Review

Treatment for posttraumatic stress disorder in patients with a history of traumatic brain injury: A systematic review

Ana Mikolić*, Suzanne Polinder, Isabel R.A. Retel Helmrich, Juanita A. Haagsma, Maryse C. Cnossen

Department of Public Health, Erasmus MC-University Medical Center, Rotterdam, the Netherlands

HIGHLIGHTS

- We reviewed 23 studies and 26 case studies involving treatment for PTSD in patients with traumatic brain injury
- Cognitive and behavioral therapies seem effective for patients with history of traumatic brain injury
- Evidence is less strong for complementary and alternative, hyperbaric oxygen, and brain and vestibular therapies
- The relationship between injury severity and the magnitude of treatment gains is unclear
- High-quality studies are required, particularly involving civilians, women and patients with severe injuries

ARTICLE INFO

ABSTRACT

Posttraumatic stress disorder (PTSD) frequently co-occurs with traumatic brain injury (TBI). We conducted a systematic review to evaluate the appropriateness and effectiveness of treatments for PTSD in adult patients with a history of TBI. We searched for longitudinal studies aimed at treatments for PTSD patients who sustained a TBI, published in English between 1980 and February 2019. Twenty-three studies were found eligible, and 26 case studies were included for a separate overview. The quality of eligible studies was assessed using the Research Triangle Institute item bank. The majority of studies included types of cognitive-behavioral therapy (CBT) in male service members and veterans with a history of mild TBI in the United States. Studies using prolonged exposure (PE), cognitive-processing therapy (CPT) or other types of CBT, usually in combination with additional treatments, showed favorable outcomes. A smaller number of studies described complementary and novel therapies, which showed promising results. Overall, the quality of studies was considered low. We concluded that CBT seem appropriate for the patient population with history of TBI. The evidence is less strong for other therapies. We recommend controlled studies of PTSD treatments including more female patients and those with a history of moderate to severe TBIs in civilian and military populations.

1. Introduction

Posttraumatic stress disorder (PTSD) can develop after exposure to a traumatic event, and in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5; American Psychiatric Association, 2013) it is characterized by trauma-related intrusion and avoidance responses, changes in cognition, mood, arousal and reactivity, and functional impairment. The lifetime prevalence of PTSD varies between countries and populations. For the general population it typically ranges from 0.5 to 10%, however, higher rates have been found in post-conflict areas and in service members and veterans (Atwoli, Stein, Koenen, & McLaughlin, 2015; Dückers, Alisic, & Brewin, 2016). PTSD can have a

strong negative impact on overall functioning due to elevated risk of other health conditions (O'Donovan et al., 2015; Spitzer et al., 2009), lower work productivity (Zatzick et al., 2008) and impaired social relationships (Taft, Watkins, Stafford, Street, & Monson, 2011).

Clinical practice guidelines (American Psychological Association; APA, 2017) recommend or suggest several therapies for the treatment of PTSD, with the strongest support for cognitive-behavioral therapy (CBT), such as trauma-focused psychotherapy. Nevertheless, previous research has shown that PTSD treatments have a significant dropout rate of approximately 20% (Bradley, Greene, Russ, Dutra, & Westen, 2005; Imel, Laska, Jakupcak, & Simpson, 2013) and high nonresponse rates of 20 to 60% of patients (Bradley et al., 2005; Schottenbauer,

Glass, Arnkoff, Tendick, & Gray, 2008). Thus, it is questionable whether all groups of patients can equally benefit from PTSD treatments (van Minnen, Harned, Zoellner, & Mills, 2012; Watts et al., 2013).

One of the characteristics that could potentially influence the course of PTSD treatment, is a history of traumatic brain injury (TBI). TBI can be defined as "an alteration in brain function or other evidence of brain pathology, caused by an external force" (Menon, Schwab, Wright, & Maas, 2010). Approximately 70 to 80% of TBI cases can be classified as mild TBI (Giza, 2016), which can be defined by "loss of consciousness (LOC) of approximately 30 minutes or less; an initial Glasgow Coma Scale (GCS) of 13–15 (after 30 minutes); and posttraumatic amnesia (PTA) not greater than 24 hours" (American Congress of Rehabilitation Medicine; ACRM, 1993). The remainder of cases, which are characterized by longer LOC and/or PTA and lower GCS, represent moderate and severe injuries. Moderate and severe TBIs can be associated with post-injury neurocognitive deficits lasting six months or longer, while in most cases mild TBIs result in a complete recovery (Dikmen et al., 2009). Nevertheless, 5 to 30% of patients who sustained a mild TBI experience persistent cognitive, emotional and physical symptoms, called post concussive symptoms (PCS), and do not fully return to their pre-injury level of functioning (Cassidy et al., 2004; McMahon et al., 2014; Sigurdardottir, Andelic, Roe, Jerstad, & Schanke, 2009; Voormolen et al., 2019).

The relationship between TBI and PTSD is strong and bidirectional, and still largely controversial (Jak, 2017; Polinder et al., 2018). Individuals with a history of TBI have a higher prevalence of PTSD compared to the general population in both civilian (Bryant et al., 2010; Carlson et al., 2011; Haagsma et al., 2015) and in military samples (Hoge et al., 2008; Kennedy, Leal, Lewis, Cullen, & Amador, 2010; Kontos et al., 2013; Tanielian et al., 2008). TBI seems to be a risk factor for developing PTSD (Yurgil et al., 2014), while pre-injury and post-injury PTSD predict persistent symptoms following TBI (Silverberg et al., 2015). Moreover, symptoms of TBI and PTSD can overlap and both groups of patients can demonstrate symptoms such as irritability, depressed mood and sleep problems, as well as memory and concentration difficulties (Bryant, 2011; Cnossen, 2017). Notably, patients with PTSD alone can show long-term impairments across different domains of neurocognitive functioning (Scott et al., 2017; Vasterling & Hall, 2018). Furthermore, the symptoms can also mutually aggravate each other (King, 2008; Turner, Smith, Jones, & Harrison, 2017). As a result, individuals with both conditions can exhibit poorer neuropsychological and overall functioning and higher PTSD and PCS severity, compared to individuals with only one condition (Brenner et al., 2010; Combs et al., 2015; Haagsma et al., 2015; Vasterling, Jacob, & Rasmusson, 2018).

Some clinicians have concerns that deficits associated with TBI and/ or PTSD can influence the effectiveness of evidence-based PTSD treatments. It has been suggested that cognitive impairments, PTA, problems with emotion regulation and impulse control, higher symptom severity, and experiencing physical pain may limit patients' ability to engage in PTSD treatments, or benefit from them (Bryant, 2011; Laskowitz & Grant, 2016; Ragsdale et al., 2018; Tanev, Pentel, Kredlow, & Charney, 2014). For instance, some clinical providers emphasize cognitive limitations that they attribute to TBI as a reason of not using CPT for treating PTSD (Cook, Dinnen, Simiola, Thompson, & Schnurr, 2014). Thus, it is of high clinical interest to investigate whether recommended PTSD treatments are appropriate and effective in this population. Moreover, the effectiveness of other available treatments aimed at relieving PTSD is still largely unknown for the population with a history of TBI, such as complementary and alternative treatments that accompany or replace conventional therapies.

