice on stress management.*
- *A person who sustains mTBI should not drive for at least 24 hours and may require medical reassessment. An extension of the recommended 24 hour time period is advised if there are symptoms or complications that result in loss of good judgment, decreased intellectual capacity (including slowed thinking), post traumatic seizures, visual impairment or loss of motor skills. If there are complications, a medical assessment is required before an individual returns to driving (Grade C evidence: Expert opinion, consensus of panel)*

2. Scottish Intercollegiate Guidelines Network (SIGN).Guidelines for traumatic brain injury rehabilitation. Edinburgh: SIGN; 2013.

AGREE II score: 7/7

This Scottish guideline aims to provide recommendations about the management of adults (16+yrs) with brain injuries of all severities. Recommendations are made for post-acute assessment, interventions for cognitive, communicative, emotional, behavioural and physical rehabilitation, optimal models and settings of care.

The recommendations for the sub section were informed by three systematic reviews Borg et al. (2004), Snell et al. (2009) and Al Sayegh, Sandford & Carson (2010).

Recommendations relevant to initial advice for patients after mTBI:

- *Patients presenting with non-specific symptoms following mild traumatic brain injury should be reassured that the symptoms are benign and likely to settle within three months. (pg. 8)(Borg et al. 2004) (Grade B: Includes good quality SRs of case control & cohort studies, or evidence extrapolated from SRs of RCTs, or RCTs at low risk of bias)*
- *All patients should be offered reassurance about the nature of their symptoms and advice on gradual return to normal activities after uncomplicated mild traumatic brain injury (pg.12)(Snell et al. 2009; Al Sayegh, Sandford & Carson 2010) (Grade C: Includes*

well conducted case control or cohort studies with a low risk of bias, or extrapolated from good quality SRs of case control or cohort studies)

3. SIGN 2009 Early management of patients with a head injury. Scottish Intercollegiate Guidelines Network.

AGREE II score: 7/7

‘This guideline makes recommendations on the early management of patients with head injury, focusing on topics of importance throughout NHS Scotland.’ Recommendations are made for the management of adults and children. This guideline makes recommendations for the provision of advice at discharge from ED, however the authors did not find high level evidence to underpin these. The guideline appendices include a similar information sheet exemplar as provided by Ontario Neurotrauma Foundation (2012).

Recommendations of the guideline regarding initial advice:

- *Patients and carers should be given advice and information in a variety of formats tailored to their needs* (pg 5) (Grade D: Evidence from nonanalytic studies (eg case series/case studies); or Extrapolated evidence from well conducted case control or cohort studies)

4. Motor Accidents Authority of NSW (MAA NSW). 2008 Guidelines for Mild Traumatic Brain Injury Following a Closed Head Injury.

AGREE II score: 7/7

These Australian guidelines make recommendations for the early identification and management of adults with mild traumatic brain injury. They are aimed at clinicians working pre-hospital, emergency departments and general practice settings, and address the topic of advice in some detail. The guideline appendices include the same information sheet exemplar as provided by Ontario Neurotrauma Foundation (2012).

Recommendations of the guideline regarding initial advice:

- *The patient should be advised that they are likely to experience one or more post concussion symptoms for a short period and that this is normal.* (pg 37) (British Columbia 2003; Iverson 2005a; Ponsford et al 2002; Mittenberg et al 2001)(Grade A evidence: Body of evidence can be trusted to guide practice; Several level I or II studies with low risk of bias)
- *The patient should be advised that a full recovery of symptoms is expected.* (pg 37) Iverson 2005a; Ponsford et al 2002) (Grade A evidence: Body of evidence can be trusted to guide practice; Several level I or II studies with low risk of bias)

- *Education about symptoms and reassurance that symptoms are likely to resolve should be provided to all patients with MTBI (pg 27)(Borg et al 2004; Turner-Stokes et al 2004 & 2005; Mittenberg et al 2001; Ponsford et al 2002)(Grade A evidence: Body of evidence can be trusted to guide practice; Several level I or II studies with low risk of bias)*
- *Education should be provided within one week after injury (pg 27)(Mittenberg et al 2001; Turner-Stokes et al 2005; Ponsford et al 2002)(Grade A evidence: Body of evidence can be trusted to guide practice; Several level I or II studies with low risk of bias)*
- *A patient experiencing reduced cognitive functioning in the first few days following injury, with education and support, should be expected, in the majority of cases, to have these symptoms resolve and pre-injury cognitive functioning return within days, up to three months (pg 27) (Mittenberg et al 2001; Turner-Stokes et al 2005)(Grade A evidence: Body of evidence can be trusted to guide practice; Several level I or II studies with low risk of bias)*
- *Paramedics, emergency department personnel, GPs and community based clinicians should give patients with MTBI the evidence-based patient advice sheet developed for the MTBI guidelines (pg 27) (Consensus point).*
- *The clinician should consider any additional issues, potential disadvantages or need for additional resources for the patient with MTBI and their family if the patient is of Indigenous (Aboriginal or Torres Strait Islander) heritage. (pg 28)(Consensus point).*
- *A patient who identifies themselves as Indigenous should be considered for referral to, or be offered the option of being linked with, local Aboriginal Health Services to assist with management . (pg 28)(Consensus point).*
- *The clinician should consider any additional issues, potential disadvantages or need for additional resources for patients with MTBI from culturally and linguistically diverse backgrounds and their families (pg 28) (Consensus point).*
- *The clinician should consider the use of interpreters and/or referral to Multicultural Health Services if a patient is from a culturally diverse or non-English speaking background (pg 28)(Consensus point).*
- *The paramedic should provide the MTBI evidence based patient advice sheet to a patient with head injury and/or their carer if the individual declines transport to hospital (pg 28) (Consensus point).*

The guidelines included the following studies in their review of this question:

Reference	Design	Results
Turner-Stokes et al 2005	Cochrane systematic review. Aim: To assess the effects of multiD rehab following ABI in adults, and to explore approaches that are effective in different settings and the outcomes that are affected.	Ten trials of good methodological quality included. Strong evidence that most patients with MTBI make a good recovery with provision of appropriate information without additional specific intervention.
Borg et al 2004a	Systematic review Aim: to find evidence of nonsurgical interventions and for economic costs for individuals with MTBI.	Systematic search, reviewed 16 studies. Early educational information can reduce long-term complaints. Indirect costs are probably higher than direct costs. CT scanning compared to overnight hospitalisation indicates reduced costs; however, clinical outcome were comparable.
Mittenberg et al 2001	Meta-analysis of treatment effect sizes. Review of controlled treatment outcome studies (including psychological consultation).	Early single session treatment can prevent post-concussion syndrome as effectively as traditional outpatient therapy.
Ponsford et al 2002	Pseudo-RCT Aim: Evaluate the impact of the provision of information, measured in terms of reported symptoms, cognitive performance & psychological adjustment 3mths post-injury.	Provision of information booklet reduces anxiety and reporting of ongoing problems. <i>Comments: 77% f/up, no blinding, patients had standardised assessment, P values provided, differences in overall score between group not available (PCS).</i>
Iverson 2005a	Review of outcomes in individuals with MTBI including Post Concussion Syndrome, Pathophysiology & neuropsychological outcomes.	Recovery can be incomplete for trauma patients and can be complicated by pre-existing conditions including substance abuse, poor general health, comorbid problems, orthopaedic injuries, and psychiatric problems

Other earlier or lower quality evidence on the topic

McCrory P, Meeuwisse W, Johnston K, et al. Consensus Statement on Concussion in Sport – the 3rd International Conference on Concussion in Sport held in Zurich, November 2008; *SAJSM vol 21 No. 2 2009*. (AGREE II score 4/7)

Vos P, Alekseenko L, Battistin E, et al. Mild traumatic brain injury. ENFS guidelines/CME article. *European Journal of Neurology 2012, 19: 191–198*. (AGREE II score 5/7)

AANN and ARN. *Care of patient with mild traumatic brain injury*. Clinical practice guidelines series 2011. American Association of Neuroscience Nurses and the Association of Rehabilitation Nurses. (AGREE II score 4/7)

Barbosa, R. R., R. Jawa, J. M. Watters, J. C. Knight, A. J. Kerwin, E. S. Winston, R. D. Barraco, B. Tucker, J. M. Bardes, S. E. Rowell and T. Eastern Association for the Surgery of (2012). Evaluation and management of mild traumatic brain injury: an Eastern Association for the Surgery of Trauma practice management guideline. *The Journal of Trauma and Acute Care Surgery* 73(5 Suppl 4): S307-314. (AGREE II score 3/7)

Veterans Affairs & Dept of Defence. Management of concussion/ mild traumatic brain injury. Clinical practice guideline. 2009; Washington DC. (AGREE II score 4/7)

Reed (2007), Adult trauma clinical practice guidelines: Initial management of closed head injury in adults. NSW Institute of Trauma and Injury Management. (AGREE II score 4/7)

Q 2.3.2 Outpatient rehabilitation for adults with mild TBI – Service delivery

Executive summary

Recommendations that apply to service delivery for outpatient rehabilitation are made by four guidelines (three of high quality, one moderate quality). Recommendations for rehabilitation service delivery are drawn from features that are common to community services which produce beneficial outcomes for TBI patients. These include interdisciplinary rehabilitation, planned transfers between services, ongoing family/carer support, neuropsychology rehabilitation programmes, the availability of rehabilitation long after the injury. The case management model is recommended for defence force personnel with persistent mTBI symptoms and may be applicable more broadly.

Evidence statement

Key question	Rating	Notes
Evidence Base	A	Recommendations from high and moderate quality guidelines is underpinned by (mostly) observational studies and expert opinion.
Consistency	B	There are consistent recommendations for coordinated, interdisciplinary management of mTBI rehabilitation. Only one guideline recommended a case management model.

Clinical impact	B	The coordinated, inter-disciplinary management of rehabilitation services has a potentially substantial impact for both individuals with mTBI and also clinicians working in the field
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Key guidelines regarding the outpatient rehabilitation (service delivery):

1. SIGN 2013 Brain injury rehabilitation in adults. Scottish Intercollegiate Guidelines Network

AGREE II score: 7/7

This Scottish guideline aims to provide recommendations about the management of adults (16+yrs) with brain injuries of all severities. Recommendations are made for post-acute assessment, interventions for cognitive, communicative, emotional, behavioural and physical rehabilitation, optimal models and settings of care. This guideline provides recommendations for TBI of all severities however several are relevant to outpatient rehabilitation for mild TBI. The graded strength of the underpinning evidence is cited in the guideline (Grades A-D) however details of underpinning studies are not provided.

Key recommendations for community rehabilitation service delivery :

- *Community rehabilitation services for patients with brain injuries should include a wide range of disciplines working within a co-ordinated interdisciplinary model/framework and direct access to generic services through patient pathways (pg 39) (Consensus point)*
- *Each patient should have a named worker (pg 39)(Consensus point)*
- *In the post-acute setting interventions for cognitive deficits should be applied in the context of a comprehensive/holistic neuropsychological rehabilitation programme. This would involve an interdisciplinary team using a goal-focused programme which has the capacity to address cognitive, emotional and behavioural difficulties with the aim of improving functioning in meaningful everyday activities. (pg 22)(Grade D: non-analytic studies, expert opinion or extrapolated from good case controlled or cohort studies)*

Rationale:

While there is limited research comparing the outcomes of community rehabilitation with other or no rehabilitation, there is evidence of beneficial outcomes for patients with TBI who have access to the following features of community rehabilitation services:

- Interdisciplinary rehabilitation. (Stilwell et al 1998; Cicerone et al 2008; Coetzer et al 2005)
- Planned transfer of patient care from hospital to community services (National Managed Clinical Network for ABI 2009; Stilwell et al 1998)
- Ongoing family and carers support (Stilwell et al 1998)
- Neuropsychology rehabilitation programmes (Cicerone et al 2008)
- Community rehabilitation many years post injury (Coetzer et al 2005; Powell et al 2002)

2. Marshall et al (Ontario Neurotrauma Foundation). Clinical practice guidelines for mild traumatic brain injury and persistent symptoms. *Canadian Family Physician* 2012; 58(3): 257.

AGREE II score: 6/7

The objective of this Canadian group was 'to create a set of guidelines that can be used by healthcare professionals to implement evidence-based, best practice care of individuals who incur a mild traumatic brain injury and experience persistent symptoms' (pg 1) Recommendations are made for the management of adults ≥ 18 years.

Some underpinning evidence is cited in the guideline however details of studies were not provided.

Key recommendations for community rehabilitation service delivery:

- *Persons with mTBI and pre-injury mental health conditions, or any other health or contextual risk factors, should be considered for early referral to a multidisciplinary treatment clinic capable of managing post concussive symptoms because these factors have been associated with poorer outcomes. (pg 21)(Consensus point)*
- *If evidence of cognitive dysfunction is obtained upon screening that is likely attributable to the mTBI itself or if cognitive symptoms are reported to persist at 3 months, then consideration for more formal assessment should be given and referral made. If available, refer to a neuropsychologist (ideally with experience with TBI). When a local neuropsychologist is not available or known, referral to a TBI centre can be made. For systems with long wait times, practitioners should consider referral earlier than 3 months. (pg 33)(Consensus point)*

3. Motor Accidents Authority of NSW (MAA NSW). 2008 Guidelines for Mild Traumatic Brain Injury Following a Closed Head Injury.

AGREE II score: 7/7

These Australian guidelines make recommendations for the early identification and management of adults with mild traumatic brain injury. They are aimed at clinicians working pre-hospital, emergency departments and general practice settings.

This Australian guideline provides the following recommendation:

- *The GP should consider referral of a patient with mTBI to specialist services when symptoms and concerns persist. For example, referral to a local brain injury rehabilitation service/occupational therapist for memory strategies or referral to a psychologist or psychiatrist for mental health concerns. (pg 30) (Consensus point)*

4. Veterans Affairs & Dept Defence (2009) Management of concussion/ mild traumatic brain injury. Clinical practice guideline. *J Rehab Res & Dev* 46(6): CP1-68.

AGREE II score: 4/7

This US guideline applies to adult patients (18yrs+) who are diagnosed with concussion/mTBI and complain of symptoms related to the injury and who are treated in VA/DoD clinical settings for these symptoms at least 7 days after the initial head injury. The guideline is relevant to all healthcare professionals providing or directing treatment services. Strength recommendations grading were rarely provided in this document, nor references for the underpinning evidence.

Key recommendations for rehabilitation service delivery (p vii,19,38):

- *A primary care model can be appropriate for the management of Concussion/mTBI when implemented by an interdisciplinary team with special expertise.*
- *Treatment should be coordinated and may include consultation with rehabilitation therapists, pharmacy, collaborative mental health, and social support.*
- *Patients with persistent symptoms following concussion/mTBI may be considered for case management.*
- *Case managers should complete a comprehensive psychosocial assessment of the patient and the patient's family. It may be necessary or beneficial to meet with other members of the patient's support system (family, care giver) and/or invite the patient to ask them to come to an appointment together with the patient.*
- *Case managers (in collaboration with the treatment team) should prepare and document a detailed treatment plan in the medical record describing follow-up care and services required.*

- *Case managers who provide care in the clinical setting should communicate and coordinate with other potential care coordinators that provide care for the patient*
- *Case managers may provide assistance to the patient and family who are transferred to another facility (e.g., a polytrauma rehabilitation center).*
- *Case management may serve as the main point of contact for the patient and family. This may include the following :*
 - *Provide the patient with contact information including after-hours calls*
 - *Maintain frequent contact by phone to remind about or facilitate an appointment*
 - *Facilitate access to supportive services to the patient and family*
 - *Serve as a liaison for the patient's family and as an advocate for the patient and the patient's family.*

Q 2.3.3 Outpatient rehabilitation for adults with mild TBI – interventions

Executive summary

The evidence reviewed for the topic of outpatient rehabilitation interventions included six high quality guidelines and one good quality systematic review. Recommendations are made for rehabilitation therapy/interventions or compensatory strategies for memory problems, deficits in attention and other executive cognitive functions, anxiety, communication and balance disorders.

Evidence statement

Key question	Rating	Notes
Evidence Base	A	Recommendations within high quality guidelines & systematic reviews comes from largely from systematic reviews of (mostly) observational studies, lower level experimental studies, and many primary observational studies. Some expert opinion.
Consistency	A	Consistent for the use of compensatory strategies for cognitive deficits and CBT. There is a scarcity of evidence, rather contradictory evidence, for the other recommendations.
Clinical impact	B	Potentially substantial impact for both individuals with mTBI and also clinicians working in the field

Key guidelines regarding outpatient rehabilitation (interventions):

1. **Scottish Intercollegiate Guidelines Network (SIGN).Guidelines for traumatic brain injury rehabilitation. Edinburgh: SIGN; 2013.**

AGREE II score: 7/7

This Scottish guideline aims to provide recommendations about the management of adults (16+yrs) with brain injuries of all severities. Recommendations are made for post-acute assessment, interventions for cognitive, communicative, emotional, behavioural and physical rehabilitation, optimal models and settings of care.

Key recommendation for physical rehabilitation:

- *Repetitive task-oriented activities are recommended for improving functional ability, such as sit-to-stand or fine motor control.* (pg 14)(Hellweg et al 2008) (Grade B evidence: includes high quality SRs of case control or cohort studies, or extrapolated from SRs/meta-analysis of RCTs)

Key recommendations for cognitive rehabilitation:

- *Patients with memory impairment after TBI should be trained in the use of compensatory memory strategies with a clear focus on improving everyday functioning rather than underlying memory impairment.*
For patients with mild-moderate memory impairment both external aids and internal strategies (eg use of visual imagery) may be used.
For those with severe memory impairment external compensations with a clear focus on functional activities is recommended (pg 21) (Cappa et al 2005; de Joode et al 2010; Cicerone et al 2011) (Grade D evidence: non-analytic studies, expert opinion, case series/ case reports or extrapolated from case controlled or cohort studies)
- *Patients with attention impairment in the post-acute phase after TBI should be given strategy training relating to the management of attention problems in personally relevant functional situations.* (pg 21)(Cicerone et al 2011) (Grade C evidence: includes well conducted case control or cohort studies, or extrapolated from SRs of case control or cohort studies)
- *Patients with TBI and deficits in executive functioning should be trained in meta-cognitive strategies relating to the management of difficulties with planning, problem solving and goal management in personally relevant functional situations.* (pg 22)(Cicerone et al 2005; Kennedy et al 2008; Spikman et al 2010; Vas et al 2011) (Grade B evidence: includes high quality SRs of case control or cohort studies, or extrapolated from SRs/meta-analysis of RCTs)

Key recommendations for rehabilitation of behavioural and emotional disorders (pg 26):

- *Cognitive behavioural therapy should be considered for the treatment of acute stress disorder following mild TBI.* (Soo et al 2007; Bradbury et al 2008) (Grade B evidence:
- *Cognitive behavioural therapy should be considered for the treatment of anxiety symptoms following mild to moderate TBI, as part of a broader neurorehabilitation programme.* (Soo et al 2007; Bradbury et al 2008) (Grade B evidence: includes high quality SRs of case control or cohort studies, or extrapolated from SRs/meta-analysis of RCTs)

Key recommendations for communication rehabilitation (pg 30):

- *Patients with communication deficits post TBI should be referred to speech and language therapy for assessment and management of their communication impairments.* (Expert opinion).

Key recommendations for vocational rehabilitation (pg 33):

- *Early in the rehabilitation pathway patients should be asked about vocational activities and liaison initiated with employers. Once work requirements are established patients*

should have appropriate assessments made of their ability to meet the needs of their current or potential employment. (Expert opinion)

2. Motor Accidents Authority of NSW (MAA NSW). 2008 Guidelines for Mild Traumatic Brain Injury Following a Closed Head Injury.

AGREE II score: 7/7

These Australian guidelines make recommendations for the early identification and management of adults with mild traumatic brain injury. They are aimed at clinicians working pre-hospital, emergency departments and general practice settings.

The guideline provides the following rehabilitation recommendation:

- *Psychological or cognitive rehabilitation using a cognitive behavioural approach may assist to reduce anxiety, which has the potential to influence memory* (pg 31)(Ponsforth et al 2005)

Key systematic reviews regarding outpatient rehabilitation:

Reference	Design	Results
MAA NSW 2008		
Ponsford et al 2005	Literature review <i>Aim:</i> Review current management & rehabilitation strategies for MTBI; emphasis on need to address multiple potential causative factors	Evidence base for best management of MTBI is limited. Psychological therapy using a cognitive behaviour approach may be helpful to address some symptoms.

3. Marshall et al (Ontario Neurotrauma Foundation). Clinical practice guidelines for mild traumatic brain injury and persistent symptoms. *Canadian Family Physician* 2012; 58(3): 257.

AGREE II score: 6/7

The objective of this Canadian group was 'to create a set of guidelines that can be used by healthcare professionals to implement evidence-based, best practice care of individuals who incur a mild traumatic brain injury and experience persistent symptoms' (pg 1) Recommendations are made for the management of adults ≥ 18 years.

Key recommendations for cognitive rehabilitation:

- *Following mTBI, acute cognitive deficits are common, and spontaneous cognitive improvement is expected in the majority of injured individuals. Rehabilitation of cognitive impairments should be initiated if:*
 - i. The individual exhibits persistent cognitive impairments on formal evaluation*
 - ii. The learning of compensatory strategies is necessary in order to facilitate the resumption of functional activities and work and/or there are safety issues in question (i.e., possible harm to self or others). (pg 33)(Grade C: Expert opinion, consensus)*
- *For cognitive sequelae following mTBI, the cognitive rehabilitation strategies that should be considered include compensatory strategies and restorative approaches. (pg 33)(Grade C: Expert opinion, consensus)*
- *Electronic external memory devices such as computers, paging systems or portable voice organizers have been shown to be effective aids for improving TBI patients' everyday activities. (pg 33)(Lower Level evidence: Tam et al 2004; Kirsch et al 2004; Kapur et al 2004; Hart et al 2002)(Grade B: At least one cohort comparison, case studies or other type of experimental study)*

Key recommendations for balance rehabilitation:

- *If symptoms of benign positional vertigo are present the Dix-Hallpike Manoeuvre should be used (Details provided in an appendix) (pg 36)(Hilton et al 2009) (Grade A: At least one randomized controlled trial, meta-analysis, or SR)*
- *For persons with functional balance impairments and screening positive on a balance measure, consideration for further balance assessment and treatment by physiotherapy may be warranted pending clinical course. (pg 36)(Consensus point)*
- *Vestibular rehabilitation therapy is recommended for unilateral peripheral vestibular dysfunction. (pg 36)(Hillier & Hollohan 2007) (Grade A: At least one randomized controlled trial, meta-analysis, or SR)*
- *A canalith repositioning maneuver should be used to treat Benign Positional Vertigo if the Dix-Hallpike Maneuver is positive. (pg 36)(Hilton & Pinder 2004) (Grade A: At least one randomized controlled trial, meta-analysis, or SR)*

4. Golisz K. 2009. Occupational therapy practice guidelines for adults with traumatic brain injury. American Occupational Therapy Assoc.

AGREE II score: 6/7

This US guideline is aimed at occupational therapists. Recommendations are made for the evaluation, acute care and rehabilitation of adults with TBI. The authors considered 99 articles including 32 Level I, and 10 RCTs. The strength of evidence underpinning individual recommendations is provided but details of relevant studies are unavailable. The guideline provides the following recommendations based on evidence rated as Good (A) or Fair (B), that may be relevant to mild TBI:

Recommended interventions for Occupational Therapy, focused on performance skills:

- *Errorless learning (Rating A)*
- *Compensatory approaches to cognitive rehabilitation (Rating A)*
- *Memory rehabilitation utilizing restorative (visualization, mnemonics); compensatory (internal mnemonics and external aids); and external change/adapt environment strategies for clients with mild-to-moderate impairments (Rating A)*
- *Computerized memory orthoses for prospective memory (Rating A)*
- *Awareness training embedded in functional task performance (Rating A)*
- *Group-based cognitive rehabilitation (Rating A)*
- *Social skills training (Rating B)*
- *Establishment of goals valued by the client, combined with compensatory training and environmental adaptation (Rating B)*
- *Pager systems for memory and planning problems (Rating B)*
- *PDA to remind client about therapy goals (Rating B)*
- *Mobile phones as compensatory memory aids (Rating B)*
- *Environmental cues for performance of activities of daily living (ADLs) and instrumental activities of daily living (IADLs) (Rating B)*
- *Attention remediation programs for clients in chronic phase of recovery (Rating B)*

Recommended interventions for Occupational Therapy, focused on occupational performance areas and/or participation:

- *Functional–experiential treatment for older clients with TBI and independent living goals (Rating B)*
- *Written contracts to achieve short-term goals (Rating B)*
- *Life skills training to increase community participation (Rating B)*
- *Intensive cognitive rehabilitation (ICRP) to return to work for military personnel (Rating B)*

Other earlier or lower quality evidence on the topic, which supports the above recommendations:

AANN and ARN. Clinical practice guidelines series- care of patient with mild traumatic brain injury 2011. (AGREE II Score 4/7)

Veterans Affairs & Dept of Defence. Management of concussion/ mild traumatic brain injury. Clinical practice guideline. 2009; Washington DC. (AGREE II score 4/7)

Chong CS (2008). Management strategies for post-concussion syndrome after mild head injury: a systematic review. Hong Kong J of Occupational Therapy; 18(2):59-67. (CEBM score 4/5)

Question 2.4 What is the evidence for employment participation for adults with mild TBI?

This question is answered in two subsections: (1) employment participation following mild TBI and (2) return to employment of study

Employment participation following mild TBI

Executive summary

The evidence reviewed in this project for vocational outcomes after mild TBI reports inconsistent findings. While some studies report no difference in return to work rates for mild TBI and that of controls (Temkin et al 2009), other studies report that the resumption of work or study activities can be complicated and stressful, with 10 – 15% of individuals with mild TBI still experiencing symptoms at 1 to 3 years post-injury (Ontario Neurotrauma Foundation 2012). Individuals with short term mild TBI symptoms typically return to work or study within 3-7 days of injury. The majority of those with more significant symptoms will be back to their usual occupation within 6 months (MAA NSW 2008).

Evidence statement

Key question	Rating	Notes
Evidence base	A	Information within high quality guidelines & reviews is based on data from observational studies and government agency reports
Consistency	D	Return to work evidence is inconsistent
Clinical impact	B	Substantial implications due to significant proportion of the mild TBI population experiencing difficulties in return to work

Key guidelines regarding employment participation:

5. Motor Accidents Authority of NSW (MAA NSW). 2008 Guidelines for Mild Traumatic Brain Injury Following a Closed Head Injury.

AGREE II score: 7/7

These Australian guidelines make recommendations for the early identification and management of adults with mild traumatic brain injury. They are aimed at clinicians working in pre-hospital, emergency departments and general practice settings.

Key points relevant to employment participation (p.33):

- A typical patient with mild TBI, where symptoms are short term or do not interfere or limit work capacity, will return to work within three to seven days post injury. (Work Loss Data Institute 2006).

- Most patients with mild TBI, including those with more significant symptoms, have generally returned to work within six months post injury. (British Columbia 2003).
- Even when individuals who have sustained mild TBIs return to work, up to 10–15% typically experience one or more symptoms at one to three years post injury (Stalnacke 2007; Turner-Stokes 2005).

6. Marshall et al (Ontario Neurotrauma Foundation). Clinical practice guidelines for mild traumatic brain injury and persistent symptoms. Canadian Family Physician 2012; 58(3): 257.

AGREE II Score: 6/7

The objective of this Canadian group was ‘to create a set of guidelines that can be used by healthcare professionals to implement evidence-based, best practice care of individuals who incur a mild traumatic brain injury and experience persistent symptoms’ (p.1) Recommendations are made for the management of adults >18years.

