**Treatment outcomes in mild traumatic brain injury: a systematic review of randomized controlled trials**

Proposed review article for Brain Injury

Word count 4388, Tables 7; Figures 1; Pages 18; References 45

M Arbabi1,2\*, RJG Sheldon3,4, P Bahadoran4, JG Smith5, N Poole4 ,N Agrawal4

1 Brain & Spinal Cord Injury Research Centre ,Tehran University of Medical Sciences,

Tehran, Iran

2 Psychosomatic Medicine Research Centre, Tehran University of Medical Sciences,

Tehran, Iran

3 Sussex Partnership NHS Foundation Trust, Worthing, UK

4 Department of Neuropsychiatry, St George’s Hospital, London, UK; and South West London and St George’s Mental Health NHS Trust, London, UK

5 Population Health Research Institute, St George's, University of London, London, UK

\*Corresponding author.

**Abstract:**

**Objectives**: Mild traumatic brain injury (mTBI) is a controversial and under-researched area, despite most traumatic brain injuries being classed as mild. A number of different treatment approaches are described to treat this condition. Our objective was to review the evidence underpinning these approaches to treat mTBI including educational, psychological, rehabilitative and pharmacological approaches and discuss their efficacy.

**Methods**: A systematic review of literature was carried out using Web of science, Scopus, Medline, Pubmed, Cinahl, and PsychInfo databases. Randomised Controlled Trials (RCTs) looking at treatment outcome in mTBI for adults were included, published between 1980 and 2019. A review of the methodological quality of the studies was conducted using the Scottish Intercollegiate Guideline Network (SIGN) checklist for RCTs to evaluate the risk of bias, and a synthesis of studies was conducted.

**Results**: Searches identified 3993 studies, of which 25 met inclusion criteria, and a total number of participants of 3213. Mean age was 35, and 59% male. Ten studies had <100 participants, 15 studies 100-395. Studies were grouped into education and early intervention (9), rehabilitation (8), psychological interventions (4), and pharmacotherapy (4). Ten studies were assessed as being at low, 7 moderate, and 8 high/unacceptable risk of bias. Inconsistency of definitions and outcome measures used precluded meta-analysis.

**Conclusions:** Although the number of RCTs in this field has expanded, unfortunately there are still significant methodological problems which means that no particular approach can be recommended based on good scientific evidence. However, traditional education and reassurance can no longer be recommended as having the best evidence base for efficacy as compared to psychological and rehabilitative approaches, and guidelines should begin to reflect this.

**Introduction**

Traumatic brain injury (TBI) is common. Its incidence in Europe has been estimated at 262 per 100,000, while each year in the United States 1.7 million people across all age groups suffer some degree of TBI. One third of trauma-related deaths in the United States are due to TBI (1), and it is one of the most important causes of disability in the world (2). Indeed, it has been found that brain injuries are the most likely type of injury to result in death or disability (2).

Mild traumatic brain injury (mTBI) occurs in the absence of readily detectable neurological damage (3). It accounts for 70-90% of brain injuries (4), and is a common complaint in patients attending Accident and Emergency departments, where patients may present with a complicated pattern of symptoms (5). The American Congress of Rehabilitation Medicine suggested a practical definition in 1993 in an attempt to resolve disputes concerning the diagnosis and treatment of mild traumatic brain injury (6). In addition, there is a 2004 definition of mTBI by the WHO Collaborating Centre Task Force (5). Both definitions have in common the presence of: confusion or disorientation at the time of the accident; loss of consciousness <30 minutes; an initial Glasgow Coma Scale of ≥13 30 minutes after injury; post traumatic amnesia of no more than 24 hours; and other neurological abnormalities so long as they are transient (5,6).

In patients with mTBI, early cognitive problems after the initial event are common, and despite expectation of good outcome complete recovery may be delayed (7). Indeed, patients with mTBI may suffer from chronic memory and concentration difficulties, affecting their daily activities (8). In addition to the cognitive symptoms, patients suffer from a variety of neurological, audiovestibular and neuropsychiatric symptoms such as headache, dizziness, tinnitus, fatigue, anxiety, depression, irritability and sleep disturbance (8). Despite the raised prevalence of these symptoms after TBI, many patients do not receive effective treatment for them, and most do not understand their difficulties (9). Likewise, there is evidence that professionals often do not fully appreciate the extent of the patients’ complaints or know how best to treat them. (10)

Various pharmacological and psychotherapeutic interventions have nevertheless been proposed. While some approaches appear promising in research studies, their clinical effectiveness remains uncertain (11). Due to the impact of these symptoms on functioning, an effective treatment is required in order to reduce the risk of prolonged disability.