Neurological conditions and brain injuries are often represented as exclusion criteria in PTSD trials (McAllister, 2009; Ronconi, Shiner, & Watts, 2014) and, to date, only a few systematic reviews of treatments for PTSD in patients who sustained TBI have been conducted (Carlson et al., 2011; Soo & Tate, 2007). The latest systematic review investigated studies on evidence-based treatments for individuals with mild TBI and PTSD published until 2009 (Carlson et al., 2011). Although the authors did not find any eligible studies, they did discuss two case reports (Batten & Pollack, 2008; McGrath, 1997) and a study on prevention of PTSD in patients with acute stress disorder (ASD) and TBI by Bryant, Moulds, Guthrie, and Nixon (2003). In addition, a literature review from Tanev et al. (2014) focused on psychotherapy and pharmacotherapy in patients with comorbid PTSD and TBI. Based on three uncontrolled studies in military samples (Chard, Schumm, McIlvain, Bailey, & Parkinson, 2011; Walter, Kiefer, & Chard, 2012; Wolf, Strom, Kehle, & Eftekhari, 2012) and the study by Bryant et al. (2003), they concluded that CBT might be an effective PTSD treatment in patients who sustained a TBI, but that the impact of TBI "had not been elucidated" yet. Vasterling et al. (2018) recently reviewed several successful applications of psychosocial interventions in patients with PTSD and TBI (Bryant et al., 2003; Scott et al., 2017; Sripada et al., 2013; Walter, Barnes, & Chard, 2012; Walter, Dickstein, Barnes, & Chard, 2014; Wolf et al., 2012, 2015). They suggested no barriers in using recommended CBT treatments in the context of TBI, but emphasized that the research is still in its early stages.

In summary, the effectiveness and appropriateness of PTSD treatments in patients who sustained TBI are unclear. It is therefore of great relevance to systematically gather the most recent evidence on PTSD treatments in individuals with a history of TBI and to utilize this to report on the various available treatments for the entire spectrum of TBI severity. Thus, the aims of the current systematic review are the following: 1) to provide an overview of treatments for PTSD in adult patients with a history of TBI; 2) to evaluate the appropriateness of PTSD treatments, defined by treatment attendance, dropout and adverse effects, and effectiveness, defined by reductions in PTSD symptoms; and 3) to explore the impact of methodological quality and assessment methods on obtained treatment outcomes.

2. Methods

2.1. Search strategy

To identify the maximum number of relevant studies, an extensive search strategy was developed in consultation with a medical librarian (Appendix A), encompassing treatments aimed at PTSD and broader categories of related mental disorders (e.g. anxiety, depression and ASD). The literature search was conducted via databases EMBASE, Medline Ovid, Web of science, Cochrane CENTRAL, PsycINFO Ovid and Google scholar and was restricted to papers involving human participants published in the English language until February 20th 2018. To include the most recent articles, a narrower version of this search, encompassing treatments for PTSD (Appendix A), was conducted for the period until February 21st 2019. Additionally, to encompass gray literature, such as unpublished articles, theses and reports, Google scholar and a database of clinical trials (clinicaltrials.gov) were searched.

2.2. Study selection

2.2.1. Study design

The review included longitudinal studies (e.g. randomized controlled trials (RCTs), prospective cohort studies, retrospective cohort studies, case-control studies, pre-post studies) involving a treatment aimed at PTSD. Reviews, editorials, and cross-sectional studies were excluded. Descriptive studies of one or more patients were included for a separate overview. These case studies, reports and series aimed to complement the findings, because only a small number of eligible studies were expected based on previous reviews (Carlson et al., 2011; Tanev et al., 2014).

2.2.2. Participants

Studies were included if they involved adult (16 +) civilian or

military participants diagnosed with both TBI and PTSD and provided with treatment for PTSD, or diagnosed with TBI and provided with preventive intervention and/or early treatment for PTSD. Diagnosis of PTSD had to have been confirmed by a clinician, with a structured diagnostic interview, such as Clinician-Administered PTSD Scale for DSM (CAPS; Blake et al., 1995; Weathers et al., 2013) and Structured Clinical Interview; PTSD Module (SCID PTSD Module; First, Spitzer, Gibbon, & Williams, 2002); or a medical record. There were no restrictions on TBI diagnosis or severity. TBI and PTSD could originate from the same or from a different traumatic event.

2.2.3. Treatment

The review included all types of interventions aimed at treatment of PTSD or PTSD symptoms: psychological, pharmacological, complementary, alternative and novel medical therapies. Early treatment was also included if an intervention was provided with the aim of preventing PTSD in participants who were diagnosed with ASD or considered at risk of long-term posttraumatic disturbances.

2.2.4. Outcome

Studies were selected when they measured at least one of the following outcomes after treatment aimed at PTSD: 1) changes in PTSD symptoms measured by a valid self-report e.g. Impact of Event Scale (IES; Weiss, 2007), PTSD Checklist for DSM (PCL; Blanchard, Jones-Alexander, Buckley, & Forneris, 1996; Blevins, Weathers, Davis, Witte, & Domino, 2015), PTSD Symptom Scale Self-Report Version (PSS-SR; Foa, Cashman, Jaycox, & Perry, 1997) or clinician-rated instrument (e.g. CAPS, SCID, etc.); 2) changes in diagnosis of PTSD in accordance with DSM or International Classification of Diseases (ICD) classification systems; 3) treatment adherence and retention in PTSD treatment; and lastly, 4) side effects and harms associated with PTSD treatment. In studies examining a change in PTSD symptoms, pre- and post-treatment level of these symptoms had to be clearly stated and statistically compared. The inclusion of case reports was not restricted to use of quantitative measures of PTSD symptoms.

2.2.5. Year of publication

Studies were included if they were published after 1980, when PTSD was officially included in DSM.

2.2.6. Multiple publications

When several publications used the same or overlapping data, a study was selected according to the following criteria: 1) largest sample and 2) largest percentage of patients who sustained a TBI and had PTSD. When the overlapping study contained any new outcome(s), only the new information was extracted and included in the results.

2.3. Data extraction and risk of bias assessment

The first reviewer (AM) screened all citations by titles and abstracts and subsequently screened the selected articles by full-text. The second reviewer (IRH) first screened a sample of titles and abstracts. Agreement in screening a sample of studies was above 80% (Shea et al., 2017); therefore the second reviewer screened a random 10% of titles and abstracts, and a random 10% of full-texts. In case of discrepancies and doubts, a third reviewer (MC) was consulted. Moreover, reference lists of included articles and detected literature reviews were inspected to identify potentially missed relevant articles.

Data extraction included information on study design; setting; sample size; population; inclusion and exclusion criteria; TBI characteristics (definition, severity, mechanism, number, timing and diagnosis), PTSD characteristics (diagnosis, type, timing); comorbid psychopathology; treatment characteristics (type, dose, modifications for TBI, concurrent therapies), PTSD-related and other outcomes; and attrition rates. Analyses for baseline differences, PTSD and other main outcomes, and associated effects were also extracted. Data extraction

was performed by one reviewer (AM) and checked by a second reviewer (IRH).

Risk of bias was assessed using the Research Triangle Institute (RTI) item bank (Viswanathan & Berkman, 2012) by both reviewers and differences were discussed until consensus was reached. The instrument was selected because of its applicability for assessing methodological issues of different types of study designs, including the pre-post study without a comparison group, which prevailed in this review. Moreover, it includes an assessment of the validity of relevant domains, namely selection, information, performance, reporting, detection and attrition bias. For this review, 23 items were considered applicable (Appendix B). A domain was rated as low risk when all associated items were considered low risk of bias, as a moderate risk when up to 50% of corresponding items were assessed as having risk of bias, and a high risk if > 50% of items were assessed as high or unknown risk of bias (Cnossen, 2017).