Key points relevant to employment participation:

- Within a year of sustaining a mild TBI the majority of individuals (73-88%) are able to return to their usual occupation (Dikmen et al., 1994; Nolin & Heroux, 2006, Stambrook, et al. 1990; Van der Naalt et al 1999).
- The resumption of work or school activities can be complicated and stressful for many individuals with mild TBI due to ongoing symptoms and the invisibility of their injury (Gilworth, Eyres, Carey, Bhakta & Tennant, 2008).

Key systematic review regarding employment participation:

5. Temkin N, Corrigan J, Dikmen S, Machamer J. (2009). Social Functioning After Traumatic Brain Injury. Journal of Head Trauma Rehabilitation 24(6): 460-467.

CEBM Score: 3/5

The objective of this review was ‘to determine the relationship between adult-onset traumatic brain injury (TBI) and social functioning including employment, social relationships, independent living, recreation, functional status, and quality of life 6 months or longer after injury.’ It provides evidence of social dysfunction experienced by individuals with TBI that can influence community reintegration. A section on the relationship between mild TBI and employment participation includes three studies that provide variable evidence on this topic. While some studies report no difference in return to work rates between mild TBI and control groups (Friedland & Dawson 2001), others report lingering problems following mild TBI (Edna

et al 1997; Stulemeijer et al 2006) Although there is a dose-response relationship between severity of injury and social outcomes, there is insufficient evidence to determine at what level of severity the adverse effects are demonstrated.

Key findings from the review:

- There was insufficient evidence of a relationship between unemployment and mild TBI. (p.463) (Friedland & Dawson 2001; Edna et al 1997; Stulemeijer et al 2006).

The systematic review included the following studies in their review of this question:

Reference	Design	Results
Temkin et al (2009)		
Friedland & Dawson, 2001	Observational prospective cohort study <i>Country:</i> Canada <i>Sample:</i> n= 99 MVA patients (mild TBI n=64; no TBI n=35). Age 19-58yrs. <i>Outcomes:</i> at 6mths post-injury including return to work.	No significant difference between groups on return to work at 6 months post-injury. 44% mild TBI group returned to work 41% no TBI group returned to work
Edna et al 1987	Observational prospective cohort study <i>Country:</i> Norway <i>Sample:</i> n=485 with TBI (mostly mild); controls with acute appendicitis n= 89 <i>Outcomes:</i> Return to work outcomes over 3-5yrs post-injury	Unemployment increased after hospitalisation/injury for both groups: TBI increased from 12% to 27% Controls increased from 5% to 16% ($p < 0.01$)
Stulemeijer et al 2006	Observational retrospective cohort study <i>Country:</i> Netherlands <i>Sample:</i> Patients admitted to ED in level 1 trauma centre; Mild TBI n= 299, Mild TBI +additional injuries n=89, Controls with ankle or wrist injuries n=261 <i>Outcomes:</i> change in work at 6mths	Mild TBI significantly older ($p < 0.01$), more were male ($p = 0.0001$) than controls. Change in work reported 6mths after injury : 35% in mild TBI with additional injuries, 14% in mild TBI only group, 2% of controls report change in work ($p = 0.0001$)

Other earlier or lower quality evidence on the topic

Barbosa, R. R., R. Jawa, J. M. Watters, J. C. Knight, A. J. Kerwin, E. S. Winston, R. D. Barraco, B. Tucker, J. M. Bardes, S. E. Rowell and T. Eastern Association for the Surgery of (2012). Evaluation and management of mild traumatic brain injury: an Eastern Association for the Surgery of Trauma practice management guideline. *The Journal of Trauma and Acute Care Surgery* 73(5 Suppl 4): S307-314. (AGREE II score 3/7)

Shames, J., I. Treger, H. Ring and S. Giaquinto (2007). Return to work following traumatic brain injury: trends and challenges. *Disability & Rehabilitation* 29(17): 1387-1395. (CEBM score 1/5)

Return to employment or study

Executive summary

Four guidelines (two excellent and two of high quality) provide recommendations for the management of return to work/study for individuals who may experience difficulty following mild TBI. Recommendations include a multi-factorial assessment of the individual and the work context as well as a carefully planned and negotiated re-entry program. Two guidelines focus on the role of the GP in managing the return to work while another guideline details recommendations for inter-professional vocational evaluations. Primary research on return to work management strategies for mild TBI is very limited.

Evidence statement

Key question	Rating	Notes
Evidence base	A	Recommendations within high quality guidelines is underpinned by lower level evidence (non-experimental & expert opinion)
Consistency	A	Good consistency across guideline recommendations
Clinical impact	B	Substantial impact for the proportion of mild TBI population experiencing short or long-term difficulties in return to work

Key guidelines regarding return to employment or study

Guideline recommendations are based on patient-related and work-related variables that have been identified in research (mainly observational studies) and through best available expert opinion (MAA NSW 2008).

1. **Marshall et al (Ontario Neurotrauma Foundation). Clinical practice guidelines for mild traumatic brain injury and persistent symptoms. *Canadian Family Physician* 2012; 58(3): 257.**

AGREE II Score: 6/7

The objective of this Canadian group was 'to create a set of guidelines that can be used by healthcare professionals to implement evidence-based, best practice care of individuals who incur a mild traumatic brain injury and experience persistent symptoms' (p.1) Recommendations are made for the management of adults ≥ 18 years.

This guideline provides recommendations aimed at GPs for the return to work or study following mild TBI.

Recommendations relevant to return to employment of study (p.39):

- *When managing a patient's return to work/study, the Family Physician should consider patient related and contextual variables. These include physical difficulties arising from the injury, psychosocial issues, cognitive impairment, cultural or work-related contextual factors (e.g., workload and responsibilities, workplace environment, transport or driving issues, hours/shifts/rest breaks). (Grade C: expert opinion, consensus panel)*
- *For individuals who experience persistent deficits following mTBI, or who have difficulty once back at work, a return to work program should occur which requires a carefully designed and managed plan. Specifically, referral to an occupational therapist to review return to work is recommended (Gilworth et al 2008) (Grade C: expert opinion, consensus panel)*

2. Motor Accidents Authority of NSW (MAA NSW). 2008 Guidelines for Mild Traumatic Brain Injury Following a Closed Head Injury.

AGREE II Score: 7/7

These Australian guidelines make recommendations for the early identification and management of adults with mild traumatic brain injury. They are aimed at clinicians working pre-hospital, emergency departments and general practice settings. Recommendations recognise the central role of GPs in managing the return to employment. Detailed guidance on return to work considerations is provided in appendices.

Recommendations of the guideline regarding return to work (p.33,34):

- *When managing a patient's return to work/study, the GP should consider patient-related and contextual variables. These include physical difficulties arising from the injury, psychosocial issues, cognitive impairment, cultural or work-related contextual factors. (Expert opinion)*
- *When managing a patient's return to work/study, the GP should consider the variables associated with the work tasks performed by the individual, the workplace and transport or driving issues. (Expert opinion)*
- *When managing graduated or modified return to work/study, the GP should consider a range of variables including hours, tasks, workload, responsibilities, shifts and rest breaks. (Expert opinion)*

3. SIGN 2013 Brain injury rehabilitation in adults. Scottish Intercollegiate Guidelines Network.

AGREE II Score: 7/7

This Scottish guideline aims to provide recommendations about the management of adults (16+yrs) with brain injuries of all severities. Recommendations are made for post-acute assessment, interventions for cognitive, communicative, emotional, behavioural and physical rehabilitation, optimal models and settings of care.

This guideline addresses vocational rehabilitation (VR) for TBI of all severities and concludes that 'the evidence on the effectiveness of specific VR interventions is inconclusive.'

Recommendations regarding return to work (p.33):

- *Early in the rehabilitation pathway patients should be asked about vocational activities and liaison initiated with employers. Once work requirements are established patients should have appropriate assessments made of their ability to meet the needs of their current or potential employment. (Expert opinion)*
- *NHS Boards should consider providing a specific local expert therapist to provide advice to rehabilitation teams including signposting to relevant statutory services... [local services suggested] (Expert opinion)*

4. Stergio-Kita et al. Inter-professional clinical practice guideline for vocational evaluation following traumatic brain injury: A systematic and evidence-based approach. *J Occup Rehabil* (2012) 22:166–181.

AGREE II score: 6/7

This is a Canadian inter-professional clinical practice guideline for vocational evaluation following traumatic brain injury. It 'aims to explicate the processes and factors relevant to vocational evaluation to assist evaluators (i.e. health care teams, individuals and employers) in collaboratively determining if clients are able to work and to make recommendations for work entry, re-entry or vocational planning' (p.166). This guideline details the components of vocational evaluation that should be addressed following TBI. Guideline recommendations are referenced by underpinning evidence but no details of the primary studies are provided. Although the recommendations relate to the range of TBI severities, many will apply to individuals who experience persistent deficits following mild TBI, or who have difficulty once back at work. Additional details of vocational evaluation are provided in the guideline.

Recommendations relevant to return to work:

Vocational evaluations following TBI should include (Note Level/Grade descriptions below):

- *Identification of purpose and rationale for the evaluation: referral sources, aims of the evaluation, relevant stakeholders (Level 3: evidence from non-experimental studies; Grade B: No RCTs on the subject but well-designed clinical studies)*

- *Initial intake processes: background information, pre-injury history, education & work histories, current social status, pre-injury job performance & successes/failures of any post-injury work trials.* (Level 3: evidence from non-experimental studies; Grade B: No RCTs on the subject but well-designed clinical studies)
- *Assessment of the person - individual's perspective (self-reported): work interests and preferences, perceptions of work performance, identified use of compensatory strategies & supports, readiness to work, anticipated barriers/challenges, costs & benefits of working, understanding of their options and implications of decisions not to work.* (Level 3: evidence from non-experimental studies; Grade B: No RCTs on the subject but well-designed clinical studies)
- *Assessment of the person – person domains:*
 - Physical & sensory (Level 2: At least one well-designed controlled study without randomisation OR quasi-experimental; Grade B: No RCTs on the subject but well-designed clinical studies)
 - Neuropsychological and cognitive (Level 2: At least one well-designed controlled study without randomisation OR quasi-experimental; Grade B: No RCTs on the subject but well-designed clinical studies)
 - Psychosocial (Level 3: evidence from non-experimental studies; Grade B: No RCTs on the subject but well-designed clinical studies)
 - Communication (Level 4: evidence from committee reports, opinions, expert experience; Grade C: expert opinion)
 - Functional status and independence (Level 3: evidence from non-experimental studies; Grade B: No RCTs on the subject but well-designed clinical studies)
 - Observed behaviours, observed work-related skills & behaviour in a work setting (Level 4: evidence from committee reports, opinions, expert experience; Grade C: expert opinion)
- *Assessment of the environment: physical work place environment, work culture, supports available.* (Level 3: evidence from non-experimental studies; Grade B: No RCTs on the subject but well-designed clinical studies)
- *Assessment of the occupational/job requirements: job complexity and demands, responsibilities and expectations, safety requirements.* (Level 3: evidence from non-experimental studies; Grade B: No RCTs on the subject but well-designed clinical studies)
- *Evaluation recommendations for work re-entry based on analysis of assessment findings.* (Level 3: evidence from non-experimental studies; Grade B: No RCTs on the subject but well-designed clinical studies)

Other earlier or lower quality evidence on the topic

The following articles support the information provided above.

Barbosa R, R. Jawa J, Watters J, Knight A, Kerwin E, Winston R, Barraco B, Tucker J, Bardes S, Rowell T. Eastern Association for the Surgery of (2012). Evaluation and management of mild traumatic brain injury: an Eastern Association for the Surgery of Trauma practice management guideline. *The Journal of Trauma and Acute Care Surgery* 73(5 Suppl 4): S307-314. (AGREE II score 3/7)

Department of Veterans Affairs & The Department of Defense; VA/DOD Clinical Practice Guideline for Management of Concussion/ Mild Traumatic Brain Injury. 2009; United States Army. (AGREE II score 4/7)

Kendall, E., H. Muenchberger and T. Gee (2006). Vocational rehabilitation following traumatic brain injury: a quantitative synthesis of outcome studies. *Journal of Vocational Rehabilitation* 25(3): 149-160. (CEBM score 3/5)

Shaw, W., Q. N. Hong, G. Pransky and P. Loisel (2008). A literature review describing the role of return-to-work coordinators in trial programs and interventions designed to prevent workplace disability. *Journal of Occupational Rehabilitation* 18(1): 2-15. (CEBM score 2/5)

Tyerman, A. (2012). Vocational rehabilitation after traumatic brain injury: models and services. *Neurorehabilitation* 31(1): 51-62. (CEBM score 2/5)

Question 2.5 What is the evidence for community reintegration for adults with mild TBI?

Executive summary

One guideline of moderate/low quality and one systematic review of moderate quality partially addressed this question. Individuals with mild TBI report significantly lower functional status than controls. No evidence specific to mild TBI was found for other domains or measures of community integration such as quality of life, leisure and recreation activities, social relationships, productivity. The only information found on interventions to assist community reintegration, was regarding return to driving.

Evidence statement

Key question	Rating	Justification
Evidence base	A	Evidence is provided in only one systematic review and one guideline, both of moderate quality. Findings were underpinned by observational primary studies only.
Consistency	B	Primary studies were consistent regarding the impact of mild TBI on functional status.
Clinical impact	C	Although there is potentially substantial impact for interventions that assist community reintegration, there is currently a lack of evidence on this topic

Key guideline regarding community reintegration:

Only guideline contained recommendations related to this topic.

1. **Barbosa et al. Evaluation and management of mild TBI: An Eastern Association for the Surgery of Trauma practice management guideline. J Trauma Acute Care Surg. (2012) 73:S307-S314.**

AGREE II Score: 3/7

This US guideline updates an earlier 2001 edition. Recommendations for the management of mild TBI are aimed at clinicians (primarily medical staff) working in acute care.

Recommendations relevant to return to driving:

- *The ability to safely operate a motor vehicle may be impaired for a variable length of time in patients with MTBI. The timing of resumption of driving should be individualised.* (p.S308) (Preece et al 2011, 2010; Lundqvist et al 2007) (Level 3:

recommendation is supported by available data but adequate scientific evidence is lacking)

This guideline did not provide details of the underpinning primary.

Key systematic review regarding community reintegration:

5. Temkin N, Corrigan J, Dikmen S, Machamer J. (2009). Social Functioning After Traumatic Brain Injury. *Journal of Head Trauma Rehabilitation* 24(6): 460-467.

CEBM Score: 3/5

The objective of this review was 'to determine the relationship between adult-onset traumatic brain injury (TBI) and social functioning including employment, social relationships, independent living, recreation, functional status, and quality of life 6 months or longer after injury.' It provides evidence of social dysfunction experienced by individuals with TBI that can influence community reintegration.

Key findings from the review:

- There is evidence that mild TBI is associated with significantly increased dysfunction, on various measures of functional status. (Friedlad & Dawson 2001; Stulemeijer et al 2006)
- TBI also adversely affects leisure and recreation, social relationships ... quality of life, and independent living. Although there is a dose-response relationship between severity of injury and social outcomes, there is insufficient evidence to determine at what level of severity the adverse effects are demonstrated (p.460). (Heitger et al 2007)

The systematic review included the following studies in their review of this question:

Reference	Design	Results
Temkin et al (2009) (Functional status)		
Friedland & Dawson, 2001	Observational prospective cohort case comparison. <i>Country:</i> Canada <i>Sample:</i> n= 99 MVA patients (mild TBI n=64; no TBI n=35). Age 19-58 yrs. <i>Outcomes:</i> at 6 mths post-injury including psychosocial function on the Sickness Impact Profile (SIP), and the Reintegration to Normal Living Scale.	Mild TBI group reported significantly more dysfunction on the psychosocial summary of SIP than controls ($p=0.01$) No differences between groups on the Reintegration to Normal Living Scale.
Stulemeijer et al 2006	Observational <i>Country:</i> Netherlands <i>Sample:</i> Patients admitted to ED in level 1 trauma centre;	Mild TBI significantly older ($p < 0.01$), more were male ($p = 0.0001$) than controls.

	Mild TBI n= 299; Mild TBI +additional injuries n=89; Controls with ankle or wrist injuries n=261 <i>Methods:</i> retrospective cohort study Assessed at 6mths with SF-36 Physical & social functioning scales and SF-36 perceived health Change scale	Each SF-36 measure differed significantly between the groups (each $P = .0001$). The patients with mild TBI and additional injuries showed more dysfunction than did the patients with only mild TBI, and both showed more than did the non-head injured controls (each $P < .001$).
Heitger et al 2007	Observational <i>Sample:</i> Mild closed head injuries n=37; normal matched controls n=37 <i>Methods:</i> Prospective cohort study. Social functioning assessed at 6 & 12mths with Rivermead Head Injury Follow-up Questionnaire (RHIFQ) and SF-36	RHIFQ: not administered to controls; 27% mild closed head injured report mild or worse change on one or more activities at 6 mths, 23% report mild or worse change at 12 mths compared with before injury. SF-36: no significant differences between mild closed-head injured, controls on SF-36 at 6, 12 mths

Other earlier or lower quality evidence on the topic includes

Daggett, V., T. Bakas and B. Habermann (2009). A review of health-related quality of life in adult traumatic brain injury survivors in the context of combat veterans. *Journal of Neuroscience Nursing* 41(2): 59-71. (CEBM score 1/5)

McNamee, S., W. Walker, D. X. Cifu and P. H. Wehman (2009). Minimizing the effect of TBI-related physical sequelae on vocational return. *Journal of Rehabilitation Research & Development* 46(6): 893-908. (CEBM score 1/5)

Snell, D. L., L. J. Surgenor, E. J. Hay-Smith and R. J. Siegert (2009) A systematic review of psychological treatments for mild traumatic brain injury: An update on the evidence. *Journal of Clinical and Experimental Neuropsychology*, 31, 20-38. (CEBM score 3/5; NOTE this article is cited in SIGN 2012)

Question 2.6 What is the evidence for substance abuse in adults with mild TBI?

Executive summary

Four clinical guidelines mention substance abuse in relation to TBI and two of these guidelines focused on mild TBI. The quality of all four guidelines was high or excellent. Recommendations or key points within these documents consider pre-existing substance abuse issues with regards to differential diagnosis and the use of benzodiazepines. One guideline examined the influence of substance abuse on TBI outcomes but found inconclusive evidence (MAA NSW 2008). No evidence was found for substance abuse following mild TBI.

Evidence statement

Key question	Rating	Notes
Evidence base	A	Four high quality guidelines provided evidence for this question. Recommendations are largely underpinned by low level evidence.
Consistency	B	There is consistency across the guidelines regarding the need to differentiate mild TBI symptoms from substance abuse.
Clinical impact	B	Due to the high proportion of people with concurrent TBI and substance abuse, there is a large potential impact for the adult TBI population, in terms of avoiding misdiagnosis

Key guidelines regarding substance abuse

1. SIGN 2013 Brain injury rehabilitation in adults. Scottish Intercollegiate Guidelines Network

AGREE II Score: 7/7

This Scottish guideline aims to provide recommendations about the management of adults (16+yrs) with brain injuries of all severities. A subsection of the guideline was focused solely on issues regarding mild TBI. The search strategy was outlined in a separate document. Details of the evidence underpinning the recommendations are not detailed, but references accompany the key points.

Recommendations relevant to substance abuse:

- *Assessment and consideration of pre-existing health variables such as previous neurological disorders and substance misuse should be carried out for all patients with MTBI.* (p.11) (Thornhill et al 2000) (**Grade D recommendation:** Evidence from non-analytic studies, expert opinion or extrapolated from good cohort studies)

- *After acquired brain injury medically remediable causes of agitation (including drug/alcohol intoxication and withdrawal) should be excluded before therapies are started. Therapies should take account not just of the nature of the brain injury but the characteristics of the individual affected and the potential adverse effects of treatment (p.23) (Good Practice Point: Recommended best practice based on the clinical experience of the guideline development group.)*

2. Marshall et al (Ontario Neurotrauma Foundation). Clinical practice guidelines for mild traumatic brain injury and persistent symptoms. *Canadian Family Physician* 2012; 58(3): 257.

AGREE II Score: 6/7

Summary:

The guidelines have been developed for use with an adult population with mild TBI, and focus predominantly on assessment and management of persistent symptoms associated with mild TBI and, to a lesser degree, important aspects of early management. The details of the primary studies underpinning recommendations were not provided, but the level of evidence forming each recommendation was reported. No recommendations were made regarding the risk or management of substance abuse post-TBI.

Recommendations regarding substance abuse and differential diagnosis:

- *When assessing and managing persistent symptoms/post-concussive disorder, differential diagnoses, including substance abuse, polypharmacy and Substance Dependence Syndrome should be strongly considered (Grade C: expert opinion, panel consensus)*
- *All patients with persistent symptoms should be screened for mental health symptoms and disorders (including substance use disorders) using a tool such as the Rivermead Post Concussion Symptoms Questionnaire (Grade C: expert opinion, consensus of panel).*

Recommendation regarding pre-existing substance abuse and use of benzodiazepines:

- *Benzodiazepines may be useful in managing anxiety-related symptoms in the short-term, but is not recommended long term due to the risks surrounding pre-existing substance abuse issues, and dependency (Grade C: expert opinion, panel consensus)*

Rationale:

A number of differential diagnoses exist whose signs and symptoms can closely mirror those of mild TBI, including substance abuse, polypharmacy and Substance Dependence Syndrome. Pre-existing substance use disorder is a risk factor for a slowed recovery following mild TBI (Wood 2004). Pre-existing substance abuse disorders are common in people who have suffered a mild TBI and as a result, the use of benzodiazepines is often advised against due to the links with dependency (Graham and Cardon 2008).

ICD-10 definition for Substance Dependence Syndrome (p. 65)

A cluster of behavioural, cognitive, and physiological phenomena that develop after repeated substance use and that typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal state.
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The dependence syndrome may be present for a specific psychoactive substance (e.g., tobacco, alcohol, diazepam), for a class of substances (e.g., opioid drugs), or for a wider range of pharmacologically different psychoactive substances.

3. SIGN 2009 Early management of patients with a head injury. Scottish Intercollegiate Guidelines Network

AGREE II Score: 7/7

‘This guideline makes recommendations on the early management of patients with head injury, focusing on topics of importance throughout NHS Scotland.’ Recommendations are made for the management of adults and children.

Recommendations made regarding pre-existing substance abuse:

- *After traumatic brain injury remedial causes of agitation should be excluded before therapies are started* (p.28) (Lombard & Zafonte 2005) (Grade D: non-analytic studies, expert opinion or extrapolated from good case control or cohort studies).

Rationale:

Although behavioural disturbance (agitation, restlessness and aggression) frequently accompanies recent head injury, there may be other causes other than the direct effect of TBI such as drug/alcohol intoxication or drug/alcohol withdrawal. In Scotland ‘people with a head injury constitute a vulnerable group of patients with a high proportion of individuals from socially deprived areas, who are often involved in drug and alcohol misuse’ (p.35).

4. Motor Accidents Authority of NSW (MAA NSW). 2008 Guidelines for Mild Traumatic Brain Injury Following a Closed Head Injury.

AGREE II Score: 7/7

These Australian guidelines make recommendations for the early identification and management of adults with mild traumatic brain injury. They are aimed at clinicians working pre-hospital, emergency departments and general practice settings.

Recommendations or key points related to substance abuse:

- *Post-concussion symptoms & differential diagnosis: Clinicians should regularly assess and monitor somatic, cognitive and emotional symptoms (p.21), Grade A: Body of evidence can be trusted to guide practice; several studies with low risk of bias).*
- *There is inconsistent evidence on the influence of substance abuse problems on outcomes following mild TBI (p.39) (Iverson 2005a; Iverson & McCracken 1997; Meares et al 2008).*

Rationale:

The symptoms associated with substance abuse problems can often present as those associated with post-concussive symptoms/syndrome/disorder (Iverson, Lange et al 2005b), and this can result in misdiagnosis. Inconsistent evidence exists regarding the influence of substance abuse problems on outcome for sufferers of mild TBI. A number of the studies forming the above recommendations, relating to assessment and management of symptoms which may suggest post-concussive syndrome but in fact be attributable to substance abuse-related issues are outlined in the table below.

The guideline included the following studies in their review of this question:

Reference	Design	Results
MAA NSW (2008)		
Iverson, Lange et al (2005b)	Diagnostic study <i>Methods:</i> Comparison of patients with acute mild TBI with inpatients substance abuse program	Measures of concentration, memory and processing speed in patients with uncomplicated mild TBI unable to be differentiated from patients with substance abuse problems.
<i>Level of Evidence: IV</i>		
Iverson (2005a)	Review <i>Methods:</i> Review of outcomes in individuals with mild TBI including post-concussive syndrome, pathophysiology, and neuropsychological outcomes.	Recovery can be incomplete for trauma patients and can be complicated by pre-existing conditions including substance abuse, poor general health, comorbid problems, orthopaedic injuries, and psychiatric problems.
<i>Level of Evidence n/a</i>		

Question 2.7 What is the evidence for assessment and management of depression post-TBI?

Executive Summary

The evidence sourced for this question included seven clinical guidelines (four good quality, one moderate quality, two poor quality) and four good quality systematic reviews (not included in the guidelines). One of these systematic reviews (Fann et al 2009) provided detailed information on pharmacological and psychological management of post-TBI depression, which provided more contextual information regarding drug and psychological interventions than the general information presented in the guidelines.

There was general agreement in the literature that the emotional impact of brain injury can be profound and can manifest as mood changes and various mental health diagnoses, and a process of emotional adjustment to changed circumstances is required by many TBI sufferers. There is limited experimental literature on the management of depression post-TBI, and particularly about depression occurring post mTBI. There were commonly-expressed concerns that the same medications that are used effectively for individuals with depression, who have not had a TBI, may not be as effective for individuals with post-TBI depression, as they may produce adverse effects specific to the post-TBI population (such as seizures).

Evidence statement

Key question	Rating	Notes
Evidence base	A	Evidence is provided in seven systematic reviews and four guidelines, mostly moderate to good quality. Findings were underpinned by small numbers of primary experimental studies, and mostly observational primary studies.
Consistency	B	The evidence was generally consistent regarding the aetiology of depression occurring post TBI, and its effective management
Clinical impact	C	There was small-to-moderate evidence of impact of effectiveness of management strategies.

Compiled guideline recommendations

- Depression (and anxiety) are common post-mTBI symptoms (Harmon et al 2013; Marshall et al 2012; McCrory et al 2009).
- Post-concussion mental health symptoms and mood changes are generally benign and are likely to settle within three months (SIGN 2013, VA/DoD 2009).
- Depression occurring post mTBI may not directly result from the TBI, it may be a manifestation of previously undetected pre-existing conditions (Marshall et al 2012).
- There is no evidence that the pre-existence of mood disorders predispose athletes to concussion (Harmon et al 2013).
- Depressed mood following a concussion may reflect an underlying pathophysiology consistent with a limbic–frontal model of depression (NSW MAC2008).
- Depression post-TBI is amenable to treatment with a combination of psychological and pharmacological therapies (Golisz 2009).
- *Tricyclic antidepressants*: The use of tricyclic antidepressants is recommended as an option in the treatment of TBI-related depression. Specifically, amitriptyline (up to 300 mg/day) and desipramine (150–300 mg/day) have been reported to be effective for the treatment of depression after TBI. However, side effects may limit their utility in this population. Two reports indicate that TCAs may be less effective in patients with TBI than in non-brain injured populations (Warden et al 2006).
- *Serotonin Reuptake Inhibitors*: The use of sertraline (25–200 mg/day) is recommended as an option in the treatment of depression after TBI (Warden et al 2006).