There have been a handful of systematic reviews in treatment of symptoms of mTBIs as a whole. The first, by Borg et al (12) in 2004 reviewing *non-surgical interventions*, proposed that the heterogeneity of mTBI and the diversity of symptoms makes it difficult to produce high quality research and recommendations in this area. However, on the basis of the, albeit limited, evidence available, psycho-educational approaches were recommended while rehabilitation was not. Following this, Comper et al (13) in 2005 reviewed *pharmacotherapy, cognitive rehabilitation, patient education, and other interventions* and also noted that the limited number of studies of mTBI treatment and the variability in defining mTBI rendered it difficult to form definitive conclusions. Nevertheless, they also suggested that psychoeducation had the strongest evidence of effectiveness in mTBI treatments in comparison with pharmacotherapy and rehabilitation.

Snell et al in 2009, in their review of *psychological treatments* for mTBI (14), assessed new studies published between 2004 and 2006, which provided some continuity with previous reviews. This review drew attention to the small sample sizes used in studies and inconsistent evaluation methods. The authors suggested that sub-groups at risk of developing chronic symptoms should be identified and offered preventative interventions. Although they found psychoeducational approaches to have some efficacy, they again commented on the lack of randomization and blinding in the current evidence base (14).

Carroll et al, writing in 2014, evaluated the evidence base from 2001 to 2012 regarding *persistent* *symptoms* following mTBI (15). Their conclusions favoured one study of telephone-based psychoeducation over an evaluation of bed rest, and therefore recommended (on the weak evidence available) physical activity and psychoeducation. They found only 2 studies out of 7 were at low risk of bias, and therefore recommended future randomised controlled trials to apply the Consolidated Standards of Reporting Trials (CONSORT) protocol (16). Furthermore, they commented on the use of unvalidated outcome scales, the lack of studies regarding prognostic factors in mTBI, and the conceptual problem of the overlap between symptoms of mTBI, back injury and whiplash.

The review by Thomas et al in 2017 (17) assessed RCTs of *therapies* for mTBI. However, this did not provide a synthesis of all literature, and was focused on cognitive behavioural therapy, digital assistant therapy, and physical therapy. It was again found that there was a significant problem with different studies using different definitions, multiple types of outcome measures, and a high rate of attrition.

Most recently, Sullivan et al in 2019 (45) published a systematic review of psychological treatments of persistent postconcussion symptoms after mTBI. They, however, grouped together CBT and counselling evidence with education and reassurance approaches as psychological interventions, and concluded counselling and CBT have most support. In our opinion, it is unhelpful to merge educational interventions, which are commonly used, with less frequently employed psychotherapeutic approaches into the same category.

As there has not been a broad-based systematic review covering the whole range of treatment options studied in recent years, specifically examining randomized controlled trials in mild traumatic brain injury, we conducted this systematic review to provide an update and synthesis of all RCTs investigating educational, psychological, rehabilitative and pharmacological treatments and ascertain the most effective methods to manage mTBI.

**Method**

A systematic review of all randomized controlled trials looking into treatment outcome of mTBI in adults was undertaken. The databases Web of Science, Scopus, Medline, Pubmed, Cinahl, PsychInfo, and Google Scholar grey literature were reviewed in order to find studies on the outcomes of treatments in mild traumatic brain injury (mTBI) from 1980 to 2019. References of existing articles were cross checked to reveal further studies. The systematic review was conducted in accordance with guidelines described by the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) (46) at all stages of review including search strategy, identification of studies, screening for relevancy, eligibility assessment and qualitative synthesis (44).

**Search strategy**

The search strategy included *injury* terms: ‘mild traumatic brain injury’, ‘concussion’, ‘brain concussion’, ‘commotio cerebri’, ‘intermediate concussion’, ‘severe concussion’, and ‘mild concussion’ united by the Boolean operator ‘OR’. In addition, the Boolean operator ‘AND’ combined the *injury* terms with *treatment* terms: ‘treat’, ‘treating’, ‘treatment’, treatment/prevention’, ‘management’, ‘managing’, ‘psychotherapy’, ‘psychotherapeutic’, ‘intervention’, ‘interventional’, ‘rehabilitation’, ‘clinical effectiveness’, ‘effectiveness’, and ‘efficacy’. Another Boolean operator ‘AND’ was then combined with the *injury* and *treatment* groups to also search for *outcome* terms which were themselves combined with the Boolean operator ‘OR’: ‘outcome’, ‘consequence’, ‘disability’, ‘disabilities’, ‘function(al)’, ‘functional’, ‘patient-relevant outcome’, or ‘rehabilitation outcome(s)’

**Inclusion and exclusion criteria**

The inclusion criteria were: cases of *mild* traumatic brain injury or concussion; unaccompanied by encephalitis/stroke/bullet shots; with a mean or median age over 18; randomized controlled trials (RCTs) exclusively; in English; and published in peer-reviewed journals, and for which the full text could be sourced. Studies that focused on a single post brain injury symptom, such as headache, or where the sample did not explicitly include mTBI populations, were excluded.