3. Results

3.1. Literature search

The literature search resulted in the detection of 9246 unique articles until February 2018 and additional 300 unique articles until February 2019. They were screened by title and abstract, and subsequently, 439 publications were screened by full-text. The main reasons for excluding articles for full-text screening were involving patients who did not fully meet the diagnosis of PTSD or TBI (n = 229), or an irrelevant study design or type of article (n = 115). Some studies met most of the criteria, but were still excluded for the following reasons: treatments aimed at TBI/PCS and not at PTSD (n = 6); analysis which was only focused on prediction of outcome by TBI status without stating and comparing pre- and post-treatment results in patients with history of TBI (n = 4); subsample with TBI/PTSD not clearly separated from the complete sample (n = 6) (Appendix C). Five articles were excluded as multiple publications from the articles which completely met the inclusion criteria. Therefore, the review was based on a total of 22 publications (23 studies). Furthermore, a complementary overview consisted of 20 publications (26 case studies/reports) describing a treatment outcome in a single patient (Fig. 1)

3.2. Study characteristics

Study characteristics of the included 23 studies from 22 publications are presented in Table 1. The majority of studies were conducted in the United States (US) (n = 21) and two in Australia (Browne et al., 2013; Bryant et al., 2003). All but two studies were carried out in samples of service members and veterans (n = 21) in military/veteran affairs (VA) medical centers, whereas the two Australian studies were performed in hospitals with civilian samples. Four included studies (Browne et al., 2013; Bryant et al., 2003; Jak, Jurick, Crocker, et al., 2019; Weaver et al., 2018) were RCTs. Single arm pre-post studies represented the most common study design (n = 12) (Table 1).

3.2.1. Participant characteristics

One study included a majority of females (Bryant et al., 2003), while in all other studies which reported sex, males were either overrepresented (n = 10) or the only participants (n = 11).

3.2.2. TBI characteristics

Studies involved exclusively (n = 7) or predominantly (n = 11) mild TBI; and in the remainder of studies the severity was unclear. If reported, TBI was sustained at least 9–12 months or more prior to the treatment (n = 11). Studies aimed at PTSD prevention included patients within the first two (Bryant et al., 2003) or four (Browne et al., 2013) weeks following trauma. History of TBI was typically determined based on military medical records or screening, and confirmed by a
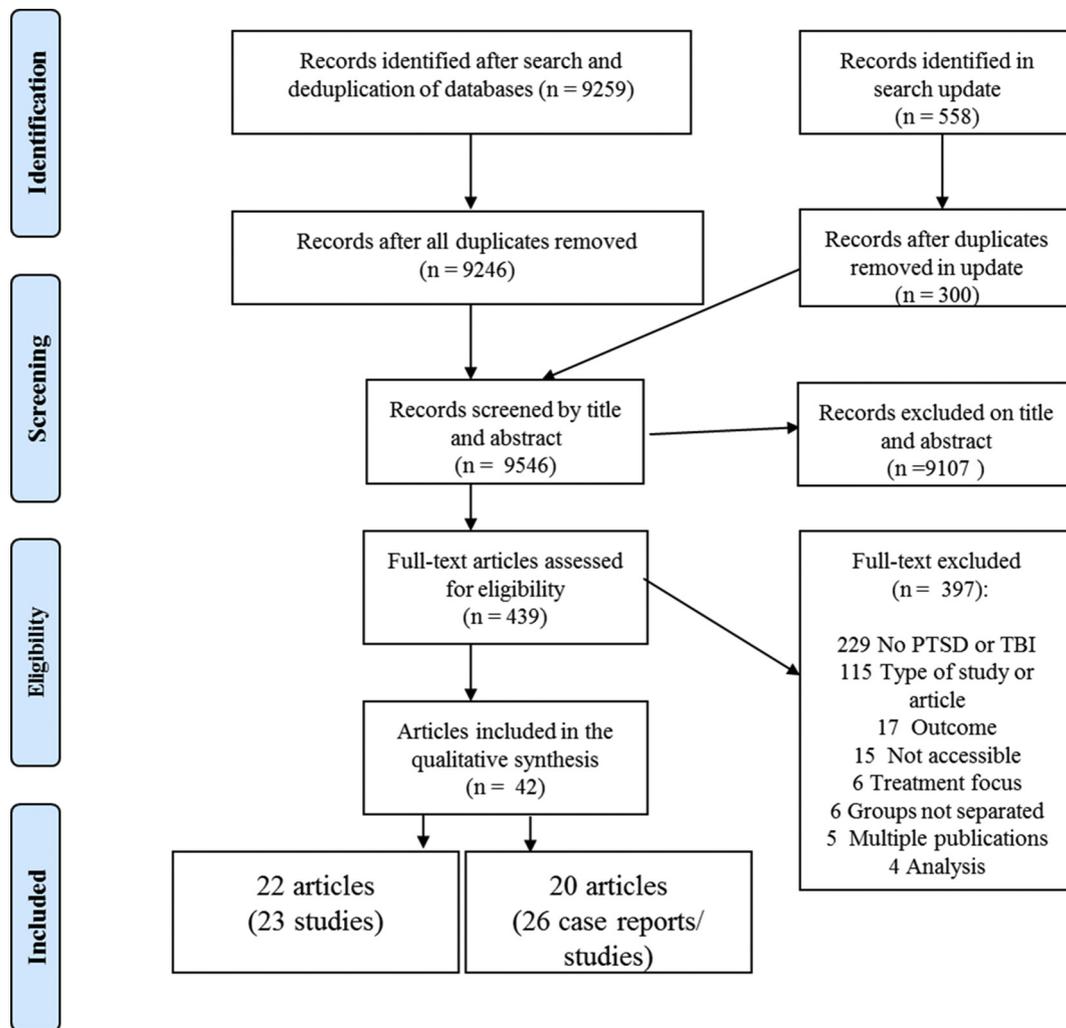
Fig. 1. Prisma flow diagram (Moher, Liberati, Tetzlaff, & Altman, 2009).

clinical assessment (n = 15). In the remaining studies, diagnosis relied on hospital referrals (n = 2); solely self-report or a screening instrument, or the source was unclear (n = 6). Six studies described neurocognitive functioning or assessed PCS in addition to TBI status (Cole et al., 2015; Harch, Andrews, Fogarty, Lucarini, & Van Meter, 2017; Jak et al., 2019; Ruff, Riechers, Wang, Piero, & Ruff, 2012; Walter, Kiefer, et al., 2012; Weaver et al., 2018).

3.2.3. PTSD characteristics

Initial PTSD diagnosis was based on CAPS (n = 17), or confirmed by a clinician/hospital and a standardized questionnaire such as PCL (n = 5) and PSS (n = 1). Trauma type was commonly unspecified. When explicitly stated, the highest share of service members and veterans was diagnosed with a combat-related PTSD (n = 6), and a smaller percentage experienced other types of trauma, e.g. sexual or physical assault. Psychiatric comorbidities were reported in the majority of samples (n = 14), which mostly included patients with depression and history of suicidality.

3.2.4. Treatment

Types of treatment are listed in Table 1. CBT (n = 2), and specific types of CBT, PE (n = 6) and/or CPT (n = 7), were the most commonly reported. One study described a type of exposure therapy called Trauma Management Therapy (TMT), which combines virtual reality and in vivo exposures. For some therapies, it was clear that they were either part of a larger intervention that included various therapies, such as

cognitive and speech rehabilitation and psychoeducation (n = 5), or involved some modifications to reduce the impact of deficits associated with TBI and/or PTSD, like memory enhancing-strategies and compensatory devices (n = 3). Concurrent pharmacotherapy was reported in ten studies.

3.3. Risk of bias included studies

There were four RCTs included in this study. Two of them represented early treatments in civilian samples, and two treatments for existing PTSD in veterans. Other studies were single-arms or lacking a control group balanced through stratification, matching or randomization, thus showing a selection bias. The performance bias represented a serious threat to validity in the majority of included studies; the concurrent therapies were frequently 1) unknown/unclear or 2) mentioned, but their effects on outcomes were impossible to control for and distinguish from a primary treatment. The high detection bias arose from unblinded/unreported assessors, while a not-treating clinician as an assessor was considered an indicator for a moderate risk of detection bias. In addition, valid self-report instruments have a lower reliability than structured clinical interviews (e.g. CAPS), which represent a gold standard for diagnosing PTSD (Weathers, Keane, & Davidson, 2001). Therefore, assessing PTSD diagnosis using only a self-reported measure was considered indicative of information bias. Moreover, certain bias was related to the assessment of TBI in the included military studies. While the lack of standardization and consistency in diagnosing TBI

Table 1
Characteristics of included studies presented by type of treatment.