Acronyms

TCAs: amitriptyline and desipramine

monoamine oxidase inhibitors (MAOIs: phenelzine and moclobemide)

selective serotonin reuptake inhibitors (SSRIs: fluoxetine, sertraline, and citalopram)

Dual action serotonin-norepinephrine reuptake inhibitor (SNRI: milnacipran)

Specific pharmacological management strategies from one comprehensive systematic review (Fann et al 2009)

Summary recommendations extracted from p2398: ‘Start with low doses of medications with slow titration toward a therapeutic response, being cognizant of adverse effects that may be more common in neurologically-injured patients (e.g., seizures, sedation, and cognitive dysfunction), and using depression measures that have been validated in the TBI population’.

- SSRIs are usually the first-line antidepressants for TBI patients. There is evidence for the use of sertraline (25–150mg=d) as a first-line option for treatment of post-TBI depression. Sertraline has the most dopaminergic effect, thus potentially having a positive impact on cognition.
- SNRIs may be another reasonable option in this population (citalopram (20–50 mg) being effective and well-tolerated).

- Evidence of possible reduced efficacy and a higher risk of side effects (e.g., seizures) for TCAs limit their use in this population.
- Traditional MAOIs are not recommended due to a lack of efficacy data and potentially serious side effects, particularly when dietary restrictions are not adhered to in a population with a high rate of cognitive difficulties. The safer MAO-A blocker meclizemide may be a viable second-line treatment for cognitively intact patients;
- ECT with possible adaptation to electrode placement and stimulus frequency acutely post-TBI, is a viable option for treatment-refractory patients, but cognitive side effects need to be monitored closely. Magnetic stimulation, biofeedback, and acupuncture remain experimental interventions at this time.

Key Guidelines relevant to depression

1. **Golisz K. 2009. Occupational therapy practice guidelines for adults with traumatic brain injury. American Occupational Therapy Assoc.**

AGREE II Score: 6/7

This US guideline is aimed at occupational therapists. Recommendations are made for the evaluation, acute care and rehabilitation of adults with TBI.

Key findings from this guideline relevant to depression following mild TBI:

The most relevant question in this guideline was ‘What is the evidence for the effect of interventions to address psychological, behavioural and social functions on the occupational performance of persons with TBI?’

‘Individuals with TBI and impaired coping skills can show signs of depression and poorer outcomes. When impaired coping skills are coupled with neurobehavioural symptoms such as impulsivity, the person with TBI may be at greater risk for alcohol and drug abuse. Depression is, however, often amenable to treatment with a combination of psychological and pharmacological therapies’ Quote taken directly from weblink

2. **Harmon, K. G., J. A. Drezner, M. Gammons, K. M. Guskiewicz, M. Halstead, S. A. Herring, J. S. Kutcher, A. Pana, M. Putukian and W. O. Roberts (2013). "American Medical Society for Sports Medicine position statement: concussion in sport." British Journal of Sports Medicine 47(1): 15-26.**

AGREE II Score: 2/7

This US position statement aims ‘to provide an evidence-based, best practises summary to assist physicians with the evaluation and management of sports concussion’ (p.15). Although primarily written for physicians, many recommendations are relevant to other sports personnel.

Key findings from this guideline relevant to depression following mild TBI:

This guideline indicates that ‘pre-injury mood disorders, learning disorders, attention deficit disorders and migraine headaches complicate diagnosis and management of a concussion. Symptoms of anxiety, depression or irritability occur in 17–46% of high-school and college athletes and affect the brain’s mood centres, including the hippocampus, amygdala and prefrontal brain regions which are also affected in concussion. There is no evidence that the pre-existence of mood disorders predispose athletes to concussion. However, when evaluating an athlete it is often difficult to determine which symptoms preceded the concussion, which have been caused by the concussion, and which symptoms are worsened after the concussion. An increased incidence of depression has been associated with a history of concussion among retired boxers and professional football players, however, these retrospective studies relied on a self-reported history and did not control for other factors that may cause depression. (p 19) (Level C: Consensus, expert opinion)

Reference numbers (42, 81-84) are noted in the text but are not provided in a reference list in the paper. The link provided in the paper to the references <http://bjism.bmjgroup.com> was broken.

- 3. Marshall, S., M. Bayley, S. McCullagh, D. Velikonja and L. Berrigan (2012). "Clinical practice guidelines for mild traumatic brain injury and persistent symptoms." Canadian Family Physician 58(3): 257.**

AGREE II Score: 6/7

The objective of this Canadian group was ‘to create a set of guidelines that can be used by healthcare professionals to implement evidence-based, best practice care of individuals who incur a mild traumatic brain injury and experience persistent symptoms’ (p.1). Recommendations are made for the management of adults ≥ 18 years. This good quality guideline mentions the development of depression as one of many persistent symptoms after mild TBI. It doesn’t deal with depression itself in detail, rather as one of a number of persistent post-mTBI symptoms. These are dealt with in more detail in Q2.10.

Background: The guideline suggests (Level C: expert consensus) that a significant proportion of individuals may develop persistent *mental health disorders*, post mTBI, with major depression and anxiety disorders observed most frequently. However it highlights the debate in the literature regarding causality, where persistent mental health symptoms after mild TBI may not necessarily be attributable directly to the TBI event, but may manifest from underlying and even precursor conditions which had not previously been detected. The guideline suggests that comorbid mental health disorders warrant treatment whenever symptoms impact on functional status or impede recovery as psychiatric and other post-concussive symptoms often negatively interact. Once identified, appropriate psychological and pharmacological treatment should be started. For more complex cases, consultation with a psychiatrist or a mental health team should be sought; although the initial steps of treatment should not be delayed. General measures can be initiated and symptoms such as

headaches, sleep disturbance, dizziness, and comorbid pain addressed, which may all be manifestations of depression. General measures include the provision of support, validation, and reassurance, as well as education regarding mTBI and positive expectations for recovery. Involvement of the family can be very helpful at this stage. Education about sleep hygiene and regular light exercise (e.g., walking or stationary cycling, depending on physical limitations) should be offered. The latter can improve mood, perceived fatigue and well-being, and counteract deconditioning.

Recommendations relevant to the management of depression (all level C: expert consensus):

- *Persons with mTBI and pre-injury mental health conditions, or any other health or contextual risk factors, should be considered for early referral to a multidisciplinary treatment clinic capable of managing post concussive symptoms because these factors have been associated with poorer outcomes (p.21).*
- *Given their prevalence and potential impact, all patients with persistent symptoms following an mTBI should be screened for mental health symptoms and disorders, including:*
 - Depressive disorders
 - Anxiety disorders, including PTSD
 - Irritability or other personality changes
 - Substance use disorders
 - Somatoform disorders
- Referral to a psychiatrist/mental health team (ideally with experience in treating individuals with persistent symptoms following mTBI, if available) should be obtained if:
 - the presentation is complex or severe
 - psychosis or bipolar disorder is suspected
 - the risk of suicide is judged significant
 - initial treatment is not effective within two months
 - failure or contraindication of medication strategies that are familiar
 - presence of risk factors known to potentially affect the course of recovery (see Table 7)
- While awaiting specialist referral, the initial steps of treatment should not be delayed, nor symptoms left unmanaged. General measures can be instituted and common symptoms such as headache, sleep disturbance, dizziness, and pain addressed in an ongoing manner.
- For medication trials, a 'start low and go slow' approach is recommended. Nonetheless, dose optimisation may be required before an antidepressant response is observed, or a trial of medication abandoned.
- A selective serotonin reuptake inhibitor is recommended as the first-line treatment for mood and anxiety syndromes after mTBI. However, in some cases the combination

of sedative, analgesic, or anti-migraine effects from a tricyclic (TCA) may be particularly desirable, although these agents may generally be considered second-line.

- Follow-up should occur at regular intervals: initially every 1 - 2 weeks, while increasing medication to monitor tolerability and efficacy. Thereafter, every 2-4 weeks may be sufficient.
- Cognitive behavioural therapy (CBT) has well-established efficacy for treatment of primary depression; as such it is appropriate in the treatment of mood symptoms following mTBI.
- Individuals with PTSD following mTBI should be offered a trial of trauma-focused CBT therapy.
- The need for concurrent pharmacotherapy should also be assessed, depending upon symptom severity, and the nature of comorbid difficulties (for example, major depression, prominent somatic symptoms, severe hyper-arousal and sleeplessness, which all may limit psychological treatment).

4. McCrory et al. 2009 SAJSM vol 21 No. 2 2009. Consensus Statement on Concussion in Sport – the 3rd International Conference on Concussion in Sport held in Zurich, November 2008

AGREE II Score: 4/7

This updated international consensus statement was 'developed for use by physicians, therapists, certified athletic trainers, health professionals, coaches and other people involved in the care of injured athletes, whether at the recreational, elite or professional level. Recommendations apply to adults, adolescents and children. The guideline is based on a literature review, however details of its methodology were not provided. No information was provided on the references underpinning this guideline (regarding component study designs, country of origin, sample, intervention or outcomes).

Key findings relevant to the management of depression:

- Mental health issues (such as depression) have been reported as a long-term consequence of traumatic brain injury including sports related concussion. Neuroimaging studies using fMRI suggest that a depressed mood following concussion may reflect an underlying pathophysiological abnormality consistent with a limbic-frontal model of depression (p.40). (Lima et al 2008; Fleminger 2008; Chen et al 2008; Bryant 2008; Vanderploeg et al 2007; Guskiewicz et al 2007; Kashluba et al 2006b; Iverson et al 2006; Chamelain et al 2006; Mooney et al 2005; Broshek & Freeman 2005; Pellman 2003)

5. **Motor Accidents Authority of NSW (MAA NSW). *Guidelines for Mild Traumatic Brain Injury following a Closed Head Injury*; 2008.**

AGREE II Score: 7/7

These Australian guidelines make recommendations for the early identification and management of adults with mild traumatic brain injury. They are aimed at clinicians working pre-hospital, emergency departments and general practice settings. The evidence base presented in this guideline is built on three primary studies.

Key findings relevant to the management of depression:

- Depressed mood following a concussion may reflect an underlying pathophysiology consistent with a limbic–frontal model of depression (Chen, J. et al 2008).
- Major depression may be associated with female gender, disability and cognitive impairment, comorbid with PTSD.(Levin, H.S. et al 2001).
- Depression may be prevalent in mTBI but it is unlikely to mediate deficits observed on measures of problem solving, visual motor speed, prose and figural recall. (Ruttan, L.A. et al 2003).

The guideline included the following studies in their review of depression:

Reference	Design	Results
NSW MAA (2008)		
Chen et al, 2008	Cross-sectional study <i>Country:</i> not stated <i>Sample:</i> Control comparison, male athletes only, non-consecutive sampling <i>Outcomes:</i> ongoing pathophysiological change	Depressed mood following a concussion may reflect an underlying pathophysiology consistent with a limbic–frontal model of depression
Levin et al 2001	Prospective cohort <i>Country:</i> not stated <i>Sample:</i> Control group general trauma patients n= 69 with MTBI n= 60, Control group n= 52. <i>Outcomes:</i> frequency and risk factors of major depressive disorder after mild to moderate TBI.	Female gender was related to major depression. Major depressions was associated with disability and cognitive impairment, comorbid with PTSD.
Ruttan & Heinrichs, 2003	Retrospective study <i>Country:</i> not stated <i>Sample:</i> Archival data (n= 122) obtained from clinical files of MTBI patients at two private clinics <i>Outcomes:</i> relationship between depression and performance on selected neurocognitive tests.	Depression may be prevalent in MTBI but it is unlikely to mediate deficits observed on measures of problem solving, visual motor speed, prose and figural recall..

6. SIGN 2013 Brain injury rehabilitation in adults. Scottish Intercollegiate Guidelines Network

AGREE II score: 7/7

This Scottish guideline aims to provide recommendations about the management of adults (16+ yrs) with brain injuries of all severities. Recommendations are made for post-acute assessment, interventions for cognitive, communicative, emotional, behavioural and physical rehabilitation, optimal models and settings of care.

There is inconclusive evidence regarding pharmacological management or psychotherapeutic treatment of depression after head injury and SIGN made no specific recommendation (Level C evidence strength). *General guidance is available in SIGN 114 on the non-pharmaceutical management of depression in adults.*

Background- Quoting directly from p25. 'The emotional impact of brain injury can be profound. For many people, a process of emotional adjustment to changed circumstances is required. Rates of disorders of emotion are high after brain injury. Although estimates of the prevalence of depression and anxiety have varied widely, findings have indicated that rates of mood disorder are typically considerably higher than in non-brain-injured populations and may occur at any stage after a head injury (Bombardier et al 2010).

For some people, low mood or anxiety are transient and part of the adjustment process. For others, symptoms may persist to the extent that they can be classified as a formal mood disorder. Levels of disability a year after a head injury are significantly related to psychological disorders rather than physical impairment (Whitnall et al 2006).

There is therefore a compelling need to treat depression and anxiety after brain injury. However, overall there is a limited body of evidence relating to the treatment of depression and anxiety following TBI. An important issue to consider in relation to TBI is injury severity. Although there is a broad range of severity represented in the evidence considered, the majority of studies include participants with mild-moderate injury. This limits the generalisability of the evidence and any recommendations, such that conclusions may be less applicable to people with more severe injury.

Another difficulty commonly reported is emotional lability. This is the tendency for a person's emotion to be quick to change and to be more extreme than usual and is associated with poor self regulation of emotion. No evidence was identified that specifically addressed the treatment of emotional lability in patients with ABI. The literature that is relevant to the treatment of mood disorder after brain injury is varied in the extent to which mood disorder is the primary focus of an intervention or a primary outcome measure. For example, mood management interventions are common components of comprehensive or holistic neuropsychological rehabilitation programmes. This presents a difficulty in relation to

reviewing the evidence as the precise relationship between specific components of a comprehensive programme and outcomes are difficult to determine. In some studies mood may not be the primary focus of an intervention programme, but may improve as part of a rehabilitation programme that is addressing the factors that are contributing to the development or maintenance of a mood disorder. For example, someone who is depressed as a result of inability to return to work may be supported through a vocational rehabilitation programme to gain some form of employment, with an associated improvement in mood. So while the therapeutic intervention was not a traditional treatment for mood disorder (pharmacological or psychotherapy), improvement in mood is a secondary outcome.

A survey of 666 people after TBI reported that 27% of the participants reported five or more symptoms of depression (Seel et al 2003). Another large single cohort study found higher rates in a sample of 559 participants followed for up to a year post injury. They found that 53.1% of their sample met criteria for depression at some point in the year after injury, almost eight times the rate in the general population who did not have a brain injury. At any one point in time around 20-30% of participants were depressed (Bombardier et al 2010).

Few details other than hierarchy / research design are given on component references.

7. Warden et al. Guidelines for the pharmacologic treatment of neurobehavioral sequelae of traumatic brain injury. *J Neurotrauma*; 2006; Volume 23(10): 1468-1501

AGREE II Score: 6/7

These US guidelines provide recommendations on the pharmacological treatment of neurobehavioural problems after TBI in three key areas: aggression, cognitive disorders, and affective disorders/anxiety/psychosis. Recommendations appear to apply to adults only.

Key findings & recommendations relevant to depression and mTBI:

- Depression, anxiety and psychotic disorders occur with greater rates in TBI sufferers than in the general community. There is no conclusive effective way of treating them.
- *Tricyclic Antidepressants (TCAs)*

The use of tricyclic antidepressants is recommended as an option in the treatment of TBI related depression. Specifically, amitriptyline (up to 300 mg/day) and desipramine (150–300 mg/day) have been reported to be effective for the treatment of depression after TBI (Dinan & Mobayed 1992; Saran 1985; Wroblewski et al 2006). However, side effects may limit their utility in this population, and TCAs may be less effective in patients with TBI than in non-brain injured populations.

- *Serotonin Reuptake Inhibitors:*

The use of sertraline (25–200 mg/day) is recommended as an option in the treatment of depression after TBI based upon an 87% response rate in one class III study (Fann et al 2006).

The key studies which informed the guidelines included:

Reference	Design	Results
Warden (2006)		
Dinan & Mobayed 1992	<i>Study:</i> Cohort study <i>Country:</i> NS <i>Sample:</i> 13 MTBI patients with depression matched with 13 depressed patients without TBI <i>Intervention:</i> Amitriptyline (up to 250mg) <i>Outcomes:</i> change in depression	Amitriptyline was effective in 4/13 TBI patients compared with 11/13 patients without TBI. . Depression following MTBI is relatively resistant to amitriptyline
Fann 2000	<i>Study:</i> Nonrandomised, single-blind, placebo <i>Sample:</i> 16 outpatients with mild TBI and depression <i>Intervention:</i> Sertraline (25–200 mg/day) <i>Outcome:</i> Hamilton Depression score	87% of patients responded and responders and 67% were classed as in remission.
Saran 1985	<i>Study:</i> Open label cohort study <i>Country:</i> NS <i>Sample:</i> 21 depressed patients (10 with history of MTBI) <i>Intervention:</i> Amitriptyline (200–300mg) <i>Outcomes:</i> Hamilton depression score	Significant improvement in non-TBI group, TBI group improved but scores were still in clinically depressed range. Depression following MTBI is relatively resistant to treatment with tricyclic antidepressants.
Wroblevski 1992	Randomised, placebo-controlled prospective cross-over study <i>Country:</i> NS <i>Sample:</i> 10 individuals with TBI and severe depression <i>Intervention:</i> Desipramine (150–300 mg/day) <i>Outcomes:</i> change in depression	Of the 7 patients who completed the study, 6 improved

1. Davidson, J. R., C. Crawford, J. A. Ives and W. B. Jonas (2011) "Homeopathic treatments in psychiatry: a systematic review of randomized placebo-controlled studies (Provisional abstract)." *Journal of Clinical Psychiatry* 72, 795-805.

CEBM Score: 4/5

This SR considered placebo-controlled RCTs of homeopathy for psychiatric conditions. The search was not specific to mTBI. No placebo controlled trials for depression were found.

2. Fann, J. R., T. Hart and K. G. Schomer (2009). "Treatment for depression after traumatic brain injury: A systematic review." *Journal of Neurotrauma* 26(12): 2383-2402.

CEBM Score: 4/5)

This relevant systematic review of 26 articles documents that there is a paucity of randomised controlled trials for the management of depression following TBI. Considering pharmacological management for depression, there were only 13 studies, of which three (Ashman et al 2009, Lee et al 2005, Saran 1985) provided the highest level evidence, and the remainder being case studies. Details on the three higher level hierarchy studies are provided here. There was a scant evidence base for psychotherapeutic interventions, with eight studies. Serotonergic antidepressants and cognitive behavioural interventions appear to have the best preliminary evidence for treating depression following TBI.

Quoting directly from p2398: 'current best evidence suggests starting with low doses of medications with slow titration toward a therapeutic response, being cognizant of adverse effects that may be more common in neurologically-injured patients (e.g., seizures, sedation, and cognitive dysfunction), and using depression measures that have been validated in the TBI population, such as the Patient Health Questionnaire-9 depression scale (PHQ-9) (Fann et al 2005).

Due to their favourable side-effect profile, SSRIs are usually the first-line **antidepressants** for TBI patients. There is evidence for the use of sertraline (25–150mg=d) for depression after TBI, and the Neurobehavioural Guidelines Working Group (Warden et al., 2006) recommends the use of sertraline as a first-line option for treatment of post-TBI depression. Among the SSRIs, sertraline has the most dopaminergic effect, thus potentially having a positive impact on cognition (Fann et al., 2001). Limited evidence also suggests that citalopram (20–50 mg) may be effective and well-tolerated. While more data are needed on the efficacy and tolerability of SNRIs in this population, data from a small study of milnacipran (not available in the U.S. or the U.K.) after TBI, and SNRI efficacy data from other populations suggesting higher rates of remission and documenting analgesic effects (Thase 2008) indicate that SNRIs may be another reasonable option in this population. Evidence of possible reduced efficacy

and a higher risk of side effects (e.g., seizures) for TCAs may limit their use in this population. Traditional MAOIs are not recommended due to a lack of efficacy data and potentially serious side effects, particularly when dietary restrictions are not adhered to in a population with a high rate of cognitive difficulties. The safer MAO-A blocker moclobemide may be a viable second-line treatment for cognitively intact patients; however, this medication is not available in the U.S. ECT, with possible adaptation to electrode placement and stimulus frequency acutely post-TBI, appears to be a viable option for treatment-refractory patients, but cognitive side effects need to be monitored closely.

Magnetic stimulation, biofeedback, and acupuncture remain experimental interventions at this time.

From the studies reviewed, there is insufficient evidence to support practice recommendations regarding any of the **psychotherapeutic or rehabilitation interventions** for depression following TBI. This is due not only to inconsistency in the quality of the research designs, but to the earlier noted difficulty in specifying “active ingredients” for depression within these complex treatments, many of which were deliberately multifaceted. To some extent this difficulty is inevitable in studies of complex interventions (Hart, 2009; Medical Research Council, 2000). With these caveats, it is still of interest to note correspondence between the treatments for TBI that reported improved effects on mood in the studies reviewed, and treatment models with demonstrated efficacy for depression in the general population. For example, CBT has shown efficacy comparable to that of antidepressant medication (DeRubeis et al., 2005). Dismantling designs that compare the cognitive components of CBT (e.g., examination and correction of distorted thinking) to its behavioural components (e.g., engaging in more reinforcing activities), have tended to show superiority for the latter (Dimidjian et al., 2006). According to one meta-analysis (Cuijpers et al., 2007a), therapies focusing on behavioural activation, even in simple forms such as activity scheduling, are at least as effective for depression as CBT. Holistic treatment programs for TBI that include activity scheduling and increasing positive interaction with the environment may therefore improve participants’ mood, along with functional outcomes and productivity. Other treatment components such as problem-solving and goal-setting training, that are commonly used in multidisciplinary programs for TBI including two reviewed here (Powell et al., 2002; Svendsen et al., 2004), are also mirrored by depression treatments with proven efficacy (e.g., problem-solving therapy and social problem-solving therapy [Cuijpers et al., 2007b]).

The review included the following studies in their review of this question:

Reference	Design	Results
Fann et al (2009)		
Pharmacology		
Ashman et al 2009	Study: double-blind RCT 10 weeks Country: NS	Among the 41 who completed the trial, HAM-D, Beck Anxiety Inventory, and Life-3 Quality of Life scores improved significantly from pre-to

	<p><i>Sample:</i> 52 subjects, 35.5% mild, 38.7% moderate, 25.8% severe TBI (mean 17.7±13.7 y post-TBI)</p> <p><i>Intervention:</i> sertraline (25–200mg/d)</p> <p><i>Outcomes:</i> HAM-D, Beck Anxiety Inventory, and Life-3 Quality of Life</p>	<p>post-treatment, but there were no group differences; 59% in the sertraline group and 32% in the placebo group had a 50% drop in baseline HAM-D score (p=0.15)</p>
Lee et al 2005	<p><i>Study:</i> double blind RCT</p> <p><i>Country:</i> NS</p> <p><i>Sample:</i> n 30 Mild to moderate TBI Within 1 y of TBI</p> <p><i>Intervention:</i> methylphenidate (20mg=d), sertraline (100mg=d), or placebo for 4wk</p> <p><i>Outcomes:</i> HAM-D scores, BDI</p>	<p>Both drugs improved HAM-D scores more than placebo; methylphenidate improved cognition, alertness, and PCS more than sertraline</p>
Saran 1985	<p><i>Study:</i> Open trial</p> <p><i>Country:</i> NS</p> <p><i>Sample:</i> 10 minor TBI versus 12 non-TBI controls LOC <20 min, Hospitalised <48 h Normal EEG and CT <1 yr post TBI</p> <p><i>Intervention:</i> amitriptyline (200–300mg/d, mean 175mg/d) for 4 wk; amitriptyline non-responders (n=10) had 3- to 7-day washout, then a trial of phenelzine (60–90mg/d, mean 65mg/d)</p> <p><i>Outcomes:</i> HAM-D SDS</p>	<p>No significant improvement (50% drop in HAM-D) observed with either drug among subjects with TBI, whereas all non-TBI controls improved on amitriptyline; controls also improved on SDS affective, psychomotor, and psychological subtests</p>
Psychological interventions		
Powell et al 2002	<p><i>Study:</i> RCT with masked outcome assessment</p> <p><i>Country:</i> NS</p> <p><i>Sample:</i> 110 At least moderate TBI (PTA>24 h or neurosurgical intervention); nearly all had PTA>1 wk; majority had PTA>1mo 3 mo–20 y post-TBI; median 1.37 y</p> <p><i>Intervention:</i> Experimental: individualised, goal-planning-oriented multi-disciplinary team treatment in home or community setting, 2–6 h=wk for mean of 28wk Control: information condition; 1 home visit with individualised resource booklet</p> <p><i>Outcomes:</i> BICRO-39, HADS</p>	<p>68% of experimental and 50% of control group improved on BICRO-39 psych subscale (p<0.05); 50% of experimental and 54% of control group improved on HADS (ns)</p>
McMillan 2002	<p><i>Study:</i> RCT with masked outcome assessment</p> <p><i>Country:</i> NS</p>	<p>No significant group differences</p>

	<p><i>Sample:</i> 145 TBI (any severity) with attention complaints or deficits on neuropsychological testing; mean PTA between 1 and 3 mo–12 mo post-TBI</p> <p><i>Intervention:</i> Experimental was attention control training: five 45-min sessions supervised practice using audio tape for 4 wk; daily independent practice with tape</p> <p>Control 1 was physical fitness training with same amount of therapist contact and independent practice; Control 2 was no treatment, no therapist contact</p> <p><i>Outcome:</i> HADS</p>	
Tiersky et al., 2005	<p><i>Study:</i> RCT with masked outcome assessment</p> <p><i>Country:</i> NS</p> <p><i>Sample:</i> 20 Mild=moderate TBI (GCS>8, LOC_4 h); 40% had no LOC At least 1 y post-TBI; mean 6 y</p> <p><i>Intervention:</i> Experimental was “comprehensive neuropsychological rehabilitation:” cognitive remediation (attention process training, memory notebook, problem solving) plus CBT; two 50-min individualised sessions, daily 30-min homework, 3 times per wk for 11 wk; Control was wait list attention control for 11 wks, with a total of 2 to 3 45-min contacts from primary investigator</p> <p><i>Outcome:</i> SCL-90-R depression scale</p>	<p>SCL-90-R GSI; experimental<control (p<.05) Depression scale on SCL-90-R, experimental<control (p<0.05)</p> <p>Authors noted that post-treatment means remained above “caseness” levels</p>

3. **Panayiotou, A., M. Jackson and S. F. Crowe (2010). "A meta-analytic review of the emotional symptoms associated with mild traumatic brain injury." *Journal of Clinical and Experimental Neuropsychology* 32(5): 463-473.**

CEBM Score: 4/5

Not directly relevant to the management of depression, this review investigated the prevalence of mild traumatic brain injury (mTBI) and enduring subjective complaints (post-concussion symptoms (PCS)), using meta-analytic techniques to integrate data on the emotional symptoms associated with mTBI. Small effect sizes were found across domains of depression, anxiety, coping, and psychosocial disability. Significance of effect size depended upon the weighting method employed. The results indicated that mTBI had a small to negligible effect on emotional symptom reporting. This has implications for the etiology of PCS, the delivery of therapeutic interventions, and medico-legal disputations. For depression, weighted by sample size (SD) from 11 studies 0.09 (0.07).