The abstracts were reviewed by two authors (MA and PB). Disagreement between these two was resolved by a third author (NA). The Scottish Intercollegiate Guidelines Network Tool (SIGNtool) (18) was used to measure the risk of study bias, and produce a rating of very high, high, moderate or low risk. This tool considers the appropriateness and focus of the research question and includes evaluative items concerning key methodological aspects of Randomised Clinical Trial, including randomisation, treatment concealment, allocation blindness, outcome measures and analysis(18).

**Results**

The initial database search identified 6081 records, which was reduced to 3993 after removal of duplicates. Assessment of the abstracts on the basis of inclusion and exclusion criteria left 408 full text articles for evaluation. The examination of bibliographies produced two additional articles. A total of 383 full text articles were found not to meet the inclusion and exclusion criteria, leaving 25 articles for inclusion in this systematic review. Please see **Figure 1** for details of article selection in this review. There were four categories of intervention: education and early intervention (19-27); rehabilitation (28-35); psychological interventions (36-39); and pharmacotherapy (40-43).

*Please insert Figure 1. here*

**Study characteristics**

There were 3213 patients in total, across 25 articles, broken down into 1653 subjects who underwent an intervention and 1560 controls. Three articles were follow-up studies of previous trials (23, 25, 32); and two were studies of all severities of TBI but with an mTBI subgroup analysis (19, 20). Education and early intervention comprised 1154 patients; rehabilitation comprised 1055 patients, psychological therapy comprised 859 patients, and pharmacotherapy 145 patients.

The age range overall was from 15 to 76 years, but in twelve studies was not reported (19-24, 33-37, 42). Mean age was not clear in two studies (19-20), but in the rest it was between ages 24 and 49, and overall was 35. Sex ratios ranged from 93% male (39) to 39% male (25-26), but overall was 59% male. Patients were recruited by consecutive admissions to hospital (19-29, 34, 36-38, 41-42), via direct mailing of healthcare professionals (30, 43), via automatic enrolment from a military TBI clinic (39), consecutive referrals from a military TBI clinic (33, 35), medical record review (35), via letters sent to patients discharged from civilian TBI or head injury clinics (30, 43) flyers (30, 35), and contacting the local brain injury association and advertising in their online and print newsletters (30). In two cases, recruitment was inadequately described (31-32), and in one case not described at all (40). There is likely to be a significant selection bias in studies, given that most mTBI is likely to be unreported to medical professionals and unstudied (13).

The cause of mTBI varied from motor vehicle/road traffic accident/motor vehicle collision/traffic/vehicle/vehicular (19-28, 30-31, 34, 36-37, 39), fall (21-23, 25-27, 30-31, 34, 36-37, 39), fall downwards vs fall on ground (31), thrown (39), assault/violence/blow (19-23, 25-28, 31, 34, 37, 39), riding (19-20, 25-26), sports (19-23, 25-28, 30, 34, 37), bicycle (21-23, 25-26, 34), domestic accident (19-20, 28), work accident (19-20, 28), falling object (30), blunt object/struck/fragment (36, 39), blast (39), pedestrian in motor vehicle collision (30), and other (19-23, 25-28, 34, 36-37). In nine cases it was not reported (29, 32-33, 35, 38, 40-43).

The various definitions used for mTBI can be seen in **Table 1**. Ten studies used the consensus definition put forward by the American College of Rehabilitation Medicine (22-24, 30-32, 38, 41-43), with the rest employed their own criteria, based on a variety of factors including post traumatic amnesia, loss of consciousness, and the Glasgow Coma Scale. The US Department of Defence criteria were used in one study (33), a retrospective screening questionnaire in another (35), and one used the cursory definition “clinically confirmed TBI” (39). Importantly, most studies did not explain how parameters such as duration of post traumatic amnesia (PTA) were measured. However, it was possible to determine the time/setting where it was assessed in all except six studies (22-23, 33, 40-42). It was assessed at the emergency department contemporaneously in eleven (21, 25-26, 28-9, 31-32, 34, 36-38), and retrospectively in eight (19-20, 24, 27, 30, 35, 39, 43).