First author; country; setting	Study design/groups	Inclusion (incl.)/exclusion (excl.) criteria	TBI diagnosis	Pre-treatment; post-treatment sample	Patients: population, % male, M age (SD), TBI severity	Primary treatment – Dosage
Types of cognitive and/or behavioral therapies (CBT)						
Browne et al., 2013; Australia, hospital	RCT: Usual care (UC) vs. multidisciplinary intervention (MI)	Incl.: 18–80 yo, within 4 weeks post-TBI, admitted for > 24 h. Excl.: moderate to severe TBI; current suicidality or intoxication.	Hospital referral	n = 142 (MI = 69, UC = 73) 1 mo: MI = 33 3 mos: MI = 36 6 mos: MI = 31 UC = 35	Civilian (mostly MVA) MI 74% male, M = 38 (13.3) UC = 75% male, M = 36 (14.6) Mild 100%	MI (incl. trauma-focused and CBT) - Individually tailored
Bryant et al., 2003; Australia, hospital	RCT: CBT vs. supportive counselling (SC)	Incl.: 18–60 yo, MVA or nonsexual assaults within 2 weeks; acute stress disorder; English proficiency; mild TBI.	Hospital referral	n = 24 n = 24	Civilian 34% male CBT & SC CBT M = 29 (13.9) SC M = 33 (14.4) Mild 100%	CBT (incl. exposure) vs. SC - Individual, 5 sessions × 90 min (8 sessions), 5 wks
Davis, Walter, Chard, Parkinson, & Houston, 2013; US, VA medical center (outpatient)	Retrospective cohort - TBI status cross-sectionally (with/without TBI) - retrospective chart review	Incl.: OEF/OIF veterans with combat-related PTSD, outpatient program, initiated CPT. Excl.: ongoing treatment, subthreshold PTSD, moderate/severe TBI.	VA medical record/self-report	n = 136 (PTSD + TBI = 44)	Veterans PTSD M = 30 (7.6) PTSD + TBI M = 30 (8.2) Mild 100%	CPT - Individual, 12 sessions (or less if sign. symptom reduction)
Gros, Lancaster, Horner, Szafranski, and Back, 2017; US, VA medical center (outpatient)	Pre-post study - TBI status cross-sectionally (with/without TBI)	Incl.: veteran, reservist, or National Guard, 18–65 yo, current SUD (DSM-IV) and PTSD; English proficiency. Excl.: psychosis[a], current suicidality or homicidality; eating/dissociative identity disorder; ongoing PTSD or SUD treatment; severe cognitive impairment.	Screening (SAFE-TBI)	n = 51 (PTSD + TBI = 30); n = 51	Veterans PTSD 86% male, M = 39 (10.4) PTSD + TBI 97% male, M = 41 (11.1) Mild 93% to moderate–severe	PE + relapse prevention - Individual, 12 wks × 90-min sessions
Jak et al., 2019; US, VA medical center	RCT: CPT vs. CPT enhanced with Cognitive Symptom Management and Rehabilitation Therapy (CogSMART)	Incl.: written consent, OEF/OIF veterans, PTSD, mild to moderate TBI, cognitive complaints; none or stable psychopharmacology. Excl.: SUD, suicidality, psychosis, dementia, non-English speaking, other interventions, prior sessions.	Medical record and WARCAT	n = 100 (CPT = 49, SMART CPT = 50) PT: CPT = 23 SMART CPT = 27 3 mos: CPT = 16, SMART CPT = 22	Veterans CPT 88% male, M = 34 (7.3) SMART-CPT 90% male, M = 35 (8.5) Mild 94% to moderate	CPT, SMART CPT - Individual, 12 wks × 60–75 min sessions
Ragsdale & Voss Horrell, 2016; US, VA medical center (outpatient)	Pre-post - TBI status cross-sectionally (with/without TBI)	Incl.: veterans with PTSD receiving individual CPT or PE.	Screening and neuropsychological evaluation, TBI designation	n = 41 (PTSD + TBI = 19; CPT = 20, PE = 21) n = 41	Veterans 87.8% male M = 33 (8.2), range = 23–57 Severity unknown	CPT or PE - CPT 12 sessions, PE 10–15
Ragsdale et al., 2018; US, VA medical center (outpatient)	Retrospective cohort - TBI status cross-sectionally (with/without TBI)	Incl.: OIF/OEF/OND veterans with combat-related PTSD participating in a trial	Self-report and telephone interview with TBI criteria (VA/DoD)	n = 88 (PTSD = 43; PTSD + TBI = 45)	Veterans PTSD 93% male, M = 39 (9.7) PTSD + TBI 96% male, M = 36 (8.7) Severity unknown	TMT - 14 individual and group sessions (or less if not necessary) × 90 min
Speicher, Walter, & Chard, 2014; US, VA Clinic (residential)	Uncontrolled pre-post - retrospective chart review	Incl.: male veterans, PTSD, history of TBI; received occupational therapy and CPT. Excl.: current SUD; unmanaged psychosis[a]; serious medical condition; suicidality or homicidality (intent).	Medical record and neuropsychological interview	n = 26 n = 26.	Veterans 100% male M = 39 (11.9) Mild (81%) to severe	CPT - 14 individual sessions and 14 group sessions × 60–90 min
Sripada et al., 2013 (Study 1); US, VA medical center (outpatient)	Observational cohort	Incl.: all patients with PTSD and PE treatment. Excl.: no criteria in place.	TBI designation in the patient record: positive screen and TBI consultation; service connected for	n = 51 (TBI = 11) n = 51 (ITT)/40 (TBI = 8)	Veterans 100% male	PE

Table 1 (continued)