4. **Price, A., L. Rayner, E. Okon-Rocha, A. Evans, K. Valsraj, I. J. Higginson and M. Hotopf (2011). "Antidepressants for the treatment of depression in neurological disorders: A systematic review and meta-analysis of randomised controlled trials." *Journal of Neurology, Neurosurgery & Psychiatry* 82(8): 914-923.**

CEBM Score: 4/5

This relevant systematic review found that antidepressants are effective for the treatment of depression in patients with neurological disorders but the evidence for the efficacy of antidepressants in improving quality of life, and functional and cognitive outcomes is inconclusive.

This review contained only one RCT for TBI (Ashman et al 2009).

Reference	Design	Results
Ashman et al 2009	10 week RCT <i>Sample:</i> n= 41 (all with TBI) <i>Intervention:</i> Sertraline 25e200 mg (n=22); placebo (n=19) <i>Outcomes:</i> HRSD score	HRSD score and treatment response (50% reduction in HRSD score or HRSD score <10)

Question 2.8 What is the evidence for the aetiology, assessment and management of challenging behaviours following TBI?

Executive Summary

The evidence sourced for this question included seven clinical guidelines (five good quality, one moderate quality, one poor quality) and seven systematic reviews (4 good quality, 3 moderate quality). Six systematic reviews were not cited in the guidelines, and the Cochrane review by Fleminger et al (2006) was cited in SIGN (2013). However, it was retained as a separate reference for this question because it provided more contextual and additional information to that presented in the SIGN guideline.

Aetiology of challenging behaviours

Molloy et al (2011) suggest an increased risk of schizophrenia following TBI, with a larger effect in those with a genetic predisposition to psychosis.

There is a higher prevalence of TBI among incarcerated individuals than the general population, although a causal relationship is unable to be determined (Farrer 2011)

TBI sufferers often demonstrate a response-inhibition deficit which may lead to challenging behaviours (Dimoska-DiMarco et al 2011)

Effectiveness of occupational therapy for challenging behaviours

The occupational therapy interventions with positive effects related to management of aggression are Awareness training embedded in functional task performance (**A**), Group-based cognitive rehabilitation (**A**), Social skills training (**B**), Establishment of goals valued by the client, combined with compensatory training and environmental adaptation (**B**) (Golisz et al 2009)

Pharmacology for challenging behaviours

Beta-blockers have the best evidence for efficacy in managing challenging behaviours post TBI (Fleminger 2008, Warden et al 2006). The evidence is relatively old, and studies reported the efficacy of both propranolol (maximum dose 420–520 mg/day) and pindolol (maximum dose 40–100 mg/day) in the treatment of aggression in this population. (**B**)

Evidence statement

Key question	Rating	Notes
Evidence base	A	Evidence is provided in seven clinical guidelines and seven systematic reviews, of generally moderate to good quality. Findings were underpinned by RCTs and observational primary studies.
Consistency	B	Studies were generally consistent regarding the effectiveness of a range of strategies on the management of challenging behaviours

Clinical impact	C	Although there is potentially substantial impact for interventions that effectively address challenging behaviours, there is currently a lack of clear evidence on the best approach
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Key Guidelines relevant to challenging behaviours

1. **Golisz K. Occupational therapy practice guidelines for adults with traumatic brain injury. Bethesda (MD): American Occupational Therapy Association (AOTA); 2009. 258 p**

AGREE II Score: 6/7

This US guideline is aimed at occupational therapists. Recommendations are made for the evaluation, acute care and rehabilitation of adults with TBI. The most relevant question in this guideline was ‘What is the evidence for the **effect of interventions** to address **psychosocial, behavioural, and social functions** on the occupational performance of persons with TBI?’

This guideline provides text-based recommendations regarding occupational therapy engagement in acute and chronic rehabilitation phases of TBI. It defines agitation as ‘a state of aggression during posttraumatic amnesia in the absence of physical, medical, or psychiatric causes that may involve a component of akathisia (i.e., a constant sensation of inner restlessness), impulsivity, decreased frustration tolerance, disinhibition, and inappropriate social behaviour. This phase of recovery from TBI encompasses a spectrum of behaviours that fluctuate with changes in situational factors such as environmental stimulation, task demands, and time of day. Agitated behaviour may limit the client's engagement and progress in rehabilitative therapy; however, occupational therapists may engage clients in structured self-care activities, simple games and activities requiring use of cognitive skills, and simple gross motor activities to expend excess energy and deal with the restlessness or akathisia. Frequent breaks may be needed and treatment sessions may need to be shortened or varied to maintain the client's attention and lessen frustration and potential display of agitated behaviour. Although it is difficult to focus on restoring underlying impairments because the client's capacity for new learning is significantly limited by the posttraumatic amnesia that typically accompanies the period of agitation, the occupational therapist can structure tasks and the environment to regulate overstimulation, confusion, and frustration. The therapist also may provide environmental cues to help orient the client during periods of confusion (e.g., wall calendars, clocks, labelled photos of rehabilitative staff, signs indicating the client's room). As the agitation lessens, the cognitive and motor challenges presented to the client gradually can be increased to address underlying impairments.’ (quote directly from weblink)

The occupational therapy interventions related to management of aggression which have positive effects are:

- Awareness training embedded in functional task performance (Grade **A**: Strongly recommend that occupational therapy practitioners routinely provide the intervention to eligible clients. Good evidence found),

- Group-based cognitive rehabilitation (Grade **A: see above**),
- Social skills training (**Grade B: Recommend that occupational therapy practitioners routinely provide the intervention to eligible clients. At least fair evidence**),
- Establishment of goals valued by the client, combined with compensatory training and environmental adaptation (**Grade B : see above**).

Occupational therapy interventions for which there are no evidence-recommendations are:

- Goal management training (GMT) (Grade C: No recommendation is made for or against routine provision of the intervention by occupational therapy practitioners. The balance of the benefits and harm from the evidence, is too close to justify a general recommendation),
- Behavioural approach using positive reinforcement (**Grade C: see above**),
- Attention processing therapy (**Grade C: see above**),
- Prospective memory training (**Grade I: Insufficient evidence to recommend for or against routinely providing the intervention**),
- Treating the client within environments that are graded to reduce structure and to increase distractions equal to real-life situations (**Grade I : see above**),
- Positive talk training (**Grade I : see above**),
- Self-determination model to address integrated self-awareness (**Grade I : see above**),
- Intervention focused on perception of emotion on psychosocial functioning (**Grade I : see above**),
- Role-playing to achieve friendships and intimate relationships (**Grade I : see above**),
- Cognitive groups to achieve return to employment (**Grade I : see above**).

2. Marshall et al (Ontario Neurotrauma Foundation). Clinical practice guidelines for mild traumatic brain injury and persistent symptoms. *Canadian Family Physician* 2012; 58(3): 257.

AGREE II Score: 3/7

The objective of this Canadian group was ‘to create a set of guidelines that can be used by healthcare professionals to implement evidence-based, best practice care of individuals who incur a mild traumatic brain injury and experience persistent symptoms’ (p.1). Recommendations are made for the management of adults ≥ 18 years. This guideline does not deal directly with challenging behaviours, however it considers features of post-concussion syndrome as including

- irritability, depression, anxiety, emotional lability;
- subjective concentration, memory, or intellectual difficulties without neuropsychological evidence of marked impairment;
- irritability, depression, anxiety, emotional lability; insomnia;

- reduced alcohol tolerance; and
- preoccupation with above symptoms and fear of brain damage with hypochondriacal concern and adoption of sick role (p.258).

The most appropriate recommendations relating to challenging behaviours (not-specifically stated) was:

Assessment:

‘Given their prevalence and potential effects, all patients with persistent symptoms following MTBI should be screened for mental health symptoms and disorders, including the following:

- depressive disorders;
- anxiety disorders, including PTSD;
- irritability or other personality changes;
- substance use disorders; and
- somatoform disorders.

The use of self-report questionnaires can aid in the assessment and monitoring of common mental health disorders, such as the depression module of the PHQ-9 (Appendix 8.2) and the PTSD Checklist–Civilian Version (Appendix 8.3). Screen for other symptoms using the Rivermead Post-Concussion Symptoms Questionnaire’ (p 263) (Grade C: Expert opinion, panel consensus).

Management:

‘Those with MTBI and pre-injury mental health conditions, or any other health or contextual risk factors, should be considered for early referral to a multidisciplinary treatment clinic capable of managing post-concussive symptoms, because these factors have been associated with poorer outcomes. (p.263) (Grade C: Expert opinion, panel consensus).

3. McCrory et al. Consensus Statement on Concussion in Sport – the 3rd International Conference on Concussion in Sport held in Zurich, Nov 2008. *SAJSM*; 2009;vol 21 No. 2.

AGREE II Score: 4/7

This updated international consensus statement was ‘developed for use by physicians, therapists, certified athletic trainers, health professionals, coaches and other people involved in the care of injured athletes, whether at the recreational, elite or professional level. Recommendations apply to adults, adolescents and children. The guideline is based on a literature review, however details of its methodology are not provided. This guideline does not deal directly with challenging behaviours, however it addresses violence in sport: ‘The competitive/aggressive nature of sport which makes it fun to play and watch should not be discouraged. However, sporting organisations should be encouraged to address violence that

may increase concussion risk (Reece & Sege 2000, Shaw 2004). Fair play and respect should be supported as key elements of sport (p.41).

No information was provided on the study methods, sampling, interventions or outcomes of the cited references.

4. Motor Accidents Authority of NSW (MAA NSW). *Guidelines for Mild Traumatic Brain Injury following a Closed Head Injury*; 2008.

AGREE II Score: 7/7

These Australian guidelines make recommendations for the early identification and management of adults with mild traumatic brain injury. They are aimed at clinicians working pre-hospital, emergency departments and general practice settings. This guideline does not provide recommendations specific to challenging behaviours

5. SIGN 2009 Early management of patients with a head injury. Scottish Intercollegiate Guidelines Network

AGREE II Score: 7/7

This guideline makes recommendations on the early management of patients with head injury, focusing on topics of importance throughout NHS Scotland. Recommendations are made for the management of adults and children. This guideline notes only that 'irritability' (easily annoyed) is one of many post-concussion symptoms in children and adults (p 59). This guideline cites the use of the SCAT card (Sports Concussion Assessment Tool) (McCrory et al 2005) for comprehensive post-concussion symptom assessment. As this information was provided in an appendix and was not part of the data extracted for the guideline, there is no information on study design, sample etc.

6. SIGN 2013 Brain injury rehabilitation in adults. Scottish Intercollegiate Guidelines Network

AGREE II Score: 7/7

This Scottish guideline aims to provide recommendations about the management of adults (16+yrs) with brain injuries of all severities. Recommendations are made for post-acute assessment, interventions for cognitive, communicative, emotional, behavioural and physical rehabilitation, optimal models and settings of care. This guideline provided directly-relevant information on Challenging Behaviours during rehabilitation of adults post TBI. There was little detail on the country of origin or outcome measures of the component studies for each intervention.

'Challenging behaviours are frequent neuro-behavioural sequelae of a brain injury. Behavioural disturbance may include inappropriate vocalisation, intolerance of medical

management or equipment, directed or diffuse aggressive, disinhibited or sexualised behaviour. Agitated patients may resist direct care, be disruptive or pose a physical risk to themselves, family and staff. Reported prevalence ranges from 10-96% of patients with estimates varying according to the exact definition used and the setting studied. All studies recognise that it is a major burden on care givers. Agitated behaviour in brain injured patients may not be the result of their brain injury in itself but reflect other factors including:

- 'premorbid personality
- drug/alcohol intoxication and withdrawal
- mood disorder, phobic anxiety and emotional adjustment
- pain
- urinary retention
- constipation' (p.23)

Summarising information on interventions presented on p.23-24

Contingency management and positive behaviour interventions: The guideline reported on two systematic reviews of 98 total studies (only three RCTs) dealing with contingency management procedures (CMP), positive behaviour interventions (PBI) or a combination of both (Cattalani et al 2010; Ylvisaker et al 2007). There was no conclusive evidence for any management approach.

Social and neurobehavioural rehabilitation: One systematic review reporting on one study of patients with ABI of mixed causes (n=76) with persisting aggressive behaviour, and who could not live independently (Geurtsen et al 2010). The intervention was a programme of social and neurobehavioural rehabilitation for approximately 14 months. The intervention was supported by non-professional therapy care assistants (no information on the intensity of input and make up of the rehabilitation team). Positive outcomes maintained at 2.8 years follow-up were reported in improved living arrangements, hours of care required and employment.

Cognitive behavioural therapy: One systematic review of three observational studies of CBT intervention to treat challenging behaviours (Cattalani et al 2010) found no substantive treatment effect.

Music Therapy: One systematic review of music therapy following acquired brain injury found one study (n=22) which demonstrated a positive effect of listening to live and taped music on levels of agitation (Bovend'Eerd et al 2010). The review authors concluded insufficient evidence for the use of music therapy for improving agitation following ABI.

Pharmacological interventions: One systematic review of six RCTs evaluated the effectiveness of propranolol and pindolol, methylphenidate or amantadine (Fleminger et al 2006) Some evidence was found that beta-blockers propranolol and pindolol can reduce aggressive behaviour. The studies used very large doses, although no significant adverse effects were reported and clinical experience suggests this is not usually a problem. There

were no included trials reporting the use of antipsychotics or anticonvulsants. The review found insufficient evidence for clear recommendations regarding the use of these treatments, although betablockers had the best evidence for efficacy.

Recommendations:

- *Propranolol and pindolol may be considered as a first line treatment option for moderate levels of agitation/aggression. (Grade B: Body of evidence including high quality SRs of cohort studies, or evidence extrapolated from high quality SRs of RCTs)*
- *After acquired brain injury medically remediable causes of agitation should be excluded before therapies are started. Therapies should take account not just of the nature of the brain injury but the characteristics of the individual affected and the potential adverse effects of treatment (Practice Point: expert opinion of guideline development group).*
- *The family and key members of the affected individual's social network should be provided with education about appropriate management of behaviour and emotion. (Practice Point: expert opinion of guideline development group).*
- *Drug treatments should be individually tailored and commenced in very low doses. The patient's progress should be monitored with surveillance for possible adverse effects. (Practice Point: expert opinion of guideline development group).*

7. Warden et al Guidelines for the pharmacologic treatment of neurobehavioural sequelae of traumatic brain injury. J Neurotrauma; 2006; Volume 23(10): 1468-1501

AGREE II Score: 6/7

These US guidelines provide recommendations on the pharmacological treatment of neurobehavioural problems after TBI in three key areas: aggression, cognitive disorders, and affective disorders/anxiety/psychosis. Recommendations appear to apply to adults only. This high quality guideline provides comprehensive overview of challenging behaviours and the pharmacological management of this, by addressing the question: *"What is the evidence to direct pharmacologic management of aggressive disorders following traumatic brain injury?"*

Taken directly from p.1470 'Explosive and violent behaviour has long been associated with focal brain lesions, as well as with diffuse damage to the central nervous system (CNS) (Elliott 1992). Agitation that occurs during the acute stages of recovery from brain injury can endanger the safety of patients and their caregivers. Agitation may be predictive of longer length of stay and decreased cognition (Bogner et al 2001). Subsequently, low frustration tolerance and explosive behaviour may develop that can be set off by minimal provocation or occur without warning. Aggression and irritability are major causes of disability to individuals with brain injury and sources of stress to their families. These episodes range in severity from irritability to outbursts that result in damage to property or assaults on others. Aggressive and agitated behaviours may be treated in a variety of settings, ranging from the acute brain injury

unit in a general hospital, to a “neurobehavioural” unit in a rehabilitation facility, to outpatient environments including the home setting. However, in severe cases, affected individuals cannot remain in the community or with their families, and require care in long-term psychiatric or neurobehavioural facilities.

In a survey of all skilled nursing facilities in Connecticut, 45% of facilities had individuals with a primary diagnosis of TBI who met the definition of agitation (Wolf et al 1996). It has been reported that during the acute recovery period, 35–96% of individuals with brain injury exhibit agitated behaviour (Levin & Grossman 1978; Roa et al 1985). After the acute recovery phase, irritability or bad temper is common, particularly following moderate to severe injury. In the two prospective studies of the occurrence of aggression, agitation, or restlessness that have been monitored by an objective rating instrument, the Overt Aggression Scale, 11–34% of TBI patients were found to be agitated or have aggressive behaviour (Brooke et al 1992; Tateno et al 2003).

In studies that have followed patients from 1 to 15 years after injury, irritability has occurred in up to 71%, and agitation in up to 67% (Roa et al 1985; McKinlay et al 1981; Brooks et al 1986; Oddy et al 1985; Thomsen 1984; van Zomeren et al 1985; McMillan & Glucksman 1986; Schoenhuber & Gentilini 1988; Dickmen 1986; Rutherford 1977; Levin et al 1979; Carlsson et al 1987). In one study, increased irritability has also been linked to the number of traumatic brain injuries and the presence of loss of consciousness (Carlsson et al 1987). Although there is no medication that is approved by the FDA specifically for the treatment of aggression, medications are widely used in the management of patients with acute or chronic aggression. The reported effectiveness of these medications is highly variable, as are the reported rationales for their prescription.

Recommendations (supported by experimental design studies) (p.1492):

- **Beta blockers:** *Beta blockers are recommended as a guideline for the treatment of aggression after TBI. Studies reported the efficacy of both propranolol (maximum dose 420–520 mg/day) and pindolol (maximum dose 40–100 mg/day) in the treatment of aggression in this population. This recommendation is supported by nine studies of which four are experimental (Brooke 1992, Greendyke 1986a,b, Greendyke 1989).*
- **Methylphenidate:** *Methylphenidate (dose) is recommended as an option for the treatment of aggression. Although evidence was mixed, the study with the greatest number of participants showed a positive effect. There is clear evidence that methylphenidate may be safely used without concern of adverse effects on cognition. However, it should be noted that one case report reported increased agitation with methylphenidate (Mooney 1993, Speech 1993).*
- **Cranial Electrical Stimulation (CES):** *CES is recommended at the option level for the treatment of aggression following TBI. Although the supporting class II study was well*

constructed, there were no additional supporting studies to support the recommendation of CES at the guideline level (Smith 1994)

- **Homeopathy:** Homeopathic therapy is recommended at the option level for the treatment of self-reported irritability and anger following mild TBI. This recommendation is based on a single randomised controlled trial. Although there were no other studies to offer supporting evidence, the strength of the design of this single study merits its consideration at the option level (Chapman 1993)
- **Serotonin Reuptake Inhibitors:** SSRIs are recommended at the option level for the treatment of aggression following TBI. Specifically, sertraline (25–200 mg/day) and paroxetine (20 mg/day) have been reported to be effective for the treatment of aggression in this population (Fann 2004, Kant 1998)
- **Valproate:** The use of valproate (750–2250 mg/day to reach therapeutic serum level) is recommended at the option level based on two case reports and one case series describing marked improvement in aggressive or assaultive behaviour (no high level studies)
- **Lithium:** The use of lithium is recommended at the option level for the treatment of aggression after TBI. Behavioural response was achieved at therapeutic levels ranging from 0.4 to 1.4 mEq/L. Although the majority of patients reported showed a positive response to treatment with lithium, it should be noted that one patient showed no response and two patients experienced increased irritability/agitation. Neurotoxicity and increased EEG spiking have also been reported. Thus, lithium should be used only with careful monitoring of cognitive status (no high level studies)
- **Tricyclic Antidepressants:** The use of the tricyclic antidepressants is recommended as an option for the treatment of aggression after TBI. Specifically, amitriptyline and desipramine (both up to 150 mg/day) have been reported to be effective for the treatment of aggression in this population (Jackson 1989)
- **Buspirone:** Although there are no experimental studies to support this, the use of buspirone (10–60 mg/day) is recommended as an option for the treatment of aggression after TBI. There are several case series and case reports of the use of buspirone as single agent therapy and as a component of a multi-drug regimen. The majority of patients reported showed good response to treatment. However, it should be noted that several patients had to be discontinued secondary to side effects. There is insufficient evidence in TBI populations to support or refute the use of other commonly used medications for aggression. However, evidence of efficacy in other patient populations is also a useful source of treatment options in TBI in many cases.
- **Carbamazepine, Estrogen, Amantadine, Pyritinol:** There is insufficient evidence in TBI populations to support or refute the use of other commonly used medications for aggression. However, evidence of efficacy in other patient populations is also a useful source of treatment options in TBI in many cases.

The following table reports the experimental studies associated with each drug:

Reference	Design	Results
Warden (2006)		
Betablockers		
Brooke 1982	<i>Study design:</i> High quality RCT <i>Country:</i> NA <i>Sample:</i> 21 individuals with severe TBI and agitation <i>Intervention:</i> Propranolol (up to 420 mg/day) <i>Outcomes:</i> severity and intensity of agitation on OAS	Patients experienced a significant reduction in intensity of the most severe episode per week ($p \leq 0.05$), but no significant change in frequency of episodes
Greendyke 1986a	<i>Study design:</i> Double blind, placebo controlled cross-over trial <i>Country:</i> NA <i>Sample:</i> 9 patients (4 with TBI) <i>Intervention:</i> Propranolol (520 mg/day) <i>Outcomes:</i> Assaults	There were significantly fewer assaults and attempted assaults during propranolol treatment ($p \leq 0.05$). Although the specific efficacy in TBI patients alone in this sample is difficult to determine, the significant overall group response warrants consideration.
Greendyke 1986b	<i>Study design:</i> Double blind, placebo controlled cross-over trial <i>Country:</i> NA <i>Sample:</i> 11 individuals with violent behaviour (5 with TBI) <i>Intervention:</i> Pindolol (60–100 mg/day) <i>Outcomes:</i> severity and intensity of agitation on OAS	Statistically significant improvement in number of assaultive episodes, and other aggression ratings ($p \leq 0.05$). The need for supplemental medication was reduced significantly. Optimal response was at 40–60 mg/day
Greendyke 1989	<i>Study design:</i> Double blind, placebo controlled cross-over trial <i>Country:</i> NA <i>Sample:</i> 13 individuals with violent behaviour (3 with TBI) <i>Intervention:</i> Pindolol (20 mg) <i>Outcomes:</i> decreased aggressive behaviour	There was a trend toward decreased aggressive behaviour for the group as a whole, but this did not reach statistical significance. For the three individuals with TBI, clinical improvement was rated as “marked,” “moderate,” and “none.”
Methylphenidate		
Mooney 1993	<i>Study design:</i> Randomised single-blind placebo-controlled trial <i>Sample:</i> 38 men with moderate to severe TBI. <i>Intervention:</i> 6-week trial of methylphenidate (30 mg/day) <i>Outcome:</i> measures of anger—KAS Belligerance, State-Trait Anger Scale (State), and POMS anger/hostility factor	Measures of anger significantly improved however because study entry was not based on relevant anger symptoms, one cannot determine whether anger is a significant clinical problem for this group of individuals.

Speech 1993	<p><i>Study design:</i> Randomised double-blind, placebo-controlled crossover study</p> <p><i>Sample:</i> 12 patients with moderate to severe TBI and cognition deficits</p> <p><i>Intervention:</i> methylphenidate (0.3 mg/kg BID)</p> <p><i>Outcome:</i> Katz scale</p>	This study was not designed to intervene in aggression. However the belligerence variable on Katz scale showed no significant adverse reaction to methylphenidate
Cranial electrical stimulation		
Smith 1993	<p><i>Study design:</i> Level II (design NS)</p> <p><i>Sample:</i> 10 chronic severe TBI</p> <p><i>Intervention:</i> CES (1.5 mA output, alternating current, pulsing 100 times/sec)</p> <p><i>Outcome:</i> POMS</p>	Statistically significant decreases in Tension/Anxiety and Anger/Hostility, as well as all other subscores on the POMS.
Homeopathy		
Chapman 1993	<p><i>Study design:</i> Randomised controlled trial</p> <p><i>Sample:</i> 61 outpatients with mild TBI</p> <p><i>Intervention:</i> Homeopathy (intervention not described)</p> <p><i>Outcome:</i> 34 item scale (NS)</p>	Inconclusive
Serotonin reuptake inhibitors		
Fann 2004	<p><i>Study design:</i> Single-blind study</p> <p><i>Sample:</i> 16 mild TBI patients with major depression</p> <p><i>Intervention:</i> sertraline (25–150 mg for 8 weeks)</p> <p><i>Outcome:</i> Brief Anger and Aggression Questionnaire and Head Injury Symptom Checklist</p>	Scores of irritability and loss of temper dropped significantly
Kant, 1998	<p><i>Study design:</i> Open label trial</p> <p><i>Sample:</i> 13 mixed severity TBI patients with complaints of irritability and/or aggression.</p> <p><i>Intervention:</i> 8-week trial of sertraline (50–200 mg)</p> <p><i>Outcome:</i> OAS-M</p>	Significant improvements from baseline were found in aggression and irritability scores
Tricyclic antidepressants		
Jackson, 1989	<p><i>Study design:</i> Open randomised trial</p> <p><i>Sample:</i> 15 (5 to amitriptyline, 10 to desipramine) for patients with severe agitation 2–10 months post-TBI.</p>	67% responded with ≥50% decrease in number of agitated episodes over 7 days

Intervention: amitriptyline or desipramine (both up to 150 mg / day)
Outcome: agitated episodes

Carbamazepine

Azouvi, 1999

Study design: Open trial

Sample: 10 patients with aggressive behaviour following severe TBI

Intervention: carbamazepine (400–800 mg/day)

Outcome: NS

Significant improvement on measures of agitation and disinhibited behaviour after treatment

Key systematic reviews relevant to challenging behaviours

1. Davidson, J. R., C. Crawford, J. A. Ives and W. B. Jonas (2011) "Homeopathic treatments in psychiatry: a systematic review of randomized placebo-controlled studies (Provisional abstract)." *Journal of Clinical Psychiatry* 72, 795-805.

CEBM Score: 4/5

This SR considered placebo-controlled RCTs of homeopathy for psychiatric conditions. There was only one relevant study to mTBI (Chapman et al 1999) and none specifically to challenging behaviours). The Chapman study suggested some benefit of homeopathy (albeit with an unreported outcome measure).

The systematic review included the following study in their review of this question:

Reference	Design	Results
Davidson et al (2011)		
Chapman 1993	<i>Study design:</i> Randomised controlled trial <i>Sample:</i> 61 outpatients with mild TBI <i>Intervention:</i> Homeopathy (intervention not described) <i>Outcome:</i> 34 item scale (NS)	Inconclusive

2. Dimoska-Di Marco, A., S. McDonald, M. Kelly, R. Tate and S. Johnstone (2011). "A meta-analysis of response inhibition and Stroop interference control deficits in adults with traumatic brain injury (TBI)." *Journal of Clinical and Experimental Neuropsychology* 33(4): 471-485.

CEBM Score: 3/5

This systematic review was not specific to mTBI in adults, however it indicates an association between TBI and a response-inhibition deficit which may lead to challenging behaviours. *Quoting p471:* 'The prominent clinical feature of behavioural impulsivity following traumatic

brain injury (TBI) suggests impairment of frontal inhibitory control processes. This meta-analysis consolidates the recent surge in studies across two forms of “effortful” inhibition, employing well-defined paradigms of response inhibition ($N = 20$; i.e., go/no-go, sustained attention to response, stop-signal, Conners’ continuous performance tasks) and response interference control ($N = 21$, i.e., Stroop color word tasks). Across 41 effect sizes involving 989 adults with mild to severe TBI, and 969 controls, the overall effect of TBI on reduced inhibitory control was small to moderate ($d = 0.3$) and significant. The effect was larger in studies measuring response inhibition performance ($d = 0.5$), while Stroop interference control yielded a non-significant overall effect size ($d = 0.05$). Further analysis of the latter finding revealed a large effect size when Stroop task studies used the outcome measure “total time on task” ($d = 1.4$), but not “RT per trial” or “number of stimuli” ($d = -0.8$ and -0.9). Response speed in these tasks was impaired to a large degree ($d = 0.96$). Together these findings support a response inhibition deficit following TBI but suggest factors other than interference control, such as poor processing speed, fatigue, and under-arousal, may underlie poor performance in Stroop tasks’.