*Please insert Table 1 here*

**Exclusion criteria**

Exclusion criteria apart from TBI severity markers were utilized in all bar two studies (19-20). These included: surgery requiring general anaesthesia/multiple trauma/other injuries requiring admission (21, 28-29, 33, 36-37, 39), pre-existing (major) psychiatric disorder (22-23, 25-27, 28, 31-32, 37-38, 41-43), psychosis/mania/bipolar disorder/schizophrenia specifically (30, 33, 35, 39), alcohol or substance misuse/abuse (28-32, 35, 37, 38, 41-43), pre-existing mental retardation or cognitive impairment (31-32, 34, 22-23), previous TBI (22-23, 26-8, 31-33), major medical or somatic or neurological illness or disease (22-23, 27, 30-33, 37-38, 41-43), not speaking the relevant language (22-23, 30-32, 34, 38), sensory impairment (33, 35), pregnancy (22-23), use of daily narcotic pain medications (33), mTBI from sexual assault (37), unemployment (27), incarceration (37), participation in intensive treatment for other conditions (33), not having a telephone (34), and homelessness (38). The one study of homeopathy had a variety of other exclusion criteria including use of all medications except insulin, thyroid hormones, NSAIDs, and vitamins; use of “energy therapies”; use of oral contraception; and inability to discontinue coffee, camphor, menthol and eucalyptus (43). One study reported that a variety of inclusion and exclusion criteria were employed, other than what they had discussed, but did not report what they were (40). It is likely that studies with multiple exclusion criteria will have a very homogeneous population which is not reflective of clinical practice, thus limiting the generalizability of results.

**Outcomes measures**

There were a wide variety of outcome measures used, as detailed in **Table 2**. The most frequently used was the Rivermead Post-Concussion Questionnaire (RPQ), or its derivative the Head Injury Symptom Checklist (HISC), which was employed in nine studies (as cited in 19-20, 24-27, 37-39). The Rivermead Head Injury Follow-Up Questionnaire (RHFUQ) was used in four (as cited in 19, 20, 24, 26). Other commonly used measures included the 36-Item Short Form Health Survey (SF-36) used in six (as cited in 22-23, 26, 28, 31-32), the Paced Auditory Serial Addition Test (PASAT) used in five (as cited in 21, 24, 30, 33, 40) and the Symptom Checklist-90R (SCL-90R) used in three (as cited in 21, 30, 33).

Ongoing compensation litigation is likely to be a factor associated with poor recovery from mTBI (44); however only six studies directly assessed this (22-23, 26, 29, 33, 36), with two mentioning the lack of the assessment as a limitation to the study (31, 32).

*Please insert Table 2 here*

**Study duration and time since mTBI**

The mean duration of study was 302 days or around 43 weeks, and median duration was 126 days or 18 weeks. The shortest study period was 4 days (40), and longest 10 years (32). The time since mTBI is important as symptoms may disappear shortly after injury, affecting the validity of the treatment in question, and it is estimated that most patients recovery fully by 3 months to one year (15). The range of time since mTBI that patients were recruited varied from 0-6 hours in one study (28) to 1-20 years with a mean of 6.5 years in another study (30). Time since mTBI was unclear in six studies (29, 31-32, 35-6, 38).

**Description of Education and Early Intervention studies**

This group comprised most RCTs published and was the largest group in this review with 9 studies. These are summarised in **Table 3**. Overall this group comprised educational interventions ranging from booklets (21) to extensive neuropsychological and personality assessment (22-23). There were single sessions (21-23, 25-26) and also individual and group psychoeducational programmes (24, 27). The control groups appeared to vary between no particular intervention (19-21, 24), to educational intervention (22-23, 25-27). In primary outcomes studied, only two studies reported a significant difference between intervention and control groups at follow up (20, 21). However, both of these studies had a high attrition rate and were (consecutively) acceptable or at high risk of bias according to SIGN criteria. The two studies at the lowest risk of bias in this group (26-27) both reported no significant difference between groups at follow up. The remaining studies were at moderate (19, 25) or high (22-24) risk of bias.

*Please insert Table 3 here.*

**Description of Rehabilitation studies**

This group comprised 8 studies and are summarized in **Table 4**. Interventions ranged from bed-rest (28), inpatient admission (29) and neuropsychological or cognitive rehabilitation/training (30, 33-35) to an admixture of rehabilitation specialist assessment, followed by personalized education, occupational therapy, and assessment for pharmacotherapy (31-32). Three studies in this group were considered high quality, all three of which demonstrated significant differences between control and intervention groups at follow up (30, 33, 35). The remaining six studies demonstrated no effect of the intervention tested, with two at moderate risk of bias (28, 34), and three at high risk (29, 31-32).