First author, country, setting	Study design/groups	Inclusion (incl.)/exclusion (excl.) criteria	TBI diagnosis	Pre-treatment; post-treatment sample	Patients: population, % male, M age (SD), TBI severity	Primary treatment	Dosage
	- TBI status cross-sectionally (with/without) - retrospective chart review		TBI/PCS, or current TBI-related issues		M = 49 Mild 100%		- Individual 8–15 sessions × 90-min
Sripada et al., 2013 (Study 2); VA medical center (outpatient)	Observational cohort - TBI cross-sectionally (with/without TBI) and type of treatment RCT (PE/PCT)	Incl.: all patients with PTSD and receiving treatment.		n = 22 (TBI = 8) n = 22 (TBI = 8)	Veterans 91% male M = 33(6.9) Mostly mild	PE and PCT	- Individual 10–12 sessions
Walter, Barnes, et al., 2012; VA medical center (residential)	Uncontrolled pre-post	Incl.: male veterans, completed treatment, current PTSD (CAPS), history of TBI > 1 year.	Medical record and neuropsychological interview	n = 53 n = 47	Veterans 100% male M = 35 (9.5) Mild (68%) to severe	CPT-C	- 14 individual sessions and 14 group sessions × 60–90 min, 8 wks
Walter, Kiefer, et al., 2012; VA medical center (residential)	Uncontrolled pre-post	Incl.: male veterans, completed treatment, current PTSD (CAPS), history of TBI > 1 year.	Medical record and neuropsychological interview	n = 28 n = 28	Veterans 100% male M = 36 (9.59) Mild 86% to moderate	CPT-C	- 14 individual sessions and 14 group sessions × 60–90 min, 8 wks
Walter et al., 2014; VA medical center (residential)	Pre-post study - CPT vs. CPT-C	Incl.: PTSD, TBI > 1 year; able to complete activities of daily living, no ongoing medical issues that require external care.	Medical record and neuropsychological interview	n = 86 (CPT-C = 46, CPT = 40) n = 71 (CPT-C = 39; CPT = 32)	Veterans 100% male CPT mild 79% to severe, CPT-C mild 71% to severe	CPT or CPT-C	- 14 individual and 14 group sessions × 60–90 min, 8 wks
Chard et al., 2011[c]				n = 42 n = 42	M = 36, mild 67% to severe		
Wolf et al., 2012; US, VA multicenter (outpatient, inpatient/residential)	Uncontrolled pre-post	Incl.: OEF/OIF veterans, PTSD, documented TBI and lapsed window of expected recovery; ongoing cognitive deficits Excl.: active psychosis[a]; suicidality or homicidality, self-harm; severe SUD.	Screening - self-report and medical assessment	n = 10 n = 10	Veterans 100% male M = 33(10.7), 24–52 Mild (60%) to moderate	PE	- Individual 8 to 18 sessions (M = 13.4)
Wolf et al., 2015; US, VA multicenter (outpatient, inpatient/residential)	Uncontrolled pre-post	Incl.: veterans and military members completed at least 1 PE session. Excl.: psychosis[a], suicidality or homicidality, recent aggressive behavior or self-harm; severe SUD.	Screening - self-report and medical assessment	n = 69 n = 69/44	Veterans and Active duty military 94% male M = 34(8.0) Mild (75%) to severe	PE	- Individual 1 to 8+ sessions (M = 9.5)
Wolf et al., 2017[c]				n = 44; n = 44/31	93% male; M = 33(7.3); Mild 66% to severe		
Other therapies							
Carrick, McLellan, Brock, Randall, & Oggero, 2015; US, Brain Rehabilitation Center	Uncontrolled pre-post	Incl.: 18 + yo combat veterans (OEF, OIF) with TBI and chronic PTSD (CAPS); unsuccessful treatments for PTSD; consent. Excl.: psychosis[a]; SUD[b]; suicidality.	Assessment unclear	n = 98 1 wk: n = 98 3 mos: n = 14	Veterans 100% male M = 39 (20–60) Severity unclear	Brain and vestibular rehabilitation	- Individual, 3 per day for 2 wks (5 days per wk)
Carrick et al., 2015; US, Brain Rehabilitation Center	Uncontrolled pre-post	Incl.: 18 + yo combat veterans (OEF, OIF) with TBI and chronic PTSD (CAPS); unsuccessful treatments for PTSD. Excl.: psychosis[a]; current substance dependence[b]; suicidality.	Assessment unclear	n = 26 n = 26.	Veterans 100% male M = 38.5 (25–58) Severity unclear	Brain and vestibular rehabilitation	- Individual, 3 per day for 2 wks (5 days per wk)

Table 1 (continued)

First author, country, setting	Study design/groups	Inclusion (incl.)/exclusion (excl.) criteria	TBI diagnosis	Pre-treatment; post-treatment sample	Patients: population, % male, M age (SD), TBI severity	Primary treatment - Dosage
Cole et al., 2015; US, VA medical center	Uncontrolled pre-post	Incl.: mild TBI (self-report) and continued cognitive symptoms; PTSD diagnosis Excl.: neurologic disease; learning/attention/hyperactivity disorder; current SUD; history of psychosis[a], moderate to severe TBI, TBI ≤ 12 mos, current exposure therapy.	Self-report	n = 10 n = 9 3 mos: n = 8	Veterans 100% male M = 46 (11.6) Mild 100%	Mindfulness-based Stress Reduction Treatment - Group; 8 sessions + 1 day retreat, 8 wks
Davis, Hanson, & Gilliam, 2016; US, military center (outpatient)	Uncontrolled pre-post	Incl.: accepted, but not yet received treatment, chronic PTSD; TBI (positive screen and self-report) at least 2 years prior. Excl.: shrapnel or prosthetics (spine or cranium); brain surgery; fever; acute systemic infection; intolerant to pressure on scalp or body: lactating or pregnant.	Self-report and medical record	n = 10 n = 9	Active duty military 100% male 27–45 Severity not reported.	LTMT (light touch manual therapy) - Individual, 2 × 60 min (one wk apart)
Harch et al., 2017; US, Hyperbaric Center Harch, Andrews et al., 2009; Van Meter, 2012[c]	Uncontrolled pre-post - case control study for SPECT analysis	Incl.: 18–65 yo, mild to moderate TBIs ≥ 1 year old; chronic TBI/PCS or TBI/PCS/PTSD, no acute cardiac arrest or hemorrhagic shock, 0–3 DRS, negative screen for drugs/pregnancy, good health, < 90% on PBNRS. Excl.: contraindicated medical conditions, severe confinement anxiety, active intervention, not likely to complete, previous HBOT, history of hospitalization.	Medical record, interview and neuropsychological testing	n = 30 n = 29	Veterans and Active duty military 93% male M = 30 (21–51) Mild 83% to moderate	HBOT (hyperbaric oxygen therapy) - Individual, 40 sessions, total dive = 60 min × 2 per day, 5 days per wk
Nelson & Esty, 2012; US, Brain Center	Uncontrolled pre-post	Incl.: veterans, persistent symptoms of TBI and PTSD, not progressing on standard treatments. Excl.: seizure disorder, sleep apnea, or ongoing substance abuse.	Assessment unclear	n = 7 n = 5 (+2 reductions in shorter period)	Veterans 60% male Age 23–42 Severity unclear	FNS (Flexyx Neurotherapy System) - Individual 22–25 sessions, 2–3 per wk, total stimulation = 4 s
Ruff et al., 2012; US, VA medical center (polytrauma) Ruff et al., 2009[c]	Uncontrolled pre-post observational	Incl.: at least one episode of mild TBI with LOC in combat setting, neurological deficits (incl. impaired olfaction), and PTSD.	Interview, neurological and cognitive assessment	n = 63 Prazosin = 61, sleep hygiene = 63	Veterans 90% male M = 29 ± 0.92, 20–60 Mild 100%	Sleep hygiene counselling and prazosin - Prazosin targeted dose 7 mg at bedtime; 5 sleep hygiene sessions, 9 wks
Weaver et al., 2018; US, army hospital (central assessment)	RCT:HBOT vs. sham - analyses for subgroups with and without PTSD	Incl.: active duty or veterans, 18–65 yo, mild TBI and at least 3 persistent PCS Excl. moderate/severe TBI, non-traumatic and penetrating injury, confounds of outcome measures or blinding.	Medical record and structured interview (OSU TBI-ID)	n = 71 (PTSD + TBI HBOT = 18, sham = 17; TBI HBOT = 18, sham = 18) n = 71 (ITT)	Military 99% male M = 33 (21–53) (entire sample) Mild 100%	HBOT 99% oxygen, 1.5 ATA; vs. sham (air, 1.2 ATA) - Individual 40 sessions, 60 min × 5 days, 12 wks

Note: ASD = acute stress disorder; CAPS = Clinician-Administered PTSD Scale; CPT-C = Cognitive Processing Therapy, Cognitive version; DoD = Department of Defense; DRS = Disability Rating Scale; DSM = Diagnostic and Statistical Manual of Mental Disorders; LOC = loss of consciousness; M = mean; MVA = motor vehicle accident; OEF = Operation Enduring Freedom; OIF = Operation Iraqi Freedom; OND = Operation New Dawn; PBNRS = Percent-Back-to-Normal Rating Scale; PCL = PTSD Checklist for DSM (C-Civilian, M-Military, S-Specific); OSU TBI-ID = Ohio State University TBI Identification Method; PCS = post-concussive symptoms; PCT = Person Centered Therapy; PE = prolonged exposure; PTSD = posttraumatic stress disorder; RCT = randomized controlled trial; SD = standard deviation; SPECT = Single Photon Emission Computed Tomography; SUD = Substance Use Disorder; TBI = traumatic brain injury; TMT = Trauma Management Therapy; US = United States; VA = Veteran Affairs; mo (s) = month(s); wk(s) = week(s); WARCAT = Warrior Administered Retrospective Casualty Assessment Tool; yo = years old.