3. **Farrer, T. J. and D. W. Hedges (2011). "Prevalence of traumatic brain injury in incarcerated groups compared to the general population: a meta-analysis." *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 35(2): 390-394.**

CEBM Score: 3/5

This review does not deal with the management of challenging behaviours following TBI *per se*, rather it suggests a causal association between TBI and incarceration. The directionality and causality of association is not clear. *P* 390. ‘Traumatic brain injury can cause numerous behavioural abnormalities including aggression, violence, impulsivity, and apathy, factors that can be associated with criminal behaviour and incarceration. To better characterise the association between traumatic brain injury and incarceration, we pooled reported frequencies of lifetime traumatic brain injury of any severity among incarcerated samples and compared the pooled frequency to estimates of the lifetime prevalence of traumatic brain injury in the general population. We found a significantly higher prevalence of traumatic brain injury in the incarcerated groups compared to the general population. As such, there appears to be an association between traumatic brain injury and incarceration.’

Conclusion (p394): ‘The prevalence of a history of TBI in incarcerated groups primarily based on studies done in the United States was higher than estimates of the prevalence of TBI in the general population. Although several alternative explanations such as confounding and reverse causation exist, our findings suggest that TBI may be associated with incarceration.’

4. **Fazel, S., J. Philipson, L. Gardiner, R. Merritt and M. Grann (2009). "Neurological disorders and violence: a systematic review and meta-analysis with a focus on epilepsy and traumatic brain injury." *Journal of Neurology* 256(10): 1591-1602.**

CEBM Score: 4/5

This review identified nine studies which compared the risk of violence in epilepsy (3 studies) or traumatic brain injury (6 studies), with unaffected controls. Considering only the studies on TBI, quoting from p1591: 'For traumatic brain injury, the odds ratio (of violence occurring with TBI compared to controls) was 1.66 (95% CI 1.12–2.31). Comorbid psychopathology was associated with violence.' From p1595: 'violence risk assessment of patients could consider the assessment and treatment of comorbid psychopathology, the presence of which appears to increase the risk. Improved understanding of the relationship between neurological disorders and violence should inform neuropsychiatric, public health, and public policy interventions to reduce violence'.

5. **Fleminger, S., R. J. Greenwood and D. L. Oliver (2006). "Pharmacological management for agitation and aggression in people with acquired brain injury." Cochrane Database of Systematic Reviews(4): CD003299.**

CEBM Score: 5/5

This Cochrane review was relevant to this question. It found six RCTs (four of which evaluated the use of beta-blockers, propranolol and pindolol, one which evaluated the central nervous system stimulant, methylphenidate and one which evaluated amantadine (a drug used for Parkinsonian conditions). The best evidence of effectiveness in the management of agitation and/or aggression following ABI was for beta-blockers (from 2 studies). Brooke et al 1992b (21 subjects [11 in treatment arm]) found propranolol to be effective early after injury [p5 'The average maximum intensity of agitated episodes was significantly reduced by propranolol'], and Greendyke 1986a (cross-over study with 9 subjects [8 with TBI]) found it to be effective late after injury [p6 'In the seven patients who responded to propranolol, the number of assaults fell from 88 during the eleven-week placebo to 52 during the eleven-week active period']. These study findings have not been replicated, used large doses, and did not use a global outcome measure or long-term follow-up. Comparing early agitation to late aggression, there was no evidence for a differential drug response. Firm evidence that carbamazepine or valproate is effective in the management of agitation and/or aggression following ABI is lacking.

The systematic review included the following studies in their review of this question:

Reference	Design	Results
Fleminger et al (2006)		
Betablockers		
Brooke 1982	<i>Study design:</i> High quality RCT <i>Country:</i> NA <i>Sample:</i> 21 individuals with severe TBI and agitation <i>Intervention:</i> Propranolol (up to 420 mg/day) <i>Outcomes:</i> severity and intensity of agitation on OAS	Patients experienced a significant reduction in intensity of the most severe episode per week ($p \leq 0.05$), but no significant change in frequency of episodes
Greendyke 1986a	<i>Study design:</i> Double blind, placebo controlled cross-over trial <i>Country:</i> NA <i>Sample:</i> 9 patients (4 with TBI) <i>Intervention:</i> Propranolol (520 mg/day) <i>Outcomes:</i> Assaults	There were significantly fewer assaults and attempted assaults during propranolol treatment ($p \leq 0.05$). Although the specific efficacy in TBI patients alone in this sample is difficult to determine, the significant overall group response warrants consideration.
Greendyke 1986b	<i>Study design:</i> Double blind, placebo controlled cross-over trial <i>Country:</i> NA <i>Sample:</i> 11 individuals with violent behaviour (5 with TBI) <i>Intervention:</i> Pindolol (60–100 mg/day) <i>Outcomes:</i> severity and intensity of agitation on OAS	Statistically significant improvement in number of assaultive episodes, and other aggression ratings ($p \leq 0.05$). The need for supplemental medication was reduced significantly. Optimal response was at 40–60 mg/day
Greendyke 1989	<i>Study design:</i> Double blind, placebo controlled cross-over trial <i>Country:</i> NA <i>Sample:</i> 13 individuals with violent behaviour (3 with TBI) <i>Intervention:</i> Pindolol (20 mg) <i>Outcomes:</i> decreased aggressive behaviour	There was a trend toward decreased aggressive behaviour for the group as a whole, but this did not reach statistical significance. For the three individuals with TBI, clinical improvement was rated as “marked,” “moderate,” and “none.”
Methylphenidate		
Mooney 1993	<i>Study design:</i> Randomised single-blind placebo-controlled trial <i>Sample:</i> 38 men with moderate to severe TBI. <i>Intervention:</i> 6-week trial of methylphenidate (30 mg/day) <i>Outcome:</i> measures of anger—KAS Belligerence, State-Trait Anger Scale (State), and POMS anger/hostility factor	Measures of anger significantly improved however because study entry was not based on relevant anger symptoms, one cannot determine whether anger is a significant clinical problem for this group of individuals.

Reference	Design	Results
Amantidine		
Schneider et al 1999	<p><i>Study design:</i> Double-blind, randomised, placebo-controlled cross-over trial</p> <p><i>Sample:</i> 10 patients. Mean age 31 years (range 19-56) closed head injury, no prior psychiatric history</p> <p><i>Intervention:</i> 6-week trial of amantadine 100mg/day increased to maximum of 300mg/day.</p> <p><i>Outcome:</i> Neurobehavioural rating scale b) Standard neuropsychological tests. Grouped into sub-tests measuring: attention, orientation, memory, executive/flexibility and behaviour. These tests were administered at pre-trial and at 2-week intervals</p>	No significant difference was found in any of the outcome measures between patients receiving amantadine and placebo.

6. Molloy, C., R. M. Conroy, D. R. Cotter and M. Cannon (2011). "Is traumatic brain injury a risk factor for schizophrenia? A meta-analysis of case-controlled population-based studies." *Schizophrenia Bulletin* 37(6): 1104-1110.

CEBM Score: 3/5

This review considered schizophrenia associated with TBI. This review was moderately relevant to the question. *Quoting from the abstract on p1104:* 'Traumatic brain injury (TBI) is known to lead to a range of adverse psychiatric sequelae but the question of whether TBI is a risk factor for psychosis and, in particular, schizophrenia remains unclear. Studies examining this issue have yielded conflicting results. We carried out a systematic review of the literature on TBI and psychosis in order to identify all population-based controlled studies which provide estimates of risk for schizophrenia following TBI. Odds ratios (ORs) were combined using random effects meta-analysis. Our literature search yielded 172 studies which were considered to be potentially relevant. From these, we identified 9 studies that could provide estimates of risk in the form of ORs. The pooled analysis revealed a significant association between TBI and schizophrenia (OR 1.65; 95% CI 1.17–2.32), with significant heterogeneity between the studies. Estimates from the family studies (OR 2.8; 95% CI 1.76–4.47) were higher than those from the cohort/nested case-control studies (OR 1.42; 95% CI 1.02–1.97) by a factor of almost 2. There did not appear to be a dose-response relationship between severity of head injury and subsequent risk of schizophrenia. This meta-analysis supports an increased risk of schizophrenia following TBI, with a larger effect in those with a genetic predisposition to psychosis. Further epidemiological and neuroscientific studies to elucidate the mechanisms underlying this association are warranted'.

7. **Panayiotou, A., M. Jackson and S. F. Crowe (2010). "A meta-analytic review of the emotional symptoms associated with mild traumatic brain injury." *Journal of Clinical and Experimental Neuropsychology* 32(5): 463-473.**

CEBM Score: 4/5

There is a high prevalence of mild traumatic brain injury (mTBI) and enduring subjective complaints known as post-concussion symptoms (PCS). This study used meta-analytic techniques to 'integrate the available information on the emotional symptoms associated with mTBI. Small effect sizes were found across all domains (depression, anxiety, coping, and psychosocial disability); and significance depended upon the weighting method employed. The results indicate that mTBI had a small to negligible effect on emotional symptom reporting (coping 0.10 (0.30), psychosocial disability 0.33 (0.19)). This has implications for the etiology of PCS, the delivery of therapeutic interventions, and medico-legal disputations' (p.463).

Question 2.9 What is the evidence for the long term impacts and needs of a person with mild TBI?

Executive summary

Six relevant guidelines (two excellent, two high, and two moderate) and four relevant systematic reviews (3 moderate and one high quality) informed this section.

Symptoms of MTBI usually resolve within a few weeks to three months in the majority of patients. While it is common for individuals to suffer from TBI related symptoms at 3 months (approximately 25%), only 10–15% will continue to experience any symptoms at 6–12 months post injury, and only a minority of these patients will have persistent symptoms that stretch beyond 12 months. In such cases the determinants of disability appear to be personal and social factors and not related to the brain injury. Recall bias is a common problem and pre-existing symptoms may be subsequently misattributed to MTBI. Litigation has been consistently identified as a poor prognostic factor, as CAT scans and conventional MRI generally don't show evidence of structural brain abnormalities in this group of MTBI patients. However there is some recent evidence that this may not be the case with recent reviews of advances in the biomechanical modelling of MTBI in humans and animals concluding that MTBI leads to functional neuronal disruption, and at times structural damage. There is some newer evidence to suggest the intentional exaggeration of symptoms is rare, and the potential factors that can contribute to long term effects of MTBI are many.

Evidence statement

Key question	Rating	Notes
Evidence base	A	Evidence is provided in Information is based on data from cohort, case control and systematic review studies of mixed quality.
Consistency	C	There is disagreement over whether there are long term sequelae in mild TBI
Clinical impact	D	Slight or restrictive clinical impact, as there is no agreement on the existence of long term effects of mild TBI.

Key guidelines regarding long term impact and needs

1. **Motor Accidents Authority of NSW (MAA NSW). 2008 Guidelines for Mild Traumatic Brain Injury Following a Closed Head Injury.**

AGREE II score: 7/7

These Australian guidelines make recommendations for the early identification and management of adults with mild traumatic brain injury. They are aimed at clinicians working pre-hospital, emergency departments and general practice settings.

The evidence informing these guidelines was only included by the guideline committee if it was deemed to be of good or reasonable quality, were systematic reviews (not appraised by the committee) or guidelines (appraised with the AGREE tool). Recommendations were graded according to the NHMRC Matrix system (grade and description are included in parenthesis after the recommendation).

Recommendations relevant to long term impact and needs:

Recommendations specific to emergency response teams, emergency department clinicians and general practice:

- *MTBI following closed head injury should be diagnosed early as it will positively impact on health outcomes for patients.* (p.19) (Grade A- Body of evidence can be trusted to guide practice)
 - The guideline stresses the importance of prompt diagnosis and acute management of MTBI to reduce the impact of potential chronic sequelae.
 - Six references were cited for this recommendation (Borg et al. 2004; Chambers et al. 1996; Kraus et al. 2005; Miller & Mittenberg 1998; Savola & Hillbom 2003; von Holst & Cassidy 2004); study details were not provided for Savola & Hillbom 2003.
- *Clinicians should assess and monitor somatic, cognitive and emotional post concussion symptoms* (p.21). (Grade A- Body of evidence can be trusted to guide practice)
 - Study details were provided for three (Iverson et al. 2005b; Meares et al. 2008 & 2006) of the citations, the other three (Bryant et al. 2008; Iverson & McCracken 1997; Kashluba et al. 2006a) had no details supplied.
- *Clinicians should use the Rivermead Post Concussion Symptoms Questionnaire as part of their assessment and monitoring post concussive symptoms.* (p.21). (Consensus-based on the limited evidence available and the clinical expertise of the working party)
 - While post concussion symptoms are commonly reported by patients, there is difficulty in attributing these to MTBI as the symptoms are not exclusive. A standardised assessment should be used to carefully study the history and progression of the symptoms observed or reported by the patient.
- *Where there are prolonged and significant complaints after MTBI, other contributing or confounding factors should be investigated* (p.37). (Grade A- Body of evidence can be trusted to guide practice).
 - Approximately 10-15% of MTBI patients will have symptoms >12 months post injury. With Jakola et al (2007) reporting post concussive symptoms up to 7 years after injury.

- This recommendation is supported by three studies (Jakola et al. 2007; Stalnacke 2007; Truner-Stokes et al. 2006).

Recommendations specific to general practice:

- *The clinician should consider that an individual who has sustained a MTBI is likely to experience reduced cognitive functioning post injury which may resolve in a few days or continue for months before resolving, including problems with recall of material, speed of information processing, concentration and attention (p.23). (Grade A- Body of evidence can be trusted to guide practice).*
 - The GP is well positioned to manage, support and guide the recovery process after MTBI.
 - Supporting evidence was not supplied
- *When there are ongoing cognitive difficulties, the GP should consider specialised cognitive assessment. A neuropsychological assessment is appropriate at least three months post injury when:*
 - *there are persistent symptoms of traumatic brain injury, the diagnosis is in doubt or clinical questions have not been answered*
 - *other etiological clinical conditions (anxiety, depression, etc) have been identified and considered. (p.25) (Grade B - Body of evidence can be trusted to guide practice in most situations).*
 - five studies informed this recommendation (Borg et al. 2004; Carroll et al. 2004b; EAST Practice Management Guidelines Work Group 2001; MAA NSW 2003; NZGG 2006).
- *The GP should consider referral of a patient with MTBI to specialist services when symptoms and concerns persist. For example, referral to a local brain injury rehabilitation service/occupational therapist for memory strategies or referral to a psychologist or psychiatrist for mental health concerns (p.30). (Consensus- based on the limited evidence available and the clinical expertise of the working party).*

The guideline included the following studies in their review of this question:

Reference	Design	Results
MAA NSW 2008		
Borg et al. 2004	Systematic review Country: NR Studies: n= 73 Objective: Systematic review of diagnostic studies for MTBI.	Estimated prevalence of intracranial CT scan abnormalities is 5% for those with GCS 15, and 30% higher for those with GCS 13. About 1% of individuals with MTBI require neurosurgical intervention. Skull fracture is a risk factor for intracranial lesions – little or no validity of cognitive testing and other diagnostic tools for MTBI

Borg et al. 2004	Systematic review <i>Country:</i> NR <i>Studies:</i> n= 16 <i>Objective:</i> Evidence of nonsurgical interventions and for economic costs for individuals with MTBI.	Early educational information can reduce long-term complaints. Indirect costs are probably higher than direct costs. CT scanning compared to overnight hospitalisation indicates reduced costs; however, clinical outcome were comparable.
Carroll et al. 2004b	Systematic review <i>Country:</i> NR <i>Studies:</i> n= 66 <i>Objective:</i> Systematic review of the literature on the prognosis of MTBI.	The majority of patients recover within three to 12 months. When symptoms persist, compensation/litigation is a factor; however, there is little consistent evidence for other predictors.
Chambers et al. 1996	Prospective cohort <i>Country:</i> NR <i>Sample:</i> NR <i>Objective:</i> MTBI incidence following low risk trauma patients – psychosocial dysfunction.	MTBI occurs more often among patients with blunt trauma than is commonly appreciated. Current measures in ED to screen for MTBI are inadequate. F/up protocols may be appropriate. <i>GL notes on quality:</i> Comparison not control group used – attempt to use premorbid baseline status as a type of control. 100% f/up at one month, 66% f/up at two months. Only frequencies of PCS reported.
EAST Practice Management Guidelines Work Group 2001	Systematic review / Guideline <i>Country:</i> NR <i>Studies:</i> NR <i>Objective:</i> Develop guidelines and recommendations to facilitate a safe uniform and cost-effective approach to the understanding and management of MTBI.	Level II evidence that patients with MTBI perform less well on complicated tasks requiring attention and rapid response times compared with controls – resolves by one month post-injury in the majority.
Jakola et al. 2007	Inception cohort study <i>Country:</i> NR <i>Sample:</i> Individuals with MTBI n = 89; controls, n = 89 <i>Objective:</i> Study the prevalence of PCS five to seven years after MTBI and whether the symptoms are more than the normal population.	Patients with MTBI reported significantly more PCS than controls.
Kraus et al. 2005	Inception cohort study <i>Country:</i> NR <i>Sample:</i> MTBI, n = 235; comparison cohort, n= 235.	Headaches, dizziness, vision difficulties, memory or learning problems, alcohol intolerance occur more often in individuals with MTBI six

	<p><i>Objective:</i> Evaluation of symptoms, medical services use, social and employment concerns in individuals with MTBI six months after injury.</p>	<p>months after injury compared with controls</p> <p><i>GL notes on quality:</i> Confounding factors identified, no blinding, recruited in ED.</p>
Miller et al. 1998	<p>Literature review</p> <p><i>Country:</i> NR</p> <p><i>Studies:</i> NR</p> <p><i>Objective:</i> Review of the literature related to prevention and treatment of persistent PCS.</p>	<p>Although symptoms may initially have a neurologic basis, the syndrome persists because of psychological factors – brief psychological treatment appears to significantly reduce the severity and duration of symptoms. Potentially useful diagnostic tools are discussed.</p>
Motor Accidents Authority 2003	<p>Systematic review / Guideline</p> <p><i>Country:</i> NR</p> <p><i>Studies:</i> NR</p> <p><i>Objective:</i> Guidelines for the management of anxiety following motor vehicle accidents</p>	<p>Recommendations for diagnostic criteria for anxiety and PTSD, indicators or poor prognosis, assessment, pharmacotherapy, interventions and treatment.</p>
NZ Guidelines Group 2006	<p>Systematic review / Guideline</p> <p><i>Country:</i> NR</p> <p><i>Studies:</i> NR</p> <p><i>Objective:</i> Clinical guidelines for patients and clinicians on the early management of head injury.</p>	<p>Recommendations on prehospital, hospital, surgical, and home management.</p>
von Holst et al. 2004	<p><i>Country:</i> NR</p> <p><i>Sample:</i> NR</p> <p><i>Objective:</i> Description of mandate WHO task force on MTBI.</p>	<p>Description of the background and methodology for the systematic review. Definition of MTBI and description of the synthesis of evidence.</p>
Iverson et al. 2005b	<p>Review</p> <p><i>Country:</i> NR</p> <p><i>Studies:</i> NR</p> <p><i>Objective:</i> Review of outcomes in individuals with MTBI including PCS, pathophysiology, and neuropsychological outcomes.</p>	<p>Recovery can be incomplete for trauma patients and can be complicated by pre-existing conditions including substance abuse, poor general health, comorbid problems, orthopaedic injuries, and psychiatric problems.</p>
Meares et al. 2006	<p>Prospective cohort study</p> <p><i>Country:</i> NR</p> <p><i>Sample:</i> NR</p> <p><i>Objective:</i> Investigate the relationship between PCS, neuropsychological and psychological outcome.</p>	<p>Psychological factors are present much earlier than has previously been considered in the development of PCS.</p> <p><i>GL notes on quality:</i> Implied inception cohort was studied.</p>

Meares et al. 2008	<p>Inception cohort study</p> <p><i>Country:</i> NR</p> <p><i>Sample:</i> NR</p> <p><i>Objective:</i> Examine predictors of acute outcome of MTBI by investigating the relationship between preinjury psychiatric disorder, demographic factors, injury-related characteristics, neuropsychological and psychological variables, and acute PCS</p>	<p>High rate of acute PCS in patients with MTBI and patients with nonbrain injured trauma. The use of the term PCS may be misleading as it incorrectly suggests that the basis of PCS is brain injury.</p> <p><i>GL notes on quality:</i> Use of comparison group to assist in identifying confounders – included in analysis. 92% f/up, blinding not reported, all patients measured in standard way.</p>
Stalnacke 2007	<p>Retrospective cohort study</p> <p><i>Country:</i> NR</p> <p><i>Sample:</i> Individuals with MTBI, n = 163</p> <p><i>Objective:</i> Investigate the relationship between psychosocial functioning, (community integration, life satisfaction, social support) and symptoms in individuals with MTBI three years after trauma.</p>	<p>Large proportion of individuals with MTBI experience psychosocial difficulties with low levels of life satisfaction – preinjury factors cannot be ruled out.</p>
Turner-Stokes et al. 2006	<p>Cochrane systematic review</p> <p><i>Country:</i> NR</p> <p><i>Studies:</i> 10</p> <p><i>Objective:</i> To assess the effects of multidisciplinary rehabilitation following ABI in adults, to explore approaches that are effective in different settings and the outcomes that are affected.</p>	<p>Strong evidence that most patients with MTBI make a good recovery with provision of appropriate information without additional specific intervention.</p>

2. SIGN 2013 Brain injury rehabilitation in adults. Scottish Intercollegiate Guidelines Network

AGREE II Score: 7/7

This Scottish guideline aims to provide recommendations about the management of adults (16+yrs) with brain injuries of all severities. Recommendations are made for post-acute assessment, interventions for cognitive, communicative, emotional, behavioural and physical rehabilitation, optimal models and settings of care.

Recommendations relevant to long term impact and needs:

- *Consideration should be given to alternate diagnostic explanations for ongoing symptoms post MTBI, eg coincidental mood disorder or thyroid disease, and further investigation may be warranted. Other secondary pathologies which are consequences of the original injury but not associated with, or dependent on, any brain injury may occur in the context of a head injury, eg benign positional paroxysmal vertigo, and should be treated accordingly (p.10) (good practice point- Recommended best practice based on the clinical experience of the guideline development group)*
- *As PTSD and other psychiatric disorders may contribute to the overall burden of symptoms in some individuals following MTBI, particularly where problems persist for more than three months, mental state should be routinely examined with an emphasis on symptoms of phobic avoidance, traumatic re-experiencing phenomena (eg flashbacks and nightmares) and low mood (p.11) (Grade C- A body of evidence including well conducted case control or cohort studies with low risk of confounding or bias).*
 - *In adults, evidence consistently suggests there are no MTBI-attributable cognitive deficits beyond three months after injury. However, those with complicated MTBI, ie with associated skull fractures or intracranial lesions may have significant cognitive deficits (p.10) (Carroll et al. 2004b; Frencham et al. 1995).*
 - Details of the included studies have not been provided in this guideline

3. Marshall et al (Ontario Neurotrauma Foundation). Clinical practice guidelines for mild traumatic brain injury and persistent symptoms. *Canadian Family Physician* 2012; 58(3): 257.

AGREE II Score: 6/7

The objective of this Canadian group was ‘to create a set of guidelines that can be used by healthcare professionals to implement evidence-based, best practice care of individuals who incur a mild traumatic brain injury and experience persistent symptoms’ (p.1) Recommendations are made for the management of adults ≥ 18 years.

Recommendations relevant to long term impact and needs:

- *Medical assessment should include screening for health and contextual factors (flags) to identify patients for increased risk of persistent symptoms and urgent complications, such as subdural hematoma. Refer to Table 7 outlining health factors and contextual risk factors (flags) (p.12) (Grade B- At least one cohort comparison, case studies or other type of experimental study).*
- *Because a variety of factors, including biopsychosocial, contextual, and temporal preinjury, injury and postinjury factors can impact on the outcomes of patients who have sustained mTBI, clinicians should consider these factors when planning and implementing the management of patients (Grade A- At least one randomised controlled trial, meta-analysis, or systematic review)*

- Pre-injury or current psychiatric difficulties, such as depression or anxiety, may place a patient at increased risk for persistence of symptoms. Referral to specialist services and/or multidisciplinary treatment may be required early on for these patients (Ghaffar, McCullagh, Ouchterlony & Feinstein, 2006).

4. Vos et al. Mild traumatic brain injury. *European Journal of Neurology* 2012, 19: 191–198

AGREE II Score: 5/7

This European guideline provides recommendations for the acute management of adults and children presenting with mild TBI. It is aimed primarily at medical management.

Recommendations relevant to long term impact and needs:

- *It has been shown that regular specialised outpatient follow- up visits are effective in reducing social morbidity and the severity of symptoms after MTBI (Wade et al. 1998). In a large randomised controlled trial, patients with a PTA shorter than 7 days who received specialist intervention had significantly less social disability and fewer postconcussion symptoms 6 months after injury than those who did not receive the service (Wade et al. 1998). (The guideline has classified this evidence as Evidence Level II, however, no explanation of this classification is supplied.)*

5. Veterans Affairs & Dept Defence (2009) Management of concussion/ mild traumatic brain injury. Clinical practice guideline. *J Rehab Res & Dev* 46(6): CP1-68.

AGREE II Score: 4/7

This US guideline applies to adult patients (18yrs+) who are diagnosed with concussion/mTBI and complain of symptoms related to the injury and who are treated in VA/DoD clinical settings for these symptoms at least 7 days after the initial head injury. The guideline is relevant to all healthcare professionals providing or directing treatment services (p.ii).

There is debate about the incidence of developing persistent symptoms after concussion, largely due to the lack of an accepted case definition for persistent symptoms and the fact that none of the symptoms are specific to concussion. There is no consensus on a case definition for persistent symptoms attributed to concussion/mTBI and no consensus on the time course when acute symptoms should be considered persistent (p.12).

Recommendations relevant to long term impact and needs:

- *Persons who complain about somatic, cognitive or behavioural difficulties after concussion/mTBI should be assessed and treated symptomatically regardless of the elapsed time from injury.*

- *The assessment of an individual with persistent concussion/mTBI related symptoms should be directed to the specific nature of the symptoms regardless of their etiology.*
- *The management of an individual who has sustained a documented concussion/mTBI and has persistent physical, cognitive and behavioural symptoms after one month should not differ based on the specific underlying etiology of their symptoms (i.e., concussion vs. pain, concussion vs. stress disorder).*
- *In communication with patients and the public, this guideline recommends using the term concussion or history of mild-TBI and to refrain from using the term 'brain damage' (p.12).*

In patients with persistent post-concussive symptoms that have been refractory to treatment, consideration should be given to other factors including behavioural health (e.g., stress disorders, mood disorders, and substance use disorders), psychosocial support, and compensation/litigation (p.30).

- *Follow-up after the initial interventions is recommended in all patients with concussion/mTBI to determine patient status and the course of treatment.*
- *Evaluation of patients with persistent symptoms following concussion/mTBI should include assessment for dangerousness to self or others.*
- *In assessment of patients with persistent symptoms, focus should be given to other factors including psychiatric, psychosocial support, and compensation/litigation issues and a comprehensive psychosocial evaluation should be obtained, to include:*
 - *Support systems (e.g., family, vocational)*
 - *Mental health history for pre-morbid conditions which may impact current care*
 - *Co-occurring conditions (e.g., chronic pain, mood disorders, stress disorder, personality disorder)*
 - *Substance use disorder (e.g., alcohol, prescription misuse, illicit drugs, caffeine)*
 - *Secondary gain issues (e.g., compensation, litigation)*
 - *Unemployment or/change in job status*
 - *Other issues (e.g., financial/housing/legal). (p.30)*

6. **McCrory et al. Consensus Statement on Concussion in Sport – the 3rd International Conference on Concussion in Sport held in Zurich, Nov 2008. *SAJSM*; 2009;vol 21 No. 2.**

AGREE II Score: 4/7

This updated international consensus statement was 'developed for use by physicians, therapists, certified athletic trainers, health professionals, coaches and other people involved in the care of injured athletes, whether at the recreational, elite or professional level. Recommendations apply to adults, adolescents and children. The guideline is based on a literature review, however details of its methodology are not provided.