*Please insert Table 4 here*

**Description of Psychological interventions**

There were four studies included in this group, summarized in **Table 5**. Interventions included telephone counselling (37), telephone problem solving (39), and one (36) or up to five CBT sessions (38). Three of the four studies were considered low risk of bias, and one moderate. Two out of three studies at low risk of bias showed positive early improvements at 6 months but the effects were not sustained at 12 months.

*Please insert Table 5 here*

**Description of Pharmacological interventions**

The four studies comprising pharmacological interventions, summarized in **Table 6**, were all of very short duration, except one which was four months follow up (43). However, this intervention had a very high risk of bias as it was actually randomizing patients to eighteen different homeopathic compounds vs placebo, rather than one, and was not adequately powered to do this. We included the homeopathy study here as this is an external chemical agent though it is not a pharmacological intervention in traditional sense. The other studies consisted of 4 days of administration of the experimental medicine (40), or one-off administrations of placebo or the experimental medicine (41 and 42), after one week, in a cross-over randomization design. Overall, most interventions in this group (except 43), examined very specific symptoms of mTBI, and the overall functional outcome or total symptom scores, were not assessed.

*Please insert Table 6*

**Methodological quality assessment**

According to SIGN criteria for internal validity, fourteen articles were at a low risk of bias, seven articles were at an acceptable risk of bias, seven articles were at a high risk of bias, and one was at a very high risk of bias. Please see **Table 7** for a full breakdown of SIGN methodological analysis of trial internal validity. Criticisms of internal validity could unfortunately be directed at many studies. Nine of 25 studies failed to adequately describe the randomization process, and only eight studies concealed allocation. True blinding of subjects and assessors was not possible in the non-pharmacological studies, but even in pharmacological studies where true blinding is possible, it was unclear whether it took place from the authors’ descriptions.

Fifteen studies had comparable treatment and control groups at baseline, but in four this was not possible to confirm as it was inadequately described. All primary outcomes were reliably and validly measured except in one study that used an unvalidated unpublished questionnaire specifically designed for the study (43). Attrition rates varied from 0% in some of the pharmacological studies to 61.5% in one study (29). In the 22 studies where it was needed, an intention to treat analysis was only performed in nine. The studies involving multiple recruitment sites did not assess between-site differences, except one (39).

*Please insert Table 7 here*

**Discussion:**

Since the first systematic review published in 2004, there has been progress investigating interventions for mTBI despite the various challenges. Certainly, the number of relevant RCTs published has increased from eight in Borg et al., 2004, to the 25 in our review. However, increasing the number of trials has not solved (ongoing) methodological problems including inconsistency in defining mTBI or the diversity of outcome measures. Earlier criticisms of weak internal and external validity of published trials are, unfortunately, still warranted. The heterogeneous nature of studies currently precludes meta-analysis. Indeed, this heterogeneity is likely a consequence of the multifarious factors known to be involved in recovery from mTBI, which may not be related to the injury itself. For example, personality and coping style, psychiatric illness, substance misuse, chronic pain, poor effort, and compensation and litigation effects are all factors known to influence long-term outcomes (14).

Regarding education and early intervention, there is insufficient evidence to support the use of these approaches of which *education* forms the most common clinical management approach in everyday practice in mTBI (45) in helping people recover from mTBI symptoms. The majority of studies, which had a high risk of bias, did not show any difference between control and intervention, on the primary outcome of mTBI symptoms. The only two studies that did show difference between intervention and control group, had significant problems with inadequate descriptions of participants, high loss to follow up and non-standard definitions used for mTBI (20, 21). Hence, there is little evidence to suggest these commonly used approaches are effective on their own.

For rehabilitation type interventions, again, the evidence is currently insufficient to recommend this approach in the management of mTBI. Overall, three (30, 33, 35) of the nine studies found that the intervention was effective in primary outcomes compared to the controls. However, two of these were military studies on US veterans, and extrapolation to the civilian population may be problematic. The sole civilian study of rehabilitation, while commendable for its use of a standardized diagnostic process (the ARCM definition of mTBI) and intention to treat analysis, included only 20 subjects (30). A rehabilitation approach therefore shows potential but cannot be recommended on its own for routine clinical use based on the current level of evidence and further robust studies are required..

In terms of psychological interventions, this is a relatively under-published area with only four studies, of low or moderate size, but mostly at low risk of bias. There are seemingly varied findings; for example, a one-off CBT session, quiz and manual appeared effective in lowering the duration and number of mTBI symptoms, but five CBT sessions were no better than telephone counselling in helping people to return to work (38). This is one of only two studies (27, 38) that primarily assessed real-life outcomes (i.e. returning to work). This suggests that while CBT may be a useful intervention for symptom reduction, it might not help sufferers return to work when used without additional interventions. Indeed, this study found that telephone counselling patients had significantly fewer complaints and showed more evidence of recovery by 12 months, than those randomized to CBT.