[a] Including psychotic/bipolar disorder/mania/major depression with psychotic features.

[b] Alcohol or drugs.

[c] Multiple publication.

represents a general problem (Blostein & Jones, 2003; Foks et al., 2017), military TBI is a particular challenge. It was typically based on self-report and retrospective medical assessment several months after the incident (Davis et al., 2013). Furthermore, attrition was considered a source of bias in studies including only treatment completers or with attrition rate > 20% within a year. In addition, only a minority of studies reported an additional follow-up after three, six or more months after finalizing treatment. Although the sufficient time frame for follow-up of PTSD treatment is not specified in the guidelines (APA, 2017), it could have led to biased conclusions on efficacy. Finally, only two RCTs (Bryant et al., 2003; Weaver et al., 2018) were assessed as having a low risk of bias in most assessed domains (Appendix D).

3.4. Narrative synthesis of treatment outcomes

This synthesis is based on 23 studies (Table 1). Two studies represented an early intervention to prevent PTSD, while the other studies were treatments of existing PTSD. With the exception of one study (Davis et al., 2016) that observed increases in PTSD symptoms and mostly insignificant changes in other measures following light touch manual therapy (LTMT), all included studies found at least some positive consequences and implications of PTSD treatment. Three studies showed mixed findings (Browne et al., 2013; Davis et al., 2013; Weaver et al., 2018). More detailed results, categorized by type of treatment, are presented in continuation (Table 2).

3.4.1. Cognitive and/or behavioral psychotherapies

Exposure and cognitive-processing therapies (CPT) in service members and veterans with PTSD and predominantly history of mild TBI, resulted in a significant reduction of PTSD symptoms in all studies (n = 12), with no major differences in treatment adherence, measured by attendance and dropout (Davis et al., 2013; Ragsdale et al., 2018) (Table 2). However, when patients with and without history of TBI, or with varying TBI severity were compared directly, results were inconsistent. For instance, Chard et al. (2011) observed greater improvements with greater TBI severity, but an overlapping study with greater sample size did not confirm the interaction between TBI severity and outcome (Walter et al., 2014). Several other studies did not find TBI history or severity to be predictive of treatment outcomes (Ragsdale & Voss Horrell, 2016; Sripada et al., 2013; Walter et al., 2014; Wolf et al., 2017). Nevertheless, one study found smaller treatment effects when TBI was present (Gros et al., 2017), and one found more rapid improvements with greater TBI severity (Wolf et al., 2015). Comparing standard CPT to CPT augmented with cognitive rehabilitation and modifications for cognitive deficits (SMART-CPT) showed equivalent PTSD reductions in patients with history of predominantly mild TBI and persistent cognitive complaints. SMART-CPT was, however, beneficial for cognitive functioning, and it resulted in improved attention, memory and problem solving (Jak et al., 2019). Comparing standard CPT to Cognitive-only CPT (CPT-C) without written trauma account in patients with history of mild to severe TBI revealed similar PTSD reductions, and greater depression reduction following standard CPT (Walter et al., 2014).

In civilian samples with history of mild TBI, early treatment with CBT aimed at PTSD obtained favorable or mixed results (Browne et al., 2013; Bryant et al., 2003). Following early CBT, less patients developed PTSD following treatment and after six months compared to supportive counselling. The CBT group showed lower levels of posttraumatic and anxiety symptoms, but similar level of depression. A comprehensive multidisciplinary intervention (MI), which also included CBT, showed favorable outcomes in patients at lower risk of PTSD compared to the usual care: no one, compared to 24% in usual care, was diagnosed with PTSD at 6-month follow-up. Nevertheless, an equal percentage of high risk patients were diagnosed with PTSD at follow-up, and there were no differences in the level of PTSD, pain levels and depressive symptoms between the two groups (Browne et al., 2013). Individuals at risk of

PTSD and depression in the MI group had, however, lower general practitioner (GP) attendance.

Regarding treatment attendance, in the study of Davis et al. (2013), PTSD patients with history of mild TBI showed comparable dropout rates from PTSD treatment but attended a lower number of sessions than patients without. In the study of Ragsdale et al. (2018), number of attended sessions, as well as sessions necessary to achieve fear extinction and habituation, did not differ between the two groups. Patients who sustained TBI attended six minute shorter sessions than patients without TBI history, which was not considered clinically significant.

3.4.2. Other therapies for PTSD

In summary, other treatments for PTSD showed promising results in patients with history of TBI. However, only one study conducted a RCT and some adverse effects were also reported (Table 2).

3.4.2.1. Pharmacotherapy.
Only one study included medication (prazosin) in combination with psychoeducation as the main therapy, which showed reductions in PTSD symptoms and medication intake in patients with history of mild TBI (Ruff et al., 2012). Medications were used together with other therapies, but they were not indicated as the main treatment, and their independent effects on PTSD were not reported (Browne et al., 2013; Walter, Barnes, et al., 2012; Walter et al., 2014; Wolf et al., 2015).

3.4.2.2. Complementary and alternative medicine (CAM) treatments.
Mindfulness-based stress reduction (MBSR) showed a reduction in symptoms and improvement in attention in a small sample (n = 9) of veterans with history of TBI (Cole et al., 2015).

3.4.2.3. Novel therapies.
Two studies from the same group of authors (Carrick, McLellan, et al., 2015; Carrick, Pagnacco, et al., 2015) used brain and vestibular rehabilitation (VR), an exercise-based therapy focused on resolving vestibular symptoms. They reported short- and long-term reduction in PTSD symptoms after strategies for gaze stabilization in patients who did not react to other PTSD treatments. Moreover, two studies (Harch et al., 2017; Weaver et al., 2018) applied hyperbaric oxygen therapy (HBOT), which involved exposure to 100% oxygen in a pressurized chamber. Following HBOT in an uncontrolled study, Harch et al. (2017) described clinically significant reductions in PTSD and improvements in neurocognitive functioning in patients with chronic complaints, which persisted after six months. However, one withdrawal and middle-ear barotrauma, bronchospasm, anxiety associated with aggravation of PTSD and temporary worsening of symptoms were also reported. In a RCT (Weaver et al., 2018) that compared HBOT to sham-control with air, observed post-treatment reductions in PTSD regressed over six and 12 months. Similarly, there were some improvements in sleep, emotional and neuropsychological measures, but they diminished by six months.

Nelson and Esty (2012) applied Flexyx Neurotherapy System (FNS) to a small sample with persistent symptoms. According to the authors, this novel variant of electroencephalograph biofeedback, resulted in beneficial PTSD outcomes. After a medical massage treatment called LTMT, which preceded the full-program in patients with chronic PTSD, contrary findings were observed: an increase in PTSD, maintenance of depression and anxiety, and improvement in immediate headache and anxiety (Davis et al., 2016).

3.5. Case reports/studies

Case reports/studies are summarized in Appendix E. Most reports/studies originated from the US and involved male service members and veterans, and only two studies included civilian patients (Horton Jr, 1993; Turner et al., 2017). The remaining studies were from the United Kingdom (UK) and Italy, and involved civilian patients (n = 7) (King, 2002; McGrath, 1997; McMillan, 1991; Pagani et al., 2018; Williams,

Table 2
Treatment outcomes of included studies by type of treatment.