- Epidemiological studies have suggested an association between repeated sports concussions during a career and late life cognitive impairment. Similarly, case reports have noted anecdotal cases where neuro-pathological evidence of chronic traumatic encephalopathy was observed in retired football players. (108-112) Panel discussion was held and no consensus was reached on the significance of such observations at this stage. Clinicians need to be mindful of the potential for long-term problems in the management of all athletes.
- Pharmacological therapy in sports concussion may be applied for the management of specific prolonged symptoms (e.g. sleep disturbance, anxiety etc.).

Key systematic reviews regarding long term impact and needs:

1. **Molloy, C., R. M. Conroy, D. R. Cotter and M. Cannon (2011). "Is traumatic brain injury a risk factor for schizophrenia? A meta-analysis of case-controlled population-based studies." *Schizophrenia Bulletin* 37(6): 1104-1110.**

CEBM Score: 3/5

This systematic review and meta-analysis examined the (then) current population based literature on whether TBI is a risk factor for the development of schizophrenia. They identified 9 studies of which three were not reported on here as one focused solely on severe TBI and two focussed on paediatric populations. Of the 8 studied reported on here, 2 studies were nested case-control studies (Nielsen et al. 2002; Harrison et al. 2006), 2 were cohort studies (Fann et al. 2004; Chen et al. 2011) and 2 were family studies (Abdel Malik et al. 2003; Malaspina et al. 2001). Quality of the primary studies was not assessed by the authors of the systematic review. Results were mixed across the primary studies.

Key finding from the review:

- The meta-analysis indicates TBI predisposes individuals to schizophrenia, and the risk appears to increase again when family history of schizophrenia is present, suggesting

an epigenetic connection. This connection should be investigated further, particularly in families with psychosis and TBI clusters.

- The authors found it difficult to tell if a TBI contributes to psychosis, or if behaviours associated with the psychosis contribute to incidence of TBI. Furthermore, they found no dose response relationship between severity of TBI and development of psychosis.

The systematic review included the following studies in their review of this question:

Reference	Design	Results
Risk Estimate for Psychosis Following TBI; OR (95% CI)		
Molloy et al. (2011)		
Nielsen et al. 2002	Nested case control <i>Country:</i> Denmark <i>Sample size:</i> 91168 <i>Methods:</i> Record linkage sample from Hospital admission register ICD-8 Admission for head injury (concussion and severe head injury) and Danish National Patient Register —diagnosis of schizophrenia	0.94 (0.84–1.05) Mild TBI. No increased risk of psychosis following mild TBI.
Harrison et al. 2006	Nested case control <i>Country:</i> Sweden <i>Sample size:</i> 47454 <i>Methods:</i> Record linkage sample of a cohort of Swedish men and women born between January 1973 and December 1980 from Swedish Inpatient Discharge Register (hospital admission for concussion and skull or intracranial injuries) and Swedish Inpatient Discharge Register (schizophrenia and nonaffective psychosis)	1.10 (0.82–1.47) No increased risk of psychosis following mild TBI.
Fann et al. 2004	Cohort <i>Country:</i> <i>Sample size:</i> 939 <i>Methods:</i> Adult Health Maintenance Organisation—Group Health Co-operative of Puget Sound (members 15 years or older) from Computerised databases on all inpatient and outpatient visits and diagnoses (mild, moderate and severe TBIa) and Computerised databases on all inpatient and outpatient visits and diagnoses.	1.1 (0.4–3.1) mild TBI No increased risk of psychosis following mild TBI.

Chen et al. 2011	Cohort <i>Country:</i> Taiwan <i>Sample size:</i> 20970 <i>Methods:</i> Record linkage of 2 datasets in Taiwan (adults aged >18) TBI Registry (Head and Spinal Cord Injury Research Group of the Taiwan Neurosurgical Society) 2001–2002 Taiwan National Health Insurance Research Dataset (2001–2002)	1.99 (1.28–3.08) Following mild TBI, these participants had a twofold risk of developing some form of psychosis.
Malaspina et al. 2001	Family study <i>Country:</i> NR <i>Sample size:</i> 1931 <i>Methods:</i> National Institute of Mental Genetics Initiative for Schizophrenia and Bipolar Disorders using Patient report- Diagnostic Interview for Genetic Studies question on Head Injurya (combined mild, moderate, and severe) and Diagnostic Interview for Genetic Studies	3.32 (1.77–6.22) Following mild TBI, these participants had over three times the risk of developing some form of psychosis.
Abdel Malik et al. 2003	Family study <i>Country:</i> NR <i>Sample size:</i> 169 <i>Methods:</i> Ongoing study of familial schizophrenia-genetic linkage of narrowly defined schizophrenia From SCID-1 and supplemented by collateral information from family and medical records, and consesus rating Structured Clinical Interview for DSM-III-R (diagnosis of schizophrenia and schizophrenia spectrum disorders)	2.27 (1.08–4.38) Following mild TBI, these participants had a twofold risk of developing some form of psychosis.

2. Dikmen, S. S., J. D. Corrigan, H. S. Levin, J. Machamer, W. Stiers and M. G. Weisskopf (2009). "Cognitive outcome following traumatic brain injury." *The Journal of Head Trauma Rehabilitation* 24(6): 430-438.

CEBM Score: 3/5

This systematic review examined the possibility of an association between TBI and cognitive impairment six or more months after the injury. They found insufficient evidence for long term sequelae in mild traumatic brain injury six months or more, post injury. no quality scoring or details of the study design were supplied.

- Heitger et al. (2006) indicated deficits in verbal learning in the group with mild TBI at 6 months but results at 12 months revealed no significant group differences with only a trend on 1 component of a memory measure ($P < .07$).
- Dikmen et al. (1986) found that at 1 year, none of the neuropsychological measures showed significant group differences. Thus, although selected subtle neuropsychological effects were seen at 1 month after a mild TBI, they could no longer be detected at 1 year.

3. Belanger, H. G., E. Spiegel and R. D. Vanderploeg (2010). "Neuropsychological performance following a history of multiple self-reported concussions: A meta-analysis." *Journal of the International Neuropsychological Society* 16(2): 262-267.

CEBM Score: 3/5

This systematic review examined the long term neuropsychological impact of multiple mild TBIs. A meta-analysis based on eight studies, involving 614 cases of multiple mild TBI and 926 control cases of a single mild TBI. No quality scoring or details of the individual studies were given. The authors found that:

- *the overall effect of multiple MTBI on neuropsychological functioning was minimal and not significant (weighted effect size(d) = 0.06). However, ... multiple self-reported MTBI was associated with poorer performance on measures of delayed memory and executive functioning (p.262).*

4. Temkin, N. R., et al. 2009. Social functioning after traumatic brain injury. *Journal of Head Trauma Rehabilitation* 24(6): 460-467.

CEBM Score: 3/5

This systematic review examined the relationship between adult-onset traumatic brain injury (TBI) and social functioning including employment, social relationships, independent living, recreation, functional status, and quality of life 6 months or longer after injury. They found 14 primary and 25 secondary studies which allowed comparison to controls for adults who were at least 6 months post-TBI (no further details supplied).

- There was insufficient evidence of a relationship between unemployment and mild TBI.
- Although there is a dose-response relationship between severity of injury and social outcomes, there is insufficient evidence to determine at what level of severity the adverse effects are demonstrated (p.460).
- At 6 months postinjury, Stulemeijer et al. (2006) measured social functioning with the SF-36 Physical Functioning and Social Functioning scales and the SF-36 Perceived Health change. Each SF-36 measure differed significantly between the groups (each P

= .0001). The patients with mild TBI and additional injuries showed more dysfunction than did the patients with only mild TBI, and both showed more than did the non-headinjured controls (each $P < .001$).

- Heitger et al. (2007) examined 37 persons with mild closed head injury and 37 normal controls matched to the group with TBI on age, sex, and years of education. Social functioning was assessed with the Rivermead Head Injury Follow Up Questionnaire and the SF-36 at 6 and 12 months after injury. The results showed no significant differences between the patients with mild TBI and controls on the SF-36 at 6 and 12 months after TBI (p.462).

Other earlier or lower quality evidence on the topic includes

AANN and ARN clinical practice guidelines series- care of patient with mild traumatic brain injury 2011. (AGREE II score 4/7)

Bazarian, J. J., I. Cernak, L. Noble-Haeusslein, S. Potolicchio and N. Temkin (2009). "Long-term neurologic outcomes after traumatic brain injury." *The Journal of Head Trauma Rehabilitation* 24(6): 439-451. (CEBM score 1/5)

Begaz, T., D. N. Kyriacou, J. Segal and J. J. Bazarian (2006). "Serum biochemical markers for post-concussion syndrome in patients with mild traumatic brain injury." *Journal of Neurotrauma* 23(8): 1201-1210. (CEBM score 2 /5)

Carlson, K. F., S. M. Kehle, L. A. Meis, N. Greer, R. MacDonald, I. Rutks, N. A. Sayer, S. K. Dobscha and T. J. Wilt (2011). "Prevalence, Assessment, and Treatment of Mild Traumatic Brain Injury and Posttraumatic Stress Disorder: A Systematic Review of the Evidence." *Journal of Head Trauma Rehabilitation* 26(2): 103-115. (CEBM score 2/5)

Cooper 2009. Preliminary guidelines for prosthetic care for amputees. (AGREE II score 2/7)

Daggett, V., T. Bakas and B. Habermann (2009). "A review of health-related quality of life in adult traumatic brain injury survivors in the context of combat veterans." *Journal of Neuroscience Nursing* 41(2): 59-71. (CEBM score 1/5)

Fergusson, D., B. Hutton and A. Drodge (2007). "The epidemiology of major joint contractures: A systematic review of the literature." *Clinical Orthopaedics and Related Research*(456): 22-29. (CEBM score 2/5)

Greer, D. M., S. E. Funk, N. L. Reaven, M. Ouzounelli and G. C. Uman (2008). "Impact of fever on outcome in patients with stroke and neurologic injury: a comprehensive meta-analysis." *Stroke* 39(11): 3029-3035. (CEBM score 2/5)

Harmon, K. G., J. A. Drezner, M. Gammons, K. M. Guskiewicz, M. Halstead, S. A. Herring, J. S. Kutcher, A. Pana, M. Putukian and W. O. Roberts (2013). "American Medical Society for Sports

Medicine position statement: concussion in sport." British Journal of Sports Medicine 47(1): 15-26. (AGREE II score 2/7)

Hesdorffer, D. C., S. L. Rauch and C. A. Tamminga (2009). "Long-term psychiatric outcomes following traumatic brain injury: A review of the literature." The Journal of Head Trauma Rehabilitation 24(6): 452-459. (CEBM score 2/5)

Orff, H. J., L. Ayalon and S. P. Drummond (2009). "Traumatic brain injury and sleep disturbance: a review of current research." Journal of Head Trauma Rehabilitation 24(3): 155-165. (CEBM score 1 /5)

Poole, N. A. and N. Agrawal (2008). "Cholinomimetic agents and neurocognitive impairment following head injury: a systematic review." Brain Injury 22(7-8): 519-534. (CEBM score 2/5)

Rogers, J. M. and C. A. Read (2007). "Psychiatric comorbidity following traumatic brain injury." Brain Injury 21(13-14): 1321-1333. (CEBM score 2/5)

Rutherford, G. W. and R. C. Wlodarczyk (2009). "Distant sequelae of traumatic brain injury: premature mortality and intracranial neoplasms." Journal of Head Trauma Rehabilitation 24(6): 468-474. (CEBM score 2/5)

Snell, D. L., L. J. Surgenor, E. J. Hay-Smith and R. J. Siegert (2009) A systematic review of psychological treatments for mild traumatic brain injury: An update on the evidence. Journal of Clinical and Experimental Neuropsychology, 31, 20-38. (CEBM score 3/5 NB: this was cited in the SIGN 2013 guideline)

Torrence, C. B., C. DeCristofaro, et al. (2011). "Empowering the primary care provider to optimally manage mild traumatic brain injury." Journal of the American Academy of Nurse Practitioners 23(12): 638-647. (CEBM score 1/5)

Weightman et al. 2010. physical therapy recommendations for service members with mild traumatic brain injury. (AGREE II score 3/7)

Wiseman-Hakes, C., A. Colantonio, et al. (2009). "Sleep and wake disorders following traumatic brain injury: a systematic review of the literature." Critical Reviews in Physical & Rehabilitation Medicine 21(3-4): 317-374. (CEBM score 2/5)

Question 2.10 What is the evidence for persistent symptoms and issues specific to mild TBI: fatigue, headaches, pain?

Executive summary

The evidence sourced for this question included four clinical guidelines (two excellent quality, one high and one moderate quality) and two systematic reviews not included in the guidelines (good and moderate quality). One guideline (Marshall et al 2012) dealt in depth with this question. The systematic reviews provided no new information to that presented in the guidelines.

Common and persistent symptoms attributed to post mild TBI are described by Willer and Leddy (2006) (cited in the guideline by Marshall et al 2012 p258 (Ontario Neurotrauma Foundation)).

Evidence statement

Physical	Behavioural/Emotional	Cognitive
<ul style="list-style-type: none"> • Headache • Nausea • Vomiting • Blurred or double vision • Seeing stars or lights • Balance problems • Dizziness • Sensitivity to light or noise • Tinnitus 	<ul style="list-style-type: none"> • Drowsiness • Fatigue/lethargy • Irritability • Depression • Anxiety • Sleeping more than usual • Difficulty falling asleep 	<ul style="list-style-type: none"> • Feeling “slowed down” • Feeling “in a fog” or “dazed” • Difficulty concentrating • Difficulty remembering

The guidelines address the management of persistent symptoms and issues in mild TBI, include recommendations for assessments, differential diagnosis, monitoring, interventions (pharmaceutical, rehabilitative and compensatory) and need for referral for specialist consultation.

Compilation of recommendations

Patients presenting with non-specific symptoms following mild traumatic brain injury should be reassured that the symptoms are benign and likely to settle within three months (SIGN 2013, VA/DoD 2009)	B
Early education, support and reassurance is effective, without any other specific intervention, in reducing longer term complaints of non-specific persistent symptoms (NSW MAA 2008, SIGN 2013, Chong 2008).	A
Where symptoms persist, compensation/litigation may be a factor; however, there is little consistent evidence for other predictors (Marshall et al 2012).	B
Longer-term symptoms have been reported in individuals with early high symptom load (NSW MAA 2008)	C
Assessment of persistent symptoms should be undertaken using a standard comprehensive form of assessment for comparison over time. The Rivermead Post Concussion Symptoms Questionnaire is commonly recommended (Marshall et al 2012)	C
Careful and thorough differential diagnoses should be considered for mTBI patients with persistent symptoms, as similar symptoms are common in chronic pain, depression, anxiety disorders, and other medical and psychiatric disorders (Marshall et al 2012)	C
Persistent headache is the most common feature of persistent postTBI symptoms (Nampiaparampil 2008, VA/DoD 2009)	B
Assessment of persistent headache should be undertaken using standard headache classifications. (Marshall et al 2012).	C
Its management should be tailored to the class of non-traumatic headache it most closely resembles (e.g., chronic tension, migraine, etc.)(Marshall et al 2012)	C
Patients with memory impairment after TBI should be trained in the use of compensatory memory strategies with a clear focus on improving everyday functioning rather than underlying memory impairment. For patients with mild-moderate memory impairment both external aids and internal strategies (eg use of visual imagery) may be used. For those with severe memory impairment external compensations with a clear focus on functional activities is recommended (SIGN 2013)	D
Medication for ameliorating the neurocognitive effects attributed to concussion/mTBI is not recommended (VA/DoD 2009)	B
Mood and anxiety disorders: As PTSD and other psychiatric disorders may contribute to the overall burden of symptoms in some individuals following MTBI, particularly where problems persist for more than three months, mental state should be routinely examined with an emphasis on symptoms of phobic avoidance, traumatic re-experiencing phenomena (eg flashbacks and nightmares) and low mood (SIGN 2013)	C
There is consistent evidence for the use of psychological counselling, training and other non-pharmacological methods, than for pharmacological approaches to be used in the first instance (Marshall et al 2013)	C
Referral to a psychiatrist should occur whenever there are concerns about safety of the individual or others, however other management approaches should be instigated whilst waiting for an appointment (Marshall et al 2013)	C

There is better and more consistent evidence for the effectiveness of education, relaxation and goal setting to manage sleep disturbances , than the longterm use of pharmacological agents (Marshall et al 2013)	C
Balance disorders Evaluation should minimally include balance testing, and compare these with normal values to document impairment (Marshall et al 2013) Vestibular rehabilitation therapy is recommended for unilateral peripheral vestibular dysfunction (Marshall et al 2013). If symptoms of benign positional vertigo are present, the Dix-Hallpike Maneuver should be used (Marshall et al 2013).	C A

Evidence statement

Key question	Rating	Notes
Evidence base	A	Information within high quality guidelines & systematic reviews comes from systematic reviews of (mostly) observational studies, scant primary experimental studies, and many primary observational and diagnostic studies. Sports participants and defence personnel were the target populations in the two moderate quality guidelines.
Consistency	B	The literature is generally consistent regarding the epidemiology of persistent symptoms, which generally resolve within 3-6 months of suffering a mild TBI. There are also consistent findings that persistent symptoms often have non-mTBI causes (pre-existing conditions, or conditions which had developed subsequent to the head injury). The evidence is clear however, that mTBI assessment and management should be person-centred because of the complexity of postTBI presentations.
Clinical impact	B	There are substantial implications in this evidence-based for this question due to significant proportion of the mild TBI population experiencing difficulties with persistent symptoms, and the number and range of health professionals who require guidance in assisting the mild TBI population to manage these symptoms effectively.

Key guidelines regarding persistent symptoms & issues following mild TBI

1. SIGN 2013 Brain injury rehabilitation in adults. Scottish Intercollegiate Guidelines Network.

AGREE II Score: 7/7

This Scottish guideline aims to provide recommendations about the management of adults (16+yrs) with brain injuries of all severities. Recommendations are made for post-acute assessment, interventions for cognitive, communicative, emotional, behavioural and physical rehabilitation, optimal models and settings of care.

Non-specific symptoms:

Persistent physical illness, prior neurological disease, prior head injuries, mood and anxiety disorders, being a student, sustaining the injury in a motor vehicle accident and age over 40 years have been cited as predictive of poor prognosis. In general, the nature of the MTBI itself is not predictive of outcome except for those MTBIs which are complicated or on the cusp of being graded as moderate A limited number of studies in the elderly (aged over 70 years) suggest poorer outcome.

Recommendations relevant to persistent non-specific symptoms:

- *Patients presenting with non-specific symptoms following mild traumatic brain injury should be reassured that the symptoms are benign and likely to settle within three months (p.10) (Carroll et al 2004b; Thornhill et al 2000) (Grade B: High quality systematic reviews, case control or cohort studies; or extrapolated from Level I studies).*
- *Consideration should be given to alternate diagnostic explanations for ongoing symptoms post MTBI, eg coincidental mood disorder or thyroid disease, and further investigation may be warranted. Other secondary pathologies which are consequences of the original injury but not associated with, or dependent on, any brain injury may occur in the context of a head injury, eg benign positional paroxysmal vertigo, and should be treated accordingly (p.10) (Consensus of guideline developers).*

Memory problems:

Recommendations relevant to persistent memory problems:

- *Patients with memory impairment after TBI should be trained in the use of compensatory memory strategies with a clear focus on improving everyday functioning rather than underlying memory impairment. For patients with mild-moderate memory impairment both external aids and internal strategies (eg. use of visual imagery) may be used. For those with severe memory impairment external compensations with a clear focus on functional activities is recommended (p.21) (Grade D: non-analytic studies, case studies, or extrapolated from well conducted case control or cohort studies with a low bias risk).*

Cognitive deficits:

In adults, evidence consistently suggests there are no mTBI-attributable cognitive deficits beyond three months after injury. However, those with complicated mTBI, ie with associated skull fractures or intracranial lesions may have significant cognitive deficits. (Carroll et al 2004b; Frencham et al 1995)).

Recommendations relevant to persistent cognitive deficits:

- *Referral for cognitive (psychometric) assessment is not routinely recommended after MTBI (p.11) (British Psychological Soc 2009; Carroll et al 2004) (Grade B: High quality systematic reviews, case control or cohort studies; or extrapolated from Level I studies).*
- *If a cognitive assessment has been conducted clinicians should be aware that false positives can occur and that results may be unreliable in the absence of effort testing (p.11) (Consensus of guideline developers).*

Rationale:

False positives on cognitive testing can be a problem. Effort tests have been developed for use in psychometric examinations which evaluate whether a patient's poor score on cognitive testing is likely to represent a false positive due to poor effort. A number of such tests have been developed but no recommendation can be made on the superiority of one test over another. The British Psychological Society has discussed this in greater detail. A systematic review, which identified seven studies using tools to assess malingering and incomplete effort, showed that litigation was the only consistently identified poor prognostic factor. It is not possible to distinguish between malingering and poor effort for valid reasons using such tests (p.11).

The SIGN 2013 guideline included the following studies in their review of this section:

Hierarchy	Reference
III_1	Carroll LJ, Cassidy JD, Peloso PM, Borg J, von Holst H, Holm L, et al. Prognosis for mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med 2004b;43:84-105.
1	Frencham KAR, Fox AM, Maybery MT. Neuropsychological studies of mild traumatic brain injury: A meta-analytic review of research since 1995. J Clin Exp Neuropsychol 2005;27(3):334-51.
III_1	Thornhill S, Teasdale GM, Murray GD, McEwen J, Roy CW, Penny KI. Disability in young people and adults one year after head injury: Prospective cohort study. BMJ 2000;320(7250):1631-5
IV (collation of diagnostic tests)	British Psychological Society. Assessment of effort in clinical testing of cognitive functioning for adults. 2009. [cited 21 Feb 2013]. Available from url: http://www.bps.org.uk/sites/default/files/documents/assessment_of_effort_in_clinical_testing_of_cognitive_functioning_for_adults.pdf

Mood and anxiety disorders:

Background: Cohort studies have consistently identified post-traumatic stress disorder (PTSD) and other psychiatric disorders as contributing to the disability present in both military and civilian cohorts following reported MTBI. These studies support the view that while an

incident that causes an MTBI (eg motor vehicle accident or assault) may result in some short term symptoms, these usually resolve over time. It is argued that such an incident, rather than the MTBI, is the main factor resulting in the development of longer term PTSD symptoms. The evidence suggests that any resulting association between MTBI and PTSD symptoms is therefore not causal.

Recommendations relevant to persistent mood & anxiety disorders:

- *As PTSD and other psychiatric disorders may contribute to the overall burden of symptoms in some individuals following MTBI, particularly where problems persist for more than three months, mental state should be routinely examined with an emphasis on symptoms of phobic avoidance, traumatic re-experiencing phenomena (eg flashbacks and nightmares) and low mood (p.11)(Broomhall et al 2009; Bryant et al 1998; fear et al 2009; Hill et al 2009; Vanderploeg et al 2009)(Grade C: well conducted case control or cohort studies with a low bias risk).*

The SIGN 2013 guideline included the following studies in their review of this section:

Heirarchy	Reference
III_1	Broomhall LG, Clark CR, McFarlane AC, O'Donnell M, Bryant R, Creamer M, et al. Early stage assessment and course of acute stress disorder after mild traumatic brain injury. J Nerv Ment Dis 2009;197(3):178-81
III_2	Bryant RA, Harvey AG. Relationship between acute stress disorder and posttraumatic stress disorder following mild traumatic brain injury. Am J Psychiatry 1998;155(5):625-9.
III_3	Bryant RA, O'Donnell ML, Creamer M, McFarlane AC, Clark CR, Silove D. The psychiatric sequelae of traumatic injury. Am J Psychiatry 2010;167(3):312-20
III_2	Fear NT, Jones E, Groom M, Greenberg N, Hull L, Hodgetts TJ, et al. Symptoms of post-concussional syndrome are nonspecifically related to mild traumatic brain injury in UK Armed Forces personnel on return from deployment in Iraq: an analysis of self-reported data. Psychol Med 2009;39(8):1379-87.
III_2	Hill 3rd JJ, Mobo Jr BH, Cullen MR. Separating deployment-related traumatic brain injury and posttraumatic stress disorder in veterans: preliminary findings from the Veterans Affairs traumatic brain injury screening program. Am J Phy Med Rehabil 2009;88(8):605-14.
III_2	Vanderploeg RD, Belanger HG, Curtiss G. Mild traumatic brain injury and posttraumatic stress disorder and their associations with health symptoms. Arch Phys Med Rehabil 2009;90(7):1084-93

2. Motor Accidents Authority of NSW (MAA NSW). 2008 Guidelines for Mild Traumatic Brain Injury Following a Closed Head Injury.

AGREE II Score: 7/7

These Australian guidelines make recommendations for the early identification and management of adults with mild traumatic brain injury. They are aimed at clinicians working pre-hospital, emergency departments and general practice settings.

Key findings in the guideline:

The authors provide evidence regarding the prevalence of persistent symptoms and prognostic indicators as follows:

Theme	Author	Hierarchy	Study findings
Education intervention	Borg et al 2004	1	Early educational information can reduce longer term complaints
	Turner-Stokes 2005	1 (Cochrane)	Strong evidence that most patients with MTBI make a good recovery when provided with appropriate information without additional specific intervention
Recovery prognosis	Carrol et al 2004	1	The majority of patients recover within three to 12 months. Where symptoms persist, compensation/litigation is a factor; however, there is little consistent evidence for other predictors.
	Cassidy et al 2004	1	The majority of patients recover within three to 12 months. Where symptoms persist, compensation/litigation is a factor – compensation seeking strongly predicted delayed return to work, more long-term symptoms and greater symptoms severity (independent of MTBI severity).
	De Kruijk et al (2002)	III_2	Presence of headache, dizziness, nausea in ED strongly associated with severity of most posttraumatic complaints after six months
	Kraus 2005	II	Headaches, dizziness, vision difficulties, memory or learning problems, alcohol intolerance occur more often in individuals with MTBI six months after injury compared with controls.
	Lundin 2006)	II	Symptoms gradually decline postinjury – those patients with early high symptom load are at risk of developing persistent symptoms.(
	Ponsford 2000	II	Symptoms reported at one week; however, by three months symptoms reported at one week were largely resolved. No impairments in neuropsychological measures in adults with MTBI, although they had more headaches and concentration difficulties than controls. Some had residual symptoms

	Savola 2003	II	reported that related to risk factors, such as previous psychiatric or head injury problems, or injuries from motor vehicle accident Presence of skull fracture, elevated s-100B, dizziness, headache may help to identify patients at risk of PCS
	Stalnacke 2007	III_3	Large proportion of individuals with MTBI experience psychosocial difficulties with low levels of life satisfaction – pre-injury factors cannot be ruled out.
Compensation influences	Owensworth 2006	II	Mood symptoms and heightened self awareness are significantly related to high symptom reporting independent of compensation status. Clinicians need to interpret symptoms within a biopsychosocial context
Sensitivity of testing	Iverson (2005b)	IV (diagnostic study)	Measures of concentration, memory and processing speed in patients with uncomplicated MTBI could not be reliably differentiated from patients with substance abuse problems
	Iverson (1997)	III_2	Post Concussion symptoms (PCS) are not unique to MTBI and the presence of chronic pain should be considered when interpreting complaints following closed head injury.