It is important to note that psychological intervention studies overall involved quite active control groups; for instance, the provision of *call-in numbers*, *regular nurse meetings*, and *telephone counselling*. Despite this, in three studies, there were improvements at six months in the intervention group compared to controls, although in the one study that repeated this at 12 months, it was not maintained. Overall, psychological interventions, especially telephonic counselling, show promise but there is a dearth of data about the long term sustainability of treatment effects. Given that a vast majority of patients with mTBI show a (natural) trajectory towards improvement, long term studies may not be practical or necessary. On the basis of the included studies, psychological interventions cannot be unequivocally recommended and further robust studies are warranted. However, current evidence points to probable efficacy of brief psychological interventions in the early stage, primarily for symptom reduction.

The four studies of pharmacological interventions are disappointing in terms of their methodological quality. Of all intervention groups, this was amongst the easiest in which to design studies to minimize the risk of bias, but numbers were very low and the methodology almost universally poorly described. Three of the four studies employed only memory tests and used no other symptom measure or measure of functional outcome. The study of homeopathy, although blinded and well described in terms of randomization, used a completely untested and unvalidated outcome measure. Furthermore, as previously mentioned, it actually tested eighteen different ‘treatments’ versus placebo, but lumping all the treatments together for statistical analysis, which defied credibility. Hence, based on the current evidence, pharmacological interventions cannot be recommended in mTBI.

Educational interventions based on the early trial evidence, supported by its face value and plausibility, were introduced as a proposed solution (15) and were commonly adopted into routine clinical practice. However, accumulation of evidence since highlights the limitations of traditional educational approach alone. Whilst the evidence base currently remains weak, there are indications that psychological and rehabilitative approaches may be of potential value either alone or in combination. Future large multi-centric trial with robust methodology and clinical meaningful and consistent outcome measures are needed to establish the best clinical approach in patients with mTBI.

Although this review used valid and reliable methodologies, including the use of standardized measure to assess risk of bias, it is not without limitations. Firstly, whether studies were included or not could have been subject to human error. Second, whether a study was reported at low, acceptable or high risk of bias was based on the authors’ judgement albeit using a well validated and designed tool. Time constraints limited our ability to seek clarification and elaboration about missing information from authors, meaning that a well conducted study may have been pronounced at high risk of bias. A failure to describe procedures such as randomization method, intention to treat analysis, and comparison of groups across sites, does not necessarily mean they were not undertaken (13). Publication bias could be inherent in this review as only published articles were included, and only those published in peer-reviewed journals, and it is well known that there is a tendency of journals to selectively report positive results. All other forms of articles were excluded.

**Conclusion:**

There is currently a dearth of good quality evidence to conclusively recommend the best approach to treat patients with mTBI. Despite this, the most commonly used treatment intervention in mTBI remains educational and reassurance approaches often centred on the provision of an information leaflet about head injury. Based on the currently available RCT evidence, this approach to mTBI has not been shown to be effective, however. The current evidence base suggests psychological and rehabilitative strategies may provide additional benefits. It is yet unclear whether a combination of interventions is superior to any of these approaches alone. However, no single currently published treatment intervention can be unequivocally recommended based on sound scientific evidence. The quest continues for large-scale well-designed prospective RCTs, utilising internationally agreed criteria and outcome measures, for this large and diverse population.

**Acknowledgements:**

The authors would like to thank the staff of Springfield hospital and the British Library for their assistance in article finding.

**Declaration of Interest:**

The authors report no conflict of interest.

**References**

1. Faul M, Wald MM, Xu L, Coronado VG. Traumatic brain injury in the United States; emergency department visits, hospitalizations, and deaths, 2002-2006.

2. Hyder AA, Wunderlich CA, Puvanachandra P, Gururaj G, Kobusingye OC. The impact of traumatic brain injuries: a global perspective. NeuroRehabilitation. 2007;22(5):341-53.

3. Kraus JF, Arzemanian S, Anderson CL, Harrington S, Zador P. Motorcycle design and crash injuries in California, 1985. Bull N Y Acad Med. 1988;64(7):788-803.

4. Feinstein A, Rapoport M. Mild traumatic brain injury: the silent epidemic. Can J Public Health. 2000;91(5):325-6, 32.

5. 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. 2004(43 Suppl):84-105.

6. Harrington DE, Malec J, Cicerone K, Katz HT. Current perceptions of rehabilitation professionals towards mild traumatic brain injury. Arch Phys Med Rehabil. 1993;74(6):579-86.