Study ID, primary treatment	PTSD-related outcome	Other outcomes measured	Timing of post-treatment measures	PTSD change and effect size[c]	Other outcomes effect: depression, PCS, anxiety and harms
Types of cognitive and/or behavioral therapies (CBT)					
Browne, 2013, MI (incl. CBT) vs. UC	MINI[a], PCL-C[b]	Depression (MINI), disability (FIM), depression (CES-D), pain (BPI, painDETECT), alcohol use (AUDIT), exercise (6MW), balance (BBS)	1 mo (only MI) 3 mos (only MI) 6 mos	6 mos: sig. lower % diagnosed with PTSD or depression in MI group (0% vs. 24%); equal % "at risk" diagnosed with PTSD, depression or both (57% vs. 58%); non-sig. diff in PTSD symptom severity	6 mos: non sig. difference in depressive symptoms and depressive symptom severity
Bryant, 2003, CBT. or supportive counseling	% diagnosis, CAPS[a], Impact of Event Scale[b]	Anxiety (BAI), depression (BDI)	1 wk 6 mos	1 wk: sig. lower % met criteria for PTSD in the CBT group (8% vs. 58%) (d = 1.16); sig. lower score on Avoidance (d = 2.45) and Intrusion (d = 1.83) in the CBT group 6 mos: sig. lower % met criteria for PTSD in the CBT group (17% vs. 58%) (d = 0.87); lower score on Avoidance (d = 1.65) and Intrusion (d = 1.93)	1 wk and 6 mos: non sig. difference in depressive symptoms (BDI), sig. reductions in anxiety (BAI)
Davis, 2013, CPT	Treatment completion and number of sessions	Not reported	Retrospective	Similar drop-out rates; PTSD group attended almost 2 sessions more than PTSD + TBI group (d = 0.17); trend-pattern of PTSD+TBI group to slightly greater early drop-out rates than PTSD (non-sig., φ = 0.05)	/
Gros, 2017, PE	PCL-M[b]	Substance use (MINI), depression (BDI)	Weekly; Last session	Sig. decrease in PTSD, but effect smaller for group with TBI (d = 0.85) than without TBI (d = 1.61)	Sig. decrease in depressive symptoms, bigger effect in group without TBI
Jak, 2019, CPT or SMART-CPT	PCL-S[b]	PCS (NSI), quality of life (QOLI-B), satisfaction (CSQ); various neuropsychological outcomes	Weekly Post-treatment (PT) 3 mos	Clinically sig. decrease in PTSD in both groups (r = 0.57), no difference between groups	Sig. decrease in PCS (r = 0.46), no difference between groups
Ragsdale, 2016, CPT or PE	PCL-S[b]	Depression (BDI)	PT	Sig. decrease in PTSD (combined PCL and BDI), no sig. difference between PTSD and PTSD group (partial η2 = 0.00), greater reduction in symptoms with PE than CPT in overall sample	Sig. decrease in depressive symptoms
Ragsdale, 2018, TMT	Treatment attendance and exposure process variables (EXP): fear activation, extinction rate, habituation	Influence of perceived executive functions (BRIEF-A)	Retrospective	No difference in number of attended sessions (r = 0.08), sig. shorter sessions in PTSD + TBI group (6 min); no sig. difference in EXP (r = 0.08–0.37); when controlling for PTSD severity sig. difference in overall fear activation (p = .047)	Self-reported executive dysfunction did not sig. impact any of the exposure process variables
Speicher, 2014, CPT	CAPS[a], PCL-S[b]	Occupational performance (COPM), depression (BDI)	PT	Sig. and clinically significant decrease in PTSD: CAPS (d = 2.01), PCL (d = 1.37)	Sig. decrease in depressive symptoms
Sripada, 2013a, PE	PCL-S[b]	Not reported	PT	Sig. decrease in PTSD in PTSD + TBI subsample (d = 1.81, completers 2.22); TBI status did not sig. predict slope of the scores over time	/
Sripada, 2013b, PE and PCT	CAPS[b]	Not reported	PT	Sig. decrease in PTSD in PTSD + TBI subsample (d = 1.51); change in outcomes not influenced by TBI history	/
Walter, Barnes, 2012, CPT-C	CAPS[a], PCL-S[b]	Depression (BDI)	PT (incl. mid-treatment at week 4)	Sig. decrease in PTSD (d = 1.0)	Sig. decrease in depressive symptoms; subsample with MDD-sig. greater symptoms at each assessment
Walter, Kiefer, 2012, CPT-C	CAPS[a], PCL-S[b]	PCS (NSI)	PT	Sig. decrease in PTSD: CAPS (d = 1.43) and PCL (d = 1.21)	Sig. improvements on NSI; reduction in PTSD associated with a reduction in PCS
Walter, 2014, CPT or CPT-C Chard, 2011[d]	CAPS[a], PCL-S[b]	Depression (BDI)	PT (incl. mid-treatment at week 4)	Sig. decrease in PTSD, PCL dropped below one cutoff: TBI severity not a predictor of treatment outcome CAPS: partial η2 = 0.79, PCL: partial η2 = 0.67, more improvement in the moderate/severe than mild TBI group	Sig. decrease in depressive symptoms, greater decrease with CPT than with CPT-C
Wolf, 2012, PE	PCL[b]	Depression (BDI)	PT	Sig. decrease in PTSD; 100% reliable reduction in PTSD; 90% clinically significant change and no longer met criteria for PTSD	Sig. decrease in depressive symptoms, 90% reliable reduction in depression; 40% clinically sig. reduction in depression
Wolf, 2015, PE	PCL[b]	Depression (BDI)	Weekly/PT	(d = 3.64)	Sig. decrease in depressive symptoms

Table 2 (*continued*)

Study ID, primary treatment	PTSD-related outcome	Other outcomes measured	Timing of post-treatment measures	PTSD change and effect size[c]	Other outcomes effect: depression, PCS, anxiety and harms
Wolf, 2017[d]		PCS (NSI), behavioral outcomes (KBCI) and self-efficacy (Sesx)		All: 75% reliable reduction in PTSD, 61% of participants clinically sig. change; completers: 96% reliable reduction, 86% clinically sig. change; non-completers: 40% reliable reduction, 16% clinically sig. change, n = 4 worsening of PTSD symptoms (PCL), n = 2 reliable change; moderate to severe TBI more rapid gains than mild TBI; PCL: d = 1.80; TBI severity not a predictor of treatment outcome	Sig. decrease in PCS (NSI)
Other therapies					
Carrick, McLellan 2015, BVH	CAPS[a]	Not reported	1 wk; 3 mos (not reported)	1 wk: sig. decrease in PTSD symptoms (d = 0.73); % of most severe PTSD (extreme + severe) decreased from 77% to 49%	/
Carrick, Pagnacco 2015, BVH	CAPS[a]	Not reported	1 wk; 3 mos	1 wk: sig. decrease in PTSD severity (d = 0.92); 3 mos: d = 1.20	/
Cole, 2015, MBSRT	PCL-C[b]	Attention (Cogstate); ratings of safety, feasibility, and acceptability of treatment	2 wks; 3 mos	2 wks; sig. decrease in PTSD (d = 1.56), 6/9 reliable change; 3 mos: d = 0.93, 3/8 reliable change	Sig. improved attention; rated as acceptable and enjoyable (100%) and feasible (M = 8.3/10)
Davis, 2016, LTMT	PCL-M[b]	Patient-reported outcomes (PROMIS), quality of life (Neuro-QoL), medical outcome profile (MYMOP2)	4–7 days after	Sig. increase in PTSD (d = 1.21)	Non. sig. change in depression and anxiety (Neuro-QoL Bank), sig. decrease in anxiety intensity (one item)
Harch, 2017, HBOT	PCL-M[b]	SPECT imaging, depression (PHQ-9), anxiety (GAD-7), quality of life, PCS (RPQ), various neuropsychological outcomes	PT; 6 mos	PT and 6 mo: sig. decrease in PTSD and around 50% below cutoff	Sig. decrease in depression and anxiety, sig. improvements in PCS; 1 withdrew (ear infection, bronchospasm, and middle ear barotrauma), n = 11 protocol breaks due primarily to adverse events but 10/11 finished the protocol.
Nelson, 2012, FNS	PSS[b]	Neurobehavioral functioning (NFI), current levels of symptoms on separate 0–10 scales	PT	Sig. decrease in PTSD (d = 0.79)	Sig. decreases on four NFI dimensions, decrease in medication intake; minimal transient increases in symptoms
Ruff 2012, sleep hygiene, prazosin	PCL-M[b]	Olfaction testing score, number of headaches per month, severity of headache pain, cognitive function (MOCA), impaired nocturnal sleep (ESS).	PT (9 wks from start of treatment); 6 mos	9 wks and 6 mos: sig. decrease in PTSD, progressive reduction; sig. reduction from 9 wks to 6 mos	/
Weaver, 2018, HBOT	PCL-C[b]	PCS (NSI, RPQ), depression (CES-D), various quality of life scales, neuropsychological, neurological and sleep measures	PT (13 wks from baseline); 6 mos; 12 mos	13 wks: sig. decrease in PTSD compared to sham, bigger change in PTSD + TBI subgroup; confirmed by longitudinal modelling only in total sample; 6 mos: non sig. decrease in PTSD; 12 mos: non sig. worsening of PTSD	13 wks: sig. improvement in PCS (NSI, RPQ-3), bigger in PTSD + TBI subgroup; non sig. change in RPQ-13; 6 mos and 12 mos: non sig. change; No serious adverse effects, minor barotrauma; n = 25