3. Marshall et al (Ontario Neurotrauma Foundation). Clinical practice guidelines for mild traumatic brain injury and persistent symptoms. Canadian Family Physician 2012; 58(3): 257.

AGREE II score =6/7)

The objective of this Canadian group was ‘to create a set of guidelines that can be used by healthcare professionals to implement evidence-based, best practice care of individuals who incur a mild traumatic brain injury and experience persistent symptoms’ (p.1). Recommendations are made for the management of adults >18years.

General persistent symptoms

While full recovery is expected within 3 months (King, 1997, Van der Naalt, 2001) after mTBI or concussion, not all patients experience such rapid recovery. Reasons for failure to recover include Major Depressive Disorder, Generalised Anxiety Disorder, Post Traumatic Stress Disorder (PTSD), Chronic Pain Syndrome, Cervical Strain/Whiplash Associated Disorder, Substance Abuse or Polypharmacy, Somatoform Disorder/Factitious Disorder, Malingering,

Post Traumatic Headache, Fibromyalgia syndrome (secondary), Primary Sleep Disorder such as Obstructive Sleep Apnea.

Recommendations relevant to persistent symptoms

- *Clinicians should assess and monitor persisting somatic, cognitive and emotional/behavioural symptoms following mTBI (adapted from MAA NSW Guidelines) (Grade A: At least one randomised controlled trial, meta-analysis, or systematic review).*
- *A standardised scale, such as the Rivermead Post Concussion Symptoms Questionnaire should be used to monitor symptoms. (adapted from MAA NSW Guidelines) (Grade C: expert opinion or consensus).*
- *Persistent symptoms following mTBI can be nonspecific. Therefore, careful and thorough differential diagnoses should be considered as similar symptoms are common in chronic pain, depression, anxiety disorders, and other medical and psychiatric disorders. (Grade C: expert opinion or consensus).*
- *Patients should be advised that they are likely to experience one or more persistent symptoms as a consequence of the mTBI for a short period and that this is expected (normal). (Grade A: At least one randomised controlled trial, meta-analysis, or systematic review).*
- *The patient should be advised that a full recovery of symptoms is expected. (Grade A: At least one randomised controlled trial, meta-analysis, or systematic review).*
- *Where there are prolonged and significant complaints after mTBI, Primary Care Providers should rule out other contributing or confounding factors. (Grade A: At least one randomised controlled trial, meta-analysis, or systematic review).*
- *Persons with mTBI and pre-injury mental health conditions, or any other health or contextual risk factors, should be considered for early referral to a multidisciplinary treatment clinic capable of managing post concussive symptoms because these factors have been associated with poorer outcomes. (Grade C: expert opinion or consensus).*

Persistent headache:

Headache is a common symptom following mTBI with estimates ranging between 30-90% of patients who suffer from headaches. Researchers have noted that posttraumatic headache is more common after mild TBI than after severe. Overuse of acute headache medication can be an underlying reason for persistent headache. Thus careful investigation should be undertaken of medicines used for headache management (suggest using the ICHD-II criteria for Medication Overuse in Headache)

Recommendations relevant to persistent headache:

- *Take a focused headache history identifying the headache frequency, duration, location, intensity and associated symptoms (e.g., nausea/vomiting, etc.) to try to determine which primary headache type it most closely resembles (i.e., episodic or*

chronic migraine, episodic or chronic tension-type, primary stabbing headache, occipital neuralgia, etc.). Unfortunately, some post-traumatic headaches are unclassifiable. To aid in determining the specific phenotype of headache disorder present, refer to the ICHD-II classification criteria. (Grade C: expert opinion or consensus).

- *Perform a neurologic exam and musculoskeletal exam including cervical spine examination. (Grade C: expert opinion or consensus).*
- *Management of post-traumatic headache should be tailored to the class of non-traumatic headache it most closely resembles (e.g., chronic tension, migraine, etc.). Refer to the treatment algorithms specific to the appropriate class of headache in the ICSI guideline (2009). (Grade C: expert opinion or consensus).*

Persistent sleep disorders:

Sleep disturbance is most common following mild TBI, not severe TBI. Insomnia is the most common form of sleep disturbance following TBI characterised by problems with sleep initiation and/or sleep maintenance (systematic review by Orff et al 2009).

Recommendations relevant to persistent sleep disorders:

- *Advise patients that the goal of treatment is to improve the continuity and restorative quality of sleep, not to make them "8 hour sleepers". More often than not the total sleep time will be less than 8 hours per night. (Grade C: expert opinion or consensus).*
- *Provide the sleep hygiene advice (reproduced below, developed by the British Columbia Guidelines and Protocols Advisory Committee). (Grade C: expert opinion or consensus).*
- *Relaxation training is effective and recommended therapy in the treatment of chronic insomnia. (Grade C: expert opinion or consensus).*
- *Pharmacotherapy is generally recommended at the lowest effective dose as short-term treatment lasting less than 7 days. Although long-term use of hypnotic agents is discouraged due to the potential for tolerance and dependence, there are specific situations and circumstances under which long term use of hypnotics may be appropriate. Advice provided in the Therapeutic Options table from the Alberta TOP Clinical Practice Guideline for Adult Primary Insomnia: Diagnosis to Management (http://www.topalbertadoctors.org/informed_practice/clinical_practice_guidelines/complete%20set/Insomnia/insomnia_management_guideline.pdf). (Grade C: expert opinion or consensus).*
- *Some insomnia patients spend excessive time in bed trying to attain more sleep. Sleep consolidation is accomplished by compressing the total time in bed to match the total sleep need of the patient. This improves the sleep efficiency. (Grade C: expert opinion or consensus).*

Follow these rules for healthy sleep.

- Get up at the same time each day, seven days a week, to reinforce your body's internal clock.
- Go to bed only when you are sleepy.
- If you're not asleep after about 20 minutes, go to another room and do something relaxing. Return to bed when you are drowsy-tired.
- Use your bed only for sleeping or sex. Don't worry or watch TV in bed so your body learns the bed is for sleeping.
- Keep your bedroom dark and comfortably cool.
- Exercise during the day (three to four hours before bedtime).
- Don't drink coffee or tea within six hours of bedtime.
- Don't drink alcohol in the evening. It can make you wake up in the middle of the night.
- Try eating a light carbohydrate snack before bed.

(<http://www.bcguidelines.ca/gpac/pdf/sleepcomp.pdf>)

Persistent mental health disorders:

Early post-concussive symptoms following mTBI can include irritability, anxiety, emotional lability, depressed mood, and apathy. Thereafter a significant proportion of individuals may develop persistent mental health disorders, with major depression and anxiety disorders observed most frequently. Depressive disorders following TBI are commonly associated with increased irritability and are often comorbid with anxiety syndromes. The latter include generalised anxiety, panic attacks, phobic disorders, and posttraumatic stress disorder (PTSD). These disorders comprise both new-onset conditions that develop de novo post-injury, as well as those reflecting an exacerbation of pre-injury conditions or vulnerabilities (Whelan-Goodinson et al., 2009).

Comorbid mental health disorders warrant treatment whenever symptoms impact on functional status or impede recovery as psychiatric and other post-concussive symptoms often negatively interact (Fann et al., 2001). Once identified, appropriate psychological and pharmacological treatment should be started. For more complex cases, consultation with a psychiatrist or a mental health team should be sought; although the initial steps of treatment should not be delayed. General measures can be initiated and symptoms such as headaches, sleep disturbance, dizziness, and comorbid pain addressed. General measures include the provision of support, validation, and reassurance, as well as education regarding mTBI and positive expectations for recovery. Involvement of the family can be very helpful at this stage. Education about sleep hygiene and regular light exercise (e.g., walking or stationary cycling, depending on physical limitations) should be offered. The latter can improve mood, perceived fatigue and well-being, and counteract deconditioning.

Recommendations relevant to persistent mental health issues (all Grade C: expert opinion or consensus):

- *Given their prevalence and potential impact, all patients with persistent symptoms following an mTBI should be screened for mental health symptoms and disorders, including:*
 - Depressive disorders

- Anxiety disorders, including PTSD
- Irritability or other personality changes
- Substance use disorders
- Somatoform disorders
- *Referral to a psychiatrist/mental health team (ideally with experience in treating individuals with persistent symptoms following mTBI, if available) should be obtained if:*
 - the presentation is complex or severe
 - psychosis or bipolar disorder is suspected
 - the risk of suicide is judged significant
 - initial treatment is not effective within two months
 - failure or contraindication of medication strategies that are familiar
 - presence of risk factors known to potentially affect the course of recovery (see Table 7)
- *While awaiting specialist referral, the initial steps of treatment should not be delayed, nor symptoms left unmanaged. General measures can be instituted and common symptoms such as headache, sleep disturbance, dizziness, and pain addressed in an ongoing manner.*
- *For medication trials, a 'start low and go slow' approach is recommended. Nonetheless, dose optimisation may be required before an antidepressant response is observed, or a trial of medication abandoned.*
- *A selective serotonin reuptake inhibitor is recommended as the first-line treatment for mood and anxiety syndromes after mTBI. However, in some cases the combination of sedative, analgesic, or anti-migraine effects from a tricyclic (TCA) may be particularly desirable, although these agents may generally be considered second-line.*
- *Follow-up should occur at regular intervals: initially every 1 - 2 weeks, while increasing medication to monitor tolerability and efficacy. Thereafter, every 2-4 weeks may be sufficient.*
- *Cognitive behavioural therapy (CBT) has well-established efficacy for treatment of primary depression; as such it is appropriate in the treatment of mood symptoms following mTBI.*
- *Individuals with PTSD following mTBI should be offered a trial of trauma-focused CBT therapy.*
- *The need for concurrent pharmacotherapy should also be assessed, depending upon symptom severity, and the nature of comorbid difficulties (for example, major depression, prominent somatic symptoms, severe hyperarousal and sleeplessness, which all may limit psychological treatment).*

Persistent cognitive difficulties:

mTBI is associated with disruptions in cognitive skills that include difficulties with attention/concentration, speed of information processing, memory and aspects of executive

cognitive skills (Silver et al 2009). In the acute phase of injury there are changes in cerebral metabolic activity and perfusion particularly in the frontal lobes associated with cognitive changes (Metting et al, 2009). Generally, the expected recovery from cognitive based symptoms following mTBI ranges from 1 week to 6 months, with more rapid rates of recovery found in young athletes (Iverson et al 2010). However, a small percentage of individuals experience persistent cognitive symptoms beyond the acute phase of recovery which significantly disrupts their capacity to resume many premorbid activities.

Recommendations relevant to persistent cognitive difficulties (all Grade C unless marked otherwise: expert opinion or consensus):

- *When there are persistent cognitive complaints, the Health Care Provider should make efforts to formally screen for cognitive deficits. Objective measures of those domains most commonly affected post-mTBI (i.e., attention and concentration, information processing speed, memory) should be used. Although there currently is no screening measure specific to cognitive difficulties following mTBI, the Rivermead Post Concussion Symptoms includes items assessing cognition.*
- *Consideration should be given to potential co-morbid diagnoses that could be present and have the potential to influence cognition such as anxiety, depression, PTSD, pain, fatigue, sleep disturbance, or acute stress disorder.*
- *If evidence of cognitive dysfunction is obtained upon screening that is likely attributable to the mTBI itself or if cognitive symptoms are reported to persist at 3 months, then consideration for more formal assessment should be given and referral made. If available, refer to a neuropsychologist (ideally with experience with TBI). When a local neuropsychologist is not available or known, referral to a TBI centre can be made. For systems with long wait times, practitioners should consider referral earlier than 3 months.*
- *Following mTBI, acute cognitive deficits are common, and spontaneous cognitive improvement is expected in the majority of injured individuals. Rehabilitation of cognitive impairments should be initiated if:*
 - The individual exhibits persistent cognitive impairments on formal evaluation
 - The learning of compensatory strategies is necessary in order to facilitate the resumption of functional activities and work and/or there are safety issues in question (i.e., possible harm to self or others).
 - For cognitive sequelae following mTBI, the cognitive rehabilitation strategies that should be considered include compensatory strategies and restorative approaches. Electronic external memory devices such as computers, paging systems or portable voice organisers have been shown to be effective aids for improving TBI patients' everyday activities. (Grade B: At least one cohort comparison, case studies or other type of experimental study)

Persistent balance disorders:

Impairment of the vestibular system is a common problem experienced post mild TBI with complaints ranging from vertigo to problems with dizziness, balance, vision as well as mobility (Hillier & Hollohan, 2007). Vestibular deficits can be of peripheral origin where the inner ear is affected or can also be of central/ brain origin. Benign Paroxysmal Positional Vertigo (BPPV) is a specific common cause of balance impairment where patients experience vertigo and often nausea with sudden movements or changes in position such as rolling over in bed or looking up (Parnes, Agrawal & Atlas, 2003); typically the duration of symptoms is less than 30 seconds but can occur multiple times per day and has the potential to disrupt activities.

Recommendations relevant to persistent balance disorders:

- *Clinicians should screen for balance deficits for assessment of postural stability because clinical testing of balance offers additional information about the presence of ongoing symptoms and assists in the subsequent management of patients who have sustained mTBI. Evaluation should minimally include balance testing with reference to normal values to document impairment (Vereeck et al 2008) (Grade C: expert opinion or consensus).*
- *If symptoms of benign positional vertigo are present the Dix-Hallpike Maneuver should be used (Parnes et al 2003) (Grade A: At least one randomised controlled trial, meta-analysis, or systematic review).*
- *For persons with functional balance impairments and screening positive on a balance measure, consideration for further balance assessment and treatment by physiotherapy may be warranted pending clinical course. (Grade C: expert opinion or consensus).*
- *A canalith repositioning maneuver should be used to treat Benign Positional Vertigo if the Dix-Hallpike Maneuver is positive. (Grade A: At least one randomised controlled trial, meta-analysis, or systematic review).*
- *Vestibular rehabilitation therapy is recommended for unilateral peripheral vestibular dysfunction. (Grade A: At least one randomised controlled trial, meta-analysis, or systematic review).*

Persistent vision disorders:

The types of vision disorders that people who have sustained mTBI may experience range from ambient vision disturbances to diplopia, inability to visually fixate, poor convergence, scanning deficits, poor visual acuity, accommodative dysfunction, oculomotor dysfunction, and photosensitivity (Radomski et al 2009).

Recommendations relevant to persistent vision disorders:

- *Take an appropriate history relevant to visual symptoms. (Grade C: expert opinion or consensus)*

- Perform fundoscopic exam, and exams of visual acuity, visual fields and extraocular movements for symptoms of visual disturbance including visual field, blurring, diplopia, and photosensitivity. (Grade C: expert opinion or consensus)
- If visual abnormalities are observed, refer to an ophthalmologist, ideally a neuro-ophthalmologist or one specializing in brain injury. (Grade C: expert opinion or consensus)

Persistent fatigue:

Fatigue has been conceptualised as an experience of weariness or tiredness following mental or physical exertion often resulting in a reduced capacity for work and limited efficiency to respond to stimuli. Fatigue is one of the most pervasive symptoms following TBI and it can actually be out of proportion to exertion or may even occur without any exertion (Dijkers & Bushnik, 2008). Fatigue is multidimensional and can affect physical, cognitive, and subjective aspects. Fatigue following TBI has been found to significantly impact well-being and quality of life (Cantor et al., 2008). Due to its prevalence and effects, it is recommended that all patients be assessed for fatigue through a personal history and review of the relevant items from standardised assessment instruments such as Rivermead Post Concussion Symptoms.

Recommendations relevant to persistent fatigue (all Grade C: expert opinion or consensus):

- *Determine whether fatigue is a significant symptom by taking a personal history, reviewing the relevant items from the Rivermead Post Concussion Symptoms Questionnaire or other suitable instruments.*
- *Characterise the dimensions of fatigue and identify alternative, treatable causes that may not be directly related to the injury. To do so, complete the following:*
 - Complete medical history, review medications associated with fatigue, asthenia, somnolence, and lethargy) and review systems, with particular attention to iatrogenic (medication) causes for comorbid medical conditions associated with fatigue (e.g., metabolic disorders - thyroid screen, CBC, enemic, low CA, malnourishment).
 - Obtain sleep history to help identify primary or secondary sleep disorders
 - Evaluate for depression (that is, loss of interest in activities; feelings of sadness, worthlessness, or guilt; changes in appetite or sleep; or suicidal ideation), anxiety, stress or other psychological distress.
 - Conduct a general medical examination and a focused neurologic exam.
- *If identified as a significant symptom, some key considerations that may aid in the management of persistent fatigue can include:*
 - aiming for a gradual increase in activity levels that will parallel improvement in energy levels.
 - reinforce that pacing activities across the day will help patients to achieve more and to avoid exceeding tolerance levels.

- encouraging good sleep practices (especially regularity of sleep time, and avoidance of stimulants and alcohol), and proper relaxation times.
- using a notebook to plan meaningful goals, record activity achievement and identify patterns of fatigue.
- acknowledging that fatigue can be exacerbated by low mood.
- *Provide patients with advice on coping strategies for fatigue.*
- *If fatigue is persistent then refer to a brain injury specialist for consideration of a medication trial.*

4. McCrory et al. Consensus Statement on Concussion in Sport – the 3rd International Conference on Concussion in Sport held in Zurich, Nov 2008. SAJSM; 2009;vol 21 No. 2.

AGREE II Score: 4/7

This updated international consensus statement was ‘developed for use by physicians, therapists, certified athletic trainers, health professionals, coaches and other people involved in the care of injured athletes, whether at the recreational, elite or professional level. Recommendations apply to adults, adolescents and children. The guideline is based on a literature review, however details of its methodology and strength of the evidence are not provided.

Key findings in the guideline relevant to persistent symptoms include:

Amnesia and other symptoms:

There is renewed interest in the role of post-traumatic amnesia and its role as a surrogate measure of injury severity (McCrea et al 2002, 2003; Cantu 2001). Published evidence suggests that the nature, burden and duration of the clinical post-concussive symptoms may be more important than the presence or duration of amnesia alone (Leninger et al 1990; Lovell et al 2003; McCrory et al 2000). Further it must be noted that retrograde amnesia varies with the time of measurement post-injury and hence is poorly reflective of injury severity (Yarnell et al 1970, 1973).

Depression:

Mental health issues (such as depression) have been reported as a long-term consequence of traumatic brain injury including sports related concussion. Neuroimaging studies using fMRI suggest that a depressed mood following concussion may reflect an underlying pathophysiological abnormality consistent with a limbic-frontal model of depression (Lima et al 2008; Fleminger 2008; Chen et al 2008; Bryant 2008; Vanderploeg et al 2007; Guskiewicz et al 2007; Kashluba et al 2006; Iverson 2006; Chamelian & Feinstein 2006; Mooney et al 2005; Broschek & Freeman 2005; Pellman 2003).

5. Veterans Affairs & Dept Defence (2009) Management of concussion/ mild traumatic brain injury. Clinical practice guideline. *J Rehab Res & Dev* 46(6): CP1-68.

AGREE II Score: 4/7

This US guideline applies to adult patients (18yrs+) who are diagnosed with concussion/mTBI and complain of symptoms related to the injury and who are treated in VA/DoD clinical settings for these symptoms at least 7 days after the initial head injury. The guideline is relevant to all healthcare professionals providing or directing treatment services (p.ii).

Recommendations and findings relevant to persistent symptoms:

Natural course of the disease:

- *The vast majority of patients who have sustained a concussion/mTBI improve with no lasting clinical sequelae. (Grade C: No recommendation for or against the routine provision of the intervention is made)*
- *Patients should be reassured and encouraged that the condition is transient and full recovery is expected. The term 'brain damage' should be avoided. A risk communication approach should be applied. (Grade A: Strong recommendation that the clinicians provide the intervention to eligible patients; based on good evidence)*
- *The vast majority of patients recover within hours to days, with a small proportion taking longer. In an even smaller minority, symptoms may persist beyond six months to a year. (Grade C: No recommendation for or against the routine provision of the intervention is made)*
- *The symptoms associated with Post-Concussion Syndrome (PCS) are not unique to mTBI. The symptoms occur frequently in day to day life among healthy individuals and are also found often in persons with other conditions such as chronic pain or depression. (Grade A: Strong recommendation that the clinicians provide the intervention to eligible patients; based on good evidence)*

Persistent symptom management:

- *Treatment of somatic complaints (e.g. sleep, dizziness/coordination problems, nausea, numbness, smell/taste, vision, hearing, fatigue, appetite problems) should be based upon individual factors and symptom presentation. (Grade A: Strong recommendation that the clinicians provide the intervention to eligible patients; based on good evidence).*
- *Headache is the single most common symptom associated with concussion/mTBI and assessment and management of headaches in individuals should parallel those for other causes of headache. (Grade C: No recommendation for or against the routine provision of the intervention is made).*

- *Medication for ameliorating the neurocognitive effects attributed to concussion/mTBI is not recommended.* (Grade B: A recommendation that clinicians provide (the service) to eligible patients).
- *Medications for headaches, musculoskeletal pain, or depression/anxiety must be carefully prescribed to avoid the sedating properties, which can have an impact upon a person's attention, cognition, and motor performance.* (Grade A: Strong recommendation that the clinicians provide the intervention to eligible patients; based on good evidence).
- *Treatment of psychiatric symptoms following concussion/mTBI should be based upon individual factors and the nature and severity of symptom presentation, and may include both psychotherapeutic and pharmacological treatment modalities.* (Grade A: Strong recommendation that the clinicians provide the intervention to eligible patients; based on good evidence).
- *In patients with persistent post-concussive symptoms (PPCS), which have been refractory to treatment, consideration should be given to other factors including psychiatric, psychosocial support, and compensatory/litigation.* (Grade B: A recommendation that clinicians provide (the service) to eligible patients).

Risk factors for persistent symptoms and/or poorer overall outcomes

Pre-injury	Peri-injury	Post-injury
<ul style="list-style-type: none"> - Age (older) - Gender (female) - Low SES - Less education / Lower levels of intelligence - Pre-neurological conditions - Pre- or co-occurrence of mental health disorders (depression, anxiety, traumatic stress, or substance use) 	<ul style="list-style-type: none"> - Lack of support system - Acute symptom presentation (e.g., headaches, dizziness, or nausea in the ER) - Context of injury (stress, combat-related, traumatic) 	<ul style="list-style-type: none"> - Compensation - Litigation (malingering, delayed resolution) - Co-occurrence of psychiatric disorders - Co-occurrence of chronic pain conditions - Lack of support system - Low education

Post-concussion symptoms

Somatic Symptoms	Psychological	Cognitive
<ul style="list-style-type: none"> Headache * o Fatigue * o Sensitivity to light/noise * 	<ul style="list-style-type: none"> Problems controlling emotions * o Irritability * 	<ul style="list-style-type: none"> Problems with memory * o Cognitive disorders *

<ul style="list-style-type: none"> o Insomnia & sleep disturbances * o Drowsiness * o Dizziness * o Nausea & vomiting * o Vision problems * o Transient neurological abnormalities o Seizures o Balance problems 	<ul style="list-style-type: none"> o Anxiety * o Depression * 	<ul style="list-style-type: none"> o Problems with concentration * o Functional status limitations *
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* In common with Post Concussive Syndrome (PCS)

Persistent physical symptoms – Treatment

Common Symptoms Following concussion/mTBI	Pharmacologic Treatment	Non-Pharmacologic Treatment	Referral After Failed Response to Initial Treatment
Headaches	Non narcotic pain meds - NSAIDs - Triptans (migraine type)	Sleep education - Physical therapy - Relaxation	Neurology Pain clinic
Feeling dizzy	Antibiotics, decongestants for infections and fluid		Dizzy : ENT/Neurology after ENT interventions
Loss of balance, Poor coordination		Physical therapy	Neurology
Nausea	Antiemetics	Sleep education	GI
Change in appetite			Consider mental health
Sleep disturbances - Difficulty falling or staying a sleep (insomnia)	Sleep Medications	Sleep education	Mental health PM&R Neurology
Vision problems - Blurring - Trouble seeing - Sensitivity to light		Sleep education - Light desensitisation - Sunglasses	Optometry Ophthalmology
Hearing difficulty		Environmental	Audiology

- Sensitivity to noise		modifications	ENT Sensitivity to Noise : Speech and Language Pathology
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Key systematic reviews relevant to persistent symptoms

1. **Nampiaparampil, D. E. (2008). "Prevalence of chronic pain after traumatic brain injury: A systematic review." JAMA: Journal of the American Medical Association 300(6): 711-719.**

CEBM Score: 3/5

This review investigated the prevalence of chronic pain as an underdiagnosed consequence of TBI, the interaction between severity of TBI and chronic pain and the characteristics of pain after TBI in civilian and combatant populations.

Key findings of the review:

- Chronic pain is a common complication of TBI, irrespective of level of injury severity, which is independent to psychological disorders such as post-traumatic stress disorder and depression.
- This review 'confirmed the clinical perception that patients with mild TBI have a higher prevalence of chronic pain syndromes than those with moderate to severe TBI ($P < .001$), [however] it remains unclear why this should be so.' (p716).
- In combat veterans, after adjustment for PTSD and depression, TBI was only correlated with headache pain, no other physical symptoms.

Rationale:

The authors found 10 studies that reported on the prevalence of pain in mild TBI patients, covering over 1046 participants of which 788 reported pain. This generated an overall pain prevalence rate of 75.3% (95% CI, 72.7%-77.9%).

2. **Chong, C. S. (2008). "Management strategies for post-concussion syndrome after mild head injury: a systematic review." Hong Kong Journal of Occupational Therapy 18(2): 59-67.**

CEBM Score: 4/5

This review investigated the effectiveness of management strategies for post-concussion syndrome after mild TBI.

Key findings of the review:

- The most often used management strategies for PCS were education, provision of coping techniques, and support and reassurance.
- The use of holistic outcome measures is needed to evaluate the effectiveness of the suggested treatment approaches in order to assist brain injured patients to better manage their residual symptoms so that they can return to their pre-injury level of functioning as much as possible and minimise the negative effects on their quality of life and wellbeing.
- There was a lack of consistency in the results and disagreement in the efficacy of the interventions. The efficacy of early interventions and follow-up treatment in PCS patients after mild TBI continues to be a controversial topic.

Rationale:

Only three randomised control trials were found and while there were a range of interventions strategies used, these three studies all had a main focus on education, support/reassurance, provision of coping strategies, ongoing advice and regular follow-up visits. Education included providing oral information, counselling, and encouragement. Patients were reassured that problems after injury were common and would probably disappear within a few months. Coping strategies taught included the introduction of structured daily activities and keeping a diary. Advice on gradual return to a normal level of activities and information sheets were provided.