7. Cassidy JD, Boyle E, Carroll LJ. Population-based, inception cohort study of the incidence, course, and prognosis of mild traumatic brain injury after motor vehicle collisions. Arch Phys Med Rehabil. 2014;95(3 Suppl):S278-85.

8. Ponsford J, Cameron P, Fitzgerald M, Grant M, Mikocka-Walus A. Long-term outcomes after uncomplicated mild traumatic brain injury: a comparison with trauma controls. J Neurotrauma. 2011;28(6):937-46.

9. Buck PW, Laster RG, Sagrati JS, Kirzner RS. Working with mild traumatic brain injury: voices from the field. Rehabil Res Pract. 2012;2012:625621.

10. Thurman DJ, Alverson C, Dunn KA, Guerrero J, Sniezek JE. Traumatic brain injury in the United States: A public health perspective. J Head Trauma Rehabil. 1999;14(6):602-15.

11. King NS. Post-concussion syndrome: clarity amid the controversy? Br J Psychiatry. 2003;183:276-8.

12. Borg J, Holm L, Peloso PM, Cassidy JD, Carroll LJ, von Holst H, et al. Non-surgical intervention and cost for mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med. 2004(43 Suppl):76-83.

13. Comper P, Bisschop SM, Carnide N, Tricco A. A systematic review of treatments for mild traumatic brain injury. Brain Inj. 2005;19(11):863-80.

14. Snell DL, Surgenor LJ, Hay-Smith EJ, Siegert RJ. A systematic review of psychological treatments for mild traumatic brain injury: an update on the evidence. J Clin Exp Neuropsychol. 2009;31(1):20-38.

15. Carroll LJ, Cassidy JD, Cancelliere C, Côté P, Hincapié CA, Kristman VL, Holm LW, Borg J, Nygren-de Boussard C, Hartvigsen J. Systematic review of the prognosis after mild traumatic brain injury in adults: cognitive, psychiatric, and mortality outcomes: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. Archives of physical medicine and rehabilitation. 2014 Mar 1;95(3):S152-73.

16. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMC medicine. 2010 Dec;8(1):18.

17. Thomas RE, Alves J, Vaska M, Magalhaes R. Therapy and rehabilitation of mild traumatic brain injury/concussion: systematic review

18. Scottish Intercollegiate Guidelines Network. SIGN 50: A guideline developers' handbook. Scottish Intercollegiate Guidelines Network; 2001.

19. Wade DT, Crawford S, Wenden FJ, King NS, Moss NE. Does routine follow up after head injury help? A randomised controlled trial. J Neurol Neurosurg Psychiatry. 1997;62(5):478-84.

20. Wade DT, King NS, Wenden FJ, Crawford S, Caldwell FE. Routine follow up after head injury: a second randomised controlled trial. Journal of Neurology, Neurosurgery & Psychiatry. 1998 Aug 1;65(2):177-83.

21. Ponsford J, Willmott C, Rothwell A, Cameron P, Kelly AM, Nelms R, Curran C. Impact of early intervention on outcome following mild head injury in adults. Journal of Neurology, Neurosurgery & Psychiatry. 2002 Sep 1;73(3):330-2.

22. Paniak C, Toller-Lobe G,t Durand A, Nagy J. A randomized trial of two treatments for mild traumatic brain injury. Brain Inj. 1998;12(12):1011-23.

23. Paniak C, Toller-Lobe G, Reynolds S, Melnyk A, Nagy J. A randomized trial of two treatments for mild traumatic brain injury: 1 year follow-up. Brain Inj. 2000;14(3):219-26.

24. Ghaffar O, McCullagh S, Ouchterlony D, Feinstein A. Randomized treatment trial in mild traumatic brain injury. J Psychosom Res. 2006;61(2):153-60.

25. Matuseviciene G, Borg J, Stalnacke BM, Ulfarsson T, de Boussard C. Early intervention for patients at risk for persisting disability after mild traumatic brain injury: a randomized, controlled study. Brain Inj. 2013;27(3):318-24.

26. Matuseviciene G, Eriksson G, DeBoussard CN. No effect of an early intervention after mild traumatic brain injury on activity and participation: A randomized controlled trial. J Rehabil Med. 2016;48(1):19-26.

27. Vikane E, Hellstrom T, Roe C, Bautz-Holter E, Assmus J, Skouen JS. Multidisciplinary outpatient treatment in patients with mild traumatic brain injury: A randomised controlled intervention study. Brain Inj. 2017;31(4):475-84.

28 De Kruijk JR, Leffers P, Meerhoff S, Rutten J, Twijnstra A. Effectiveness of bed rest after mild traumatic brain injury: a randomised trial of no versus six days of bed rest. Journal of Neurology, Neurosurgery & Psychiatry. 2002 Aug 1;73(2):167-72.

29 Lowdon IM, Briggs M, Cockin J. Post-concussional symptoms following minor head injury. Injury. 1989 Jul 1;20(4):193-4.

30. Tiersky LA, Anselmi V, Johnston MV, Kurtyka J, Roosen E, Schwartz T, et al. A trial of neuropsychologic rehabilitation in mild-spectrum traumatic brain injury. Arch Phys Med Rehabil. 2005;86(8):1565-74.

31. Elgmark Andersson E, Emanuelson I, Bjorklund R, Stalhammar DA. Mild traumatic brain injuries: the impact of early intervention on late sequelae. A randomized controlled trial. Acta Neurochir (Wien). 2007;149(2):151-9; discussion

32. Elgmark Andersson E, Bedics BK, Falkmer T. Mild traumatic brain injuries: a 10-year follow-up. J Rehabil Med. 2011;43(4):323-9.

33. Cooper DB, Bowles AO, Kennedy JE, Curtiss G, French LM, Tate DF, et al. Cognitive Rehabilitation for Military Service Members With Mild Traumatic Brain Injury: A Randomized Clinical Trial. J Head Trauma Rehabil. 2017;32(3):E1-e15.

34. Varner CE, McLeod S, Nahiddi N, Lougheed RE, Dear TE, Borgundvaag B. Cognitive Rest and Graduated Return to Usual Activities Versus Usual Care for Mild Traumatic Brain Injury: A Randomized Controlled Trial of Emergency Department Discharge Instructions. Acad Emerg Med. 2017;24(1):75-82.

35. Storzbach D, Twamley EW, Roost MS, Golshan S, Williams RM, O'Neil M, et al. Compensatory Cognitive Training for Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn Veterans With Mild Traumatic Brain Injury. J Head Trauma Rehabil. 2017;32(1):16-24.

36. Mittenberg W, Tremont G, Zielinski RE, Fichera S, Rayls KR. Cognitive-behavioral prevention of postconcussion syndrome. Arch Clin Neuropsychol. 1996;11(2):139-45.

37. Bell KR, Hoffman JM, Temkin NR, Powell JM, Fraser RT, Esselman PC, et al. The effect of telephone counselling on reducing post-traumatic symptoms after mild traumatic brain injury: a randomised trial. J Neurol Neurosurg Psychiatry. 2008;79(11):1275-81.

38. Scheenen ME, Visser-Keizer AC, de Koning ME, van der Horn HJ, van de Sande P, van Kessel M, et al. Cognitive Behavioral Intervention Compared to Telephone Counseling Early after Mild Traumatic Brain Injury: A Randomized Trial. J Neurotrauma. 2017.

39. Bell KR, Fann JR, Brockway JA, Cole WR, Bush NE, Dikmen S, et al. Telephone Problem Solving for Service Members with Mild Traumatic Brain Injury: A Randomized, Clinical Trial. J Neurotrauma. 2017;34(2):313-21.

40. Filipova M, Jung M, Filip V, Krejčová H. Clinical efficacy of 1‐desamino‐8‐d‐arginine‐vasopressin (DDAVP) in short‐term recovery from minor head injury. Human Psychopharmacology: Clinical and Experimental. 1989 Mar;4(1):47-50.

41. McAllister TW, McDonald BC, Flashman LA, Ferrell RB, Tosteson TD, Yanofsky NN, et al. Alpha-2 adrenergic challenge with guanfacine one month after mild traumatic brain injury: altered working memory and BOLD response. Int J Psychophysiol. 2011;82(1):107-14.

42. McAllister TW, Flashman LA, McDonald BC, Ferrell RB, Tosteson TD, Yanofsky NN, et al. Dopaminergic challenge with bromocriptine one month after mild traumatic brain injury: altered working memory and BOLD response. J Neuropsychiatry Clin Neurosci. 2011;23(3):277-86.

43. Chapman EH, Weintraub RJ, Milburn MA, Pirozzi TO, Woo E. Homeopathic treatment of mild traumatic brain injury: A randomized, double-blind, placebo-controlled clinical trial. J Head Trauma Rehabil. 1999;14(6):521-42.

44. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of internal medicine. 2009 Aug 18;151(4):264-9.

45. Sullivan, K.A., Kaye, S.A., Blaine, H., Edmed, S.L., Meares, S., Rossa, K. and Haden, C., 2019. Psychological approaches for the management of persistent postconcussion symptoms after mild traumatic brain injury: a systematic review. Disability and rehabilitation, pp.1-9.

46. Liberati A., Altman D. G., Tetzlaff J., Mulrow C., Gøtzsche P. C., Ioannidis J. P. A. et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLOS Med 2009; 6: e1000100.