The systematic review included the following studies in their review of this question:

Reference	Design	Results
Nampiarampil 2008		
Alfano et al, 2000	Cross-sectional	Pain prevalence: 88% (95% CI, 64.5%-100%) with chronic headache interfering with activities; 75% with pain elsewhere
Alfano 2006	Cross-sectional	Pain prevalence: 91.0% (95% CI, 82.6%-98.4%) with chronic pain (5.7% mild; 73.6% moderate; 32.1% severe)
Beetar et al, 1996	Retrospective	Pain prevalence: 70% (95% CI, 62.1%-78.0%) with mild TBI; 51.3% with pain at 1-12 mo; 37.8% with pain at 13-59 mo; 10.9% with pain at ≥60 mo
Jensen and Nielsen, 1990	Cross-sectional	Pain prevalence: 39.9% with preexisting headache; 64.3% (95% CI, 57.0%-71.5%) with posttraumatic headache
Lahz and Bryant, 1996	Cross-sectional	Pain prevalence: Mild TBI: 58% (95% CI, 45.2%-71.7%) with chronic pain; 47% with headache; 28% with neck/shoulder pain; 19% with low back pain
Mooney et al,	Cross-sectional	Pain prevalence: 72% (95% CI, 61.1%-82.7%) with headache; 64% with pain elsewhere 9% with mild

2005		TBI _ pain; 49% with mild TBI _ pain _ psychiatric diagnosis; 34% with history of psychological trauma; 57% of those with childhood abuse or sexual trauma and with correlation between pain and post concussive symptoms (P _ .001)
Rimel et al, 1981	Cross-sectional	Pain prevalence: 79% (95% CI, 74.8%-82.7%) with headache
Smith-Seemiller et al, 2003	Cross-sectional	Pain prevalence: 93.0% (95% CI, 82.7%-100%) with chronic pain; 81% with headache; 41% with pain elsewhere
Uomoto and Esselman, 1993	Retrospective	Pain prevalence: 94.5% (95% CI, 88.5%-100%) with mild TBI and chronic pain; 89% with mild TBI and headache; 22% (95% CI, 10.7%-34.1%)
Yamaguchi, 1992	Cross-sectional	Pain prevalence: 71.8% (95% CI, 60.9%-82.9%) with mild TBI and severe headache

Other earlier or lower quality evidence relevant to this topic

AANN and ARN clinical practice guidelines series- care of patient with mild traumatic brain injury 2011. (AGREE II Score 4/7)

Bazarian, J. J., I. Cernak, L. Noble-Haeusslein, S. Potolicchio and N. Temkin (2009). "Long-term neurologic outcomes after traumatic brain injury." *The Journal of Head Trauma Rehabilitation* 24(6): 439-451. (CEBM Score 1/5)

Begaz, T., D. N. Kyriacou, J. Segal and J. J. Bazarian (2006). "Serum biochemical markers for post-concussion syndrome in patients with mild traumatic brain injury." *Journal of Neurotrauma* 23(8): 1201-1210. (CEBM Score 2/5)

Carlson, K. F., S. M. Kehle, L. A. Meis, N. Greer, R. MacDonald, I. Rutks, N. A. Sayer, S. K. Dobscha and T. J. Wilt (2011). "Prevalence, Assessment, and Treatment of Mild Traumatic Brain Injury and Posttraumatic Stress Disorder: A Systematic Review of the Evidence." *Journal of Head Trauma Rehabilitation* 26(2): 103-115. (CEBM Score 2/5)

Daggett, V., T. Bakas and B. Habermann (2009). "A review of health-related quality of life in adult traumatic brain injury survivors in the context of combat veterans." *Journal of Neuroscience Nursing* 41(2): 59-71. (CEBM Score 1/5)

Harmon, K. G., J. A. Drezner, M. Gammons, K. M. Guskiewicz, M. Halstead, S. A. Herring, J. S. Kutcher, A. Pana, M. Putukian and W. O. Roberts (2013). "American Medical Society for Sports Medicine position statement: concussion in sport." *British Journal of Sports Medicine* 47(1): 15-26. (AGREE II Score 2/7)

Kwako, L. E., N. Glass, J. Campbell, K. C. Melvin, T. Barr and J. M. Gill (2011). "Traumatic Brain Injury in Intimate Partner Violence: A Critical Review of Outcomes and Mechanisms." *Trauma, Violence & Abuse* 12(3): 115-126. (CEBM Score 2/5)

Orff, H. J., L. Ayalon and S. P. Drummond (2009). "Traumatic brain injury and sleep disturbance: a review of current research." *Journal of Head Trauma Rehabilitation* 24(3): 155-165. (CEBM Score 1/5)

Ravishankar, K., A. Chakravarty, D. Chowdhury, R. Shukla and S. Singh (2011). "Guidelines on the diagnosis and the current management of headache and related disorders." *Annals of Indian Academy of Neurology* 14(SUPPL. 1): S40-S59. (AGREE II score 3/7)

Weightman et al. 2010. physical therapy recommendations for service members with mild traumatic brain injury. (AGREE II Score 3/7)

Wiseman-Hakes, C., A. Colantonio, et al. (2009). "Sleep and wake disorders following traumatic brain injury: a systematic review of the literature." *Critical Reviews in Physical & Rehabilitation Medicine* 21(3-4): 317-374. (CEBM Score 2/5)

Question 2.11 What is the evidence for aging well with TBI for adults with mild TBI?

Executive summary

One moderate quality recent systematic review relevant to aging with mild TBI in adult populations was found. The underpinning evidence base consisted of 24 articles published between 1989 and 2010. Of these articles only six investigated mild TBI in adults. These were not quality scored, and included a total of 93 115 participants.

Evidence statement

Key question	Rating	Notes
Evidence base	A	Information for moderate quality systematic review is based on data from studies of unknown quality and design.
Consistency	NA	Only one relevant review found
Clinical impact	D	Slight or restrictive clinical impact, as this is more applicable to moderate and severe TBI, and based on comparisons to a much younger age group.

Key systematic review regarding aging well with mild TBI

1. McIntyre, A., S. Mehta, J. Aubut, M. Dijkers and R. W. Teasell (2013). "Mortality among older adults after a traumatic brain injury: A meta-analysis." *Brain Injury* 27(1): 31-40.

CEBM Score: 3/5

This systematic review and meta-analysis examined the mortality rates of older adults (≥65 years) post traumatic brain injury. Of the 24 articles found, only six of these focused on mild TBI; five retrospective (Grossman et al. 2002; Ritchie et al. 2000; Utomo et al. 2009; Mohindra et al. 2008; Flaada et al. 2007) and one prospective (Bouras et al. 2007) (study design not further clarified. No further information on these primary studies was supplied in the review). Adults over the age of 55 years often have confounding features that can affect survival; this can impact on the validity of the Glasgow Coma Scale as an indicator of likely mortality in this group. While this is more likely for moderate to severe injuries, this is still a factor in mild injuries. The authors suggest it could be common for mild TBI to go undiagnosed in older adults, because the injury and accompanying deficits go unnoticed, leading to lower rates of transfer and aggressive treatment in older adults when compared to younger age groups. This can increase the likelihood of a mild TBI progressing to moderate or severe injury over days

or weeks, and thus increase the risk of mortality, thus explaining the higher death rate in older TBI sufferers compared to younger TBI sufferers.

Key findings from the review:

- Some means of better assessing prognosis in the elderly other than on the basis of the Glasgow Coma Scale is needed to ensure that the sub-set of older, mild TBI patients who are likely to respond to more aggressive measures are identified and treated.
- *“Medical complications can arise from concurrent injuries, co-morbidities, frailty, previous trauma and drug–drug interactions. Pre-existing diseases which predicted greater mortality post-TBI have been reported to be cancer, kidney disease, liver disease and heart and lung disease. Additionally, [it was] found that older individuals with TBI, with three or more pre-existing co-morbid diseases, had mortality rates that were 4-times higher than individuals without any pre-existing disease” (p.38).*

Other earlier or lower quality evidence on the topic

Rutherford, G. W. and R. C. Wlodarczyk (2009). "Distant sequelae of traumatic brain injury: premature mortality and intracranial neoplasms." *Journal of Head Trauma Rehabilitation* 24(6): 468-474. (CEBM score 2/7)

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APPENDIX 1

Example Medline search string

2. Mild TBI in adults Consider the specific issues relevant to mild TBI
 .7. Depression.

Question: 2.7 Mild TBI in adults and depression			
Database searched: Medline			
Search number	Search terms	Search process	Number of returns
1.	brain injuries.mp. or exp Brain Injuries/	Key word and MeSH term search	46566
2.	Craniocerebral Trauma.mp. or exp Craniocerebral Trauma/	Key word and MeSH term search	114286
3.	Cerebrovascular Trauma.mp. or exp Cerebrovascular Trauma/	Key word and MeSH term search	4990
4.	Brain Edema.mp. or exp Brain Edema/	Key word and MeSH term search	13384
5.	Brain Concussion.mp. or exp Brain Concussion/	Key word and MeSH term search	4366
6.	Unconsciousness.mp. or exp Unconsciousness/	Key word and MeSH term search	33472
7.	Glasgow Outcome Scale.mp. or exp Glasgow Outcome Scale/	Key word and MeSH term search	2524
8.	Epilepsy, post-traumatic.mp. or exp Epilepsy, Post-Traumatic/	Key word and MeSH term search	1010
9.	Cerebral haemorrhage, traumatic.mp. or exp Cerebral Hemorrhage/	Key word and MeSH term search	26157
10.	Cerebral hemorrhage, traumatic.mp. or exp Cerebral Hemorrhage, Traumatic/	Key word and MeSH term search	245
11.	Hypoxia, brain.mp. or exp Hypoxia, Brain/	Key word and MeSH term search	9653
12.	Brain injur* OR brain trauma* OR brain damag* OR brain contusion* OR cerebr* injur* OR cerebr* trauma* OR cerebr* damag* OR cerebr* contusion* OR forebrain injur* OR forebrain trauma* OR forebrain contusion* OR head injur* OR head trauma* OR intra-cran* injur* OR intra-cran* trauma* OR intra-cran* contusion* OR Diffuse axonal injur* OR diffuse axonal injur* OR concuss* OR unconscious* OR	Key word search- title and abstract	67197
13.	1-12/ OR		221962

14.	exp Depression/ or Depression.mp.	Key word and MeSH term search	251014
15.	Depressive Disorder.mp. or exp Depressive Disorder/	Key word and MeSH term search	78675
16.	Mood disorders.mp. or exp Mood Disorders/	Key word and MeSH term search	109692
17.	Affective symptoms.mp. or exp Affective Symptoms/	Key word and MeSH term search	11285
18.	(Depress* or mood disorder* or emotion* disturbance* or affective symptoms*).ab.	Key word search- title and abstract	268098
19.	14-18/ OR		379471
20.	13 AND 19		5395
21.	(Systematic review or Meta-Analysis or meta analysis or Guideline).ab.	Key word search- title and abstract	69977
22.	20 AND 21		35
23.	22	Limited to English language and year-2006-current	21

APPENDIX 2

CEBM Critical Appraisal Tool for Systematic Reviews

<http://www.cebm.net/index.aspx?o=1157>

SYSTEMATIC REVIEW: Are the results of the review valid?

1. What question (PICO) did the systematic review address?	
What is best?	Where do I find the information?
The main question being addressed should be clearly stated. The exposure, such as a therapy or diagnostic test, and the outcome(s) of interest will often be expressed in terms of a simple relationship.	The Title, Abstract or final paragraph of the Introduction should clearly state the question. If you still cannot ascertain what the focused question is after reading these sections, search for another paper!
This paper: Yes <input type="checkbox"/> No <input type="checkbox"/> Unclear <input type="checkbox"/> Comment:	
2. Is it unlikely that important, relevant studies were missed?	
What is best?	Where do I find the information?
The starting point for comprehensive search for all relevant studies is the major bibliographic databases (e.g., Medline, Cochrane, EMBASE, etc) but should also include a search of reference lists from relevant studies, and contact with experts, particularly to inquire about unpublished studies. The search should not be limited to English language only. The search strategy should include both MESH terms and text words.	The Methods section should describe the search strategy, including the terms used, in some detail. The Results section will outline the number of titles and abstracts reviewed, the number of full-text studies retrieved, and the number of studies excluded together with the reasons for exclusion. This information may be presented in a figure or flow chart.
This paper: Yes <input type="checkbox"/> No <input type="checkbox"/> Unclear <input type="checkbox"/> Comment:	
3. Were the criteria used to select articles for inclusion appropriate?	
What is best?	Where do I find the information?
The inclusion or exclusion of studies in a systematic review should be clearly defined a priori. The eligibility criteria used should specify the patients, interventions or exposures and outcomes of interest. In many cases the type of study design will also be a key component of the eligibility criteria.	The Methods section should describe in detail the inclusion and exclusion criteria. Normally, this will include the study design.
This paper: Yes <input type="checkbox"/> No <input type="checkbox"/> Unclear <input type="checkbox"/> Comment:	
4. Were the included studies sufficiently valid for the type of question asked?	
What is best?	Where do I find the information?
The article should describe how the quality of each study was assessed using predetermined quality criteria appropriate to the type of clinical question (e.g., randomisation, blinding and completeness of follow-up)	The Methods section should describe the assessment of quality and the criteria used. The Results section should provide information on the quality of the individual studies.
This paper: Yes <input type="checkbox"/> No <input type="checkbox"/> Unclear <input type="checkbox"/> Comment:	

5. Were the results similar from study to study?	
What is best?	Where do I find the information?
Ideally, the results of the different studies should be similar or homogeneous. If heterogeneity exists the authors may estimate whether the differences are significant (chi-square test). Possible reasons for the heterogeneity should be explored.	The Results section should state whether the results are heterogeneous and discuss possible reasons. The forest plot should show the results of the chi-square test for heterogeneity and if discuss reasons for heterogeneity, if present.
This paper: Yes <input type="checkbox"/> No <input type="checkbox"/> Unclear <input type="checkbox"/> Comment:	


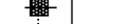




What were the results?

How are the results presented?

A systematic review provides a summary of the data from the results of a number of individual studies. If the results of the individual studies are similar, a statistical method (called meta-analysis) is used to combine the results from the individual studies and an overall summary estimate is calculated. The meta-analysis gives weighted values to each of the individual studies according to their size. The individual results of the studies need to be expressed in a standard way, such as relative risk, odds ratio or mean difference between the groups. Results are traditionally displayed in a figure, like the one below, called a forest plot.

Comparison: 03 Treatment versus Placebo

Outcome: 01 Effect of treatment on mortality

Study	Treatment n/N	Control n/N	OR (95%CI Fixed)	Weight %	OR (95%CI Fixed)
Brown 1998	24 / 472	35 / 499		9.6	0.71[0.42,1.21]
Geoffrey 1997	120 / 2850	182 / 2838		51.8	0.64[0.51,0.81]
Mason 1996	56 / 2051	84 / 2030		24.4	0.65[0.46,0.92]
Peters 2000	5 / 81	4 / 78		1.1	1.22[0.31,4.71]
Scott 1998	31 / 788	46 / 792		13.1	0.66[0.42,1.06]
Total(95%CI)	236 / 6242	351 / 6237		100.0	0.66[0.56,0.78]

Test for heterogeneity chi-square=0.92 df=4 p=0.92
Test for overall effect z=-4.82 p<0.00001

.1 .2 1 5 10
Favours treatment Favours control

The forest plot depicted above represents a meta-analysis of 5 trials that assessed the effects of a hypothetical treatment on mortality. Individual studies are represented by a black square and a horizontal line, which corresponds to the point estimate and 95% confidence interval of the odds ratio. The size of the black square reflects the weight of the study in the meta-analysis. The solid vertical line corresponds to 'no effect' of treatment - an odds ratio of 1.0. When the confidence interval includes 1 it indicates that the result is not significant at conventional levels ($P>0.05$).

The diamond at the bottom represents the combined or pooled odds ratio of all 5 trials with its 95% confidence interval. In this case, it shows that the treatment reduces mortality by 34% (OR 0.66 95% CI 0.56 to 0.78). Notice that the diamond does not overlap the 'no effect' line (the confidence interval doesn't include 1) so we can be assured that the pooled OR is statistically significant. The test for overall effect also indicates statistical significance ($p<0.0001$).

Exploring heterogeneity

Heterogeneity can be assessed using the "eyeball" test or more formally with statistical tests, such as the Cochran Q test. With the "eyeball" test one looks for overlap of the confidence intervals of the trials with the summary estimate. In the example above note that the dotted line running vertically through the combined odds ratio crosses the horizontal lines of all the individual studies indicating that the studies are homogenous. Heterogeneity can also be assessed using the Cochran chi-square (Cochran Q). If Cochran Q is statistically significant there is definite heterogeneity. If Cochran Q is not statistically significant but the ratio of Cochran Q and the degrees of freedom (Q/df) is > 1 there is possible heterogeneity. If Cochran Q is not statistically significant and Q/df is < 1 then heterogeneity is very unlikely. In the example above Q/df is < 1 ($0.92/4 = 0.23$) and the p-value is not significant (0.92) indicating no heterogeneity.

Note: The level of significance for Cochran Q is often set at 0.1 due to the low power of the test to detect heterogeneity.

APPENDIX 3

AGREE II appraisal summaries – Guidelines

Guideline	% Score average across appraisers	Overall quality score /7	Recommended
AANN and ARN (2011).Clinical practice guidelines series- care of patient with mild traumatic brain injury.	42.9	4	Yes (with modifications)
ARC & NZRC. (2010) Basic Life Support: Unconsciousness. ARC and NZRC Guideline.	28.0	1	No
Barbosa et al. (2012) Evaluation and management of mild TBI: An Eastern Association for the Surgery of Trauma practice management guideline.	57.1	3	Yes (with modifications)
Brain Trauma Foundation (US) 2006 Guidelines for surgical management of TBI	82	6	Yes
Brain Trauma Foundation (US) 2007 Guidelines for prehospital management of severe TBI	83.2	6	Yes
Brain Trauma Foundation (US) 2012 Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents- 2 nd Ed.	76.4	5	Yes
Canadian Paediatric Soc. (2012) Evaluation and management of children and adolescents with sports related concussion	37.3	1	No
Cincinnati Childrens' BESt (2012) Coordination of outpatient rehabilitative care for patients with Traumatic Brain Injury (TBI) and their families	72	4	Yes (with modifications)
Cooper (2009) Preliminary guidelines for prosthetic care for amputees with TBI.	48.4	2	No

DeWall (2009). Severe pediatric traumatic brain injury.	24.2	1	No
Golisz K. (2009). Occupational therapy practice guidelines for adults with traumatic brain injury. American Occupational Therapy Assoc	82.6	6	Yes (with modifications)
Harman et al (2013). American Medical Society for Sports Medicine position statement: concussion in sport	34.2	2	No
Hebb et al. (2007) Development of a provincial guideline for the acute assessment and management of adult and pediatric patients with head injuries.	39.8	3	Yes (with modifications)
Jacoda et al (ACEP/CDC) (2008) Clinical Policy: Neuroimaging and decision making in adult mild traumatic brain injury in the acute setting.	62.1	4	Yes (with modifications)
Japan Neurosurgical Soc. (Toshiaki et al) (2012) Guidelines for the management of severe head injury 2 nd Ed.	38.5	3	Yes (with modifications)
Liao K-H et al. (2009) Clinical practice guidelines in severe traumatic brain injury in Taiwan.	76.4	5	Yes (with modifications)
Marshall et al (2012). Clinical practice guidelines for mild traumatic brain injury and persistent symptoms.	85.1	6	Yes
McCrory et al. (2008) Consensus Statement on Concussion in Sport – the 3rd International Conference on Concussion in Sport held in Zurich, Nov 2008.	66.5	4	Yes (with modifications)
Motor Accidents Authority of NSW (MAA NSW). 2008 Guidelines for Mild Traumatic Brain Injury Following a Closed Head Injury	89.4	7	Yes
NICE (2007) Head injury: Triage, assessment, investigation and early management of head injury in infants, children and adults.	93.2	4	Yes (with modifications)
NZ Guideline Group (2007). Traumatic brain injury: Diagnosis, acute management and rehabilitation.	90.7	7	Yes
Ontario Neurotrauma Foundation. (2012) Guidelines for mild traumatic brain injury and persistent symptom	37.3	1	No

Ravishankar et al. (2011) Guidelines on the diagnosis and the current management of headache and related disorders.	42.2	3	No
Stergio-Kita et al (2012) Inter-professional clinical practice guideline for vocational evaluation following traumatic brain injury: A systematic and evidence-based approach	80.1	6	Yes
SIGN (2009) Early management of patients with a head injury.	90.1	7	Yes
SIGN (2013) Brain injury rehabilitation in adults.	98.8	7	Yes
Reed (2007), Adult trauma clinical practice guidelines: Initial management of closed head injury in adults. NSW Institute of Trauma and Injury Management.	73.9	4	Yes (with modifications)
Veterans Affairs & Dept Defence (2009) Management of concussion/ mild traumatic brain injury. Clinical practice guideline.	69.6	4	Yes (with modifications)
Vos et al. (2012) Mild traumatic brain injury.	66.5	5	Yes (with modifications)
Warden et al (2006) Guidelines for the pharmacologic treatment of neurobehavioral sequelae of traumatic brain injury.	82.6	6	Yes
Weightman et al. (2010) Physical therapy recommendations for service members with mild traumatic brain injury	42.9	3	Yes (with modifications)

APPENDIX 4

Critical appraisal summaries – Included systematic reviews

	Q1	Q2	Q3	Q4	Q5	CEMB Total out of 5
SOURCE	Clearly stated question?	Is it unlikely that important studies were missed?	Were appropriate criteria used to select articles?	Were included studies sufficiently valid for the type of Q asked? (appropriate population?)	Were the results similar from study to study? (homogeneity)?	
Alla 2009	✓	✗	✓	✓	✗	3
Babikian 2009	✓	✗	✓	✗	✓	3
Bazarian 2009	✓	✗	✗	✗	✗	1
Begaz 2006	✓	✗	✓	✗	✗	2
Belanger 2010	✓	✗	✓	✗	✓	3
Boot 2010	✓	✗	✓	✓	✗	3
Broglia 2008	✓	✗	✓	✓	✓	4
Carlson 2011	✓	✗	✓	✗	✗	2
Chong 2008	✓	✗	✓	✓	✓	4
Daggett et al. 2009	✓	✗		✗	✗	1
Davidson et al. 2011	✓	✗	✓	✓	✓	4
Davis et al. 2009	✓	✗	✗	✗		1
Deitch & Dayal 2006	✓	✗	✗	✗		1
Di Battista et al. 2012	✓	✗	✓	✗	✓	3
Dikmen et al. 2009	✓	✗	✓	✗	✓	3

Dimoska-Di Marco et al. 2011	✓	✗	✓	✗	✓	3
Eccleston et al. 2012	✓	✓	✓	✓	✓	5
Esposito and Walker 2009		✗	✗	✗		0
Fann et al. 2009	✓	✗	✓	✓	✓	4
Farrer and Hedges 2011	✓	✗	✓	✗	✓	3
Fazel et al. 2009	✓	✗	✓	✓	✓	4
Fehlings et al. 2010	✓	✗	✓	✗	✗	2
Fergusson et al. 2007	✓	✗	✗	✗	✓	2
Filippidis et al. 2010	✓	✗	✓	✗		2
Fleminger et al. 2006	✓	✓	✓	✓	✓	5
Foster et al. 2010	✓	✗	✗	✗	✗	1
Galland et al. 2012	✓	✗	✓	✓	✓	4
Gardner et al. 2012	✓	✗	✓	✓	✓	4
Greenwald and Rigg 2009	✗	✗	✗	✗	✗	0
Greer et al. 2008	✓	✗	✗	✗	✓	2
Harhangi et al. 2008	✓	✗	✗	✗	✓	2
Harnan et al. 2011	✓	✗	✓	✓	✓	4
Hesdorffer et al. 2009	✓	✗	✗	✗	✓	2
Hill et al. 2011	✓	✗	✓	✓	✓	4
Huynh et al. 2009	✓	✗	✗	✗	✗	1
Keightley et al. 2012	✓	✗	✓	✗	✓	3
Kemp et al. 2009	✓	✓	✓	✓	✓	5
Kemp et al. 2011	✓	✓	✓	✓	✓	5

Kendall 2006	✓	✗	✓	✗	✓	3
Kennedy et al. 2008	✓	✗	✓	✓	✓	4
Kochanek & Tasker 2009	✓	✗	✗	✗	✗	1
Königs et al. 2012	✓	✗	✓	✓	✓	4
Kövesdi et al. 2010	✓	✗	✗	✗	✗	1
Kwako et al. 2011	✓	✗	✓	✗	✗	2
Laatsch 2007	✓	✗	✓	✓	✓	4
Li & Liu 2012	✓	✗	✓	✓	✓	4
Li et al. 2010	✓	✗	✓	✗	✗	2
McIntyre et al. 2013	✓	✗	✓	✗	✓	3
McNamee 2009	✓	✗	✗	✗	✗	1
Molloy et al. 2011	✓	✗	✓	✗	✓	3
Morgan & Vogel 2008	✓	✗	✗	✗	✗	1
Nampiaparampil 2008	✓	✗	✓	✗	✓	3
Orff 2009	✓	✗	✗	✗	✗	1
Panayiotou et al. 2009	✓	✗	✓	✓	✓	4
Pandor et al. 2012	✓	✗	✓	✓	✓	4
Papa et al. 2013	✓	✗	✓	✗	✗	2
Pickering et al. 2011	✓	✓	✓	✓	✓	5
Poole & Agrawal 2008	✓	✗	✗	✗	✓	2
Price et al. 2011	✓	✗	✓	✓	✓	4
Provvidenza & Johnston 2009	✓	✗	✗	✗	✗	1
Putukian et al. 2009	✓	✗	✗	✗	✗	1

Rietdijk et al. 2012	✓	✗	✓	✓	✓	4
Rispoli et al. 2010	✓	✗	✓	✗	✓	3
Roberts & Sydenham 2012	✓	✓	✓	✓	✓	5
Rogers & Read 2007	✓	✗	✗	✗	✓	2
Rosema et al. 2012	✓	✗	✓	✗	✓	3
Ross et al. 2011b	✓	✗	✓	✓	✓	4
Rutherford & Włodarczyk 2009	✓	✗	✓	✗	✗	2
Sambuco et al. 2008	✓	✗	✗	✗	✗	1
Shames 2007	✓	✗	✗	✗	✗	1
Shaw 2008	✓	✗	✓	✗	✗	2
Shum 2011	✓	✗	✓	✗	✓	3
Snell 2009	✓	✗	✓	✓	✗	3
Stippler 2012	✓	✗	✓	✓	✗	3
Teasell 2007	✓	✗	✓	✓	✓	4
Temkin 2009	✓	✗	✓	✗	✓	3
Torrence 2011	✓	✗	✗	✗	✗	1
Tume & Jinks 2008	✓	✗	✓	✗	✗	2
Tyerman 2012	✓	✗	✗	✗	✓	2
Unden 2010	✓	✗	✗	✓	✓	3
von Elm et al. 2009	✓	✓	✓	✓	✓	5
Vu 2011	✓	✗	✓	✗	✓	3
Williams 2007	✓	✗	✗	✗	✓	2
Wiseman-Hakes 2009	✓	✗	✗	✓	✗	2

Ylvisaker 2007	✓	✗	✓	✗	✗	2
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APPENDIX 5

Table A1 NHMRC Evidence Hierarchy: designations of ‘levels of evidence’ according to type of research question

Level	Intervention	Diagnostic accuracy	Prognosis	Aetiology	Screening Intervention
I 4	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation	A prospective cohort study ⁷	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation	All or none	All or none	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: <ul style="list-style-type: none"> ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group 	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: <ul style="list-style-type: none"> ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study

III-3	A comparative study without concurrent controls: <ul style="list-style-type: none"> ▪ Historical control study ▪ Two or more single arm study ▪ Interrupted time series without a parallel control group 	Diagnostic case-control study ⁶	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: <ul style="list-style-type: none"> ▪ Historical control study ▪ Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

APPENDIX 6

NHMRC FORM Matrix

http://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/evidence_statement_form.pdf

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
1. Evidence base	several level I or II studies with low risk of bias	one or two level II studies with low risk of bias or a SR/multiple level III studies with low risk of bias	one or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias	level IV studies, or level I to III studies with high risk of bias
2. Consistency	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
3. Clinical impact	very large	substantial	moderate	slight or restricted