Note: in case of multiple indicators, Cohen's d presented; reliable change ≥ 5 points PCL; clinically significant change ≥ 5 points PCL; clinically significant change ≥ 15 CAPS, ≥10 PCL; AUDIT = Alcohol Use Disorders Identification Test; BAI = Beck Anxiety Inventory; BBS = Berg Balance Scale; BDI = Beck Depression Inventory; BPI = Brief Pain Inventory; CAPS = Clinician-Administered PTSD Scale for DSM; BVR = brain and vestibular rehabilitation; BRIEF-A = Behavior Rating Inventory of Executive Function–Adult Version; CES-D = Center for Epidemiological Studies Depression Scale; COPM = Canadian Occupational Performance Measure; CPT = Cognitive Processing Therapy; CSQ = Client Satisfaction Questionnaire; d = Cohen's effect size; FIM = Functional Independence Measure; FNS = Flexyx Neurotherapy System; ESS = Epworth Sleepiness Scale; FNS = Flex Neurotherapy; GAD-7 = General Anxiety Disorder Scale-7; HBOT = hyperbaric oxygen therapy; KBCI = Key Behaviors Change Inventory; LTMT = light touch manual therapy; MDD = Major Depressive Disorder; MINI = Mini-International Neuropsychiatric Interview; MBSR = mindfulness based stress reduction; MI = multidisciplinary intervention; MOCA = Montreal Cognitive Assessment; mo = months; NSI = Neurobehavioral Symptom Inventory; NF = Neurobehavioral Functioning Inventory; PCL = PTSD Checklist for DSM (C-Civilian, M-Military, S-Specific); PCS = post-concussive symptoms; PE = prolonged exposure; PHQ-9 = Personal Health Questionnaire-9; PSS = PTSD Symptom Scale; PTSD = posttraumatic stress disorder; r = Pearson r effect size; QOLI-B = Quality of Life Inventory; RPQ = Rivermead Post Concussion Symptoms Questionnaire; Sesx = TBI Self-efficacy Questionnaire; TBI = traumatic brain injury; UC = usual care; VRR = brain and vestibular rehabilitation; 6 MW = 6-min Walk Test; mo(s) = month(s); wk(s) = week(s); η2 = eta squared effect size; φ = phi effect size.

[a] Clinician-rated.
[b] Self-rated.
[c] If reported.
[d] Multiple publication.

Evans, & Wilson, 2003). In accordance with other studies, case reports/studies reported predominately positive effects of treatments, resulting in a reduction of PTSD symptoms in military and civilian patients with a history of TBI of different severities. However, some disturbances usually persisted. More detailed results of different treatments are presented below.

3.5.1. CBT

Treatments usually integrated complementary therapies aimed at enhancement of neurocognitive functioning, psychoeducation, and psychological strategies for TBI-related cognitions, such as changing negative beliefs about cognitive decline after TBI or learning memory strategies. Moreover, smaller modifications and adjustments of treatments were introduced in order to facilitate treatment adherence and effectiveness in patients who sustained TBI, such as reminder calls, backup appointments and decreased workload.

Predominately positive main outcomes of CBT were reported in civilian patients who sustained mild to severe TBIs (Horton Jr, 1993; McMillan, 1991; Williams et al., 2003). Two case studies reported improvements in some, but not all psychiatric symptoms after applying CBT in civilian patients with a history of mild TBI (King, 2002; McGrath, 1997). A significant adverse effect was reported in a patient who sustained an open head injury and had mild executive impairment. He responded to CBT with perseverations, in the form of continuously re-experiencing the most disturbing traumatic details for over a week (King, 2002). PE, CPT and CPT-C reduced PTSD symptoms in service members and veterans who sustained mild and severe TBIs (n = 6) (Batten & Pollack, 2008; Boyd, Rodgers, Aupperle, & Jak, 2016; Donovan, Petersen, Nadal-Vicens, & Kamenker-Orlov, 2019; McIlvain, Walter, & Chard, 2013; Strom, Wolf, Crawford, Blahnik, & Kretzmer, 2016) and a civilian with a history of mild TBI (Turner et al., 2017). Positive changes were also reported after a brief psychodynamic therapy (Watson, Ghani, & Correll, 2016) and Dialectical Behavior Therapy in combination with PE (Strom et al., 2016). Pagani et al. (2018) described two patients with chronic PTSD and a history of severe TBI, who showed reductions of PTSD symptoms and improvements in neuropsychological symptoms after eight sessions of Eye Movements Desensitization and Reprocessing (EMDR).

3.5.2. Pharmacotherapy

The absence of PTSD-related nightmares was reported after treatment with clonidine (Alao, Selvarajah, & Razi, 2012). Citalopram in combination with group therapy and several other medications demonstrated stabilization of symptoms in a patient who sustained severe TBI (Matthew & Gedzior, 2016).

3.5.3. Complementary and alternative medicine (CAM)

A case series described the successful usage of transcendental meditation (after PE or CPT) and its high acceptance by military patients with mild blast-related TBI (Barnes, Rigg, & Williams, 2013). Furthermore, scalp and body acupuncture (He, Chen, Pan, & Ying, 2014) and a combination of acupuncture and art therapy (Walker, Kaimal, Koffman, & DeGraba, 2016) were successfully used in military patients.

3.5.4. Novel treatments

The absence of PTSD symptoms was reported after HBOT (Harch, Fogarty, Staab, & Van Meter, 2009) in a patient with mild blast-related injury; and a reduction of persistent symptoms following neurotherapy in veterans with multiple TBIs and chronic PTSD (Nelson & Esty, 2015).

4. Discussion

This extensive systematic review indicated that recommended psychotherapies for PTSD seem appropriate for the treatment of PTSD symptoms in a population with history of TBI, while there is less evidence for other treatments aimed at PTSD symptoms. All studies using PE, CPT or other CBT, commonly in combination with additional treatments, resulted in a reduction of PTSD symptoms among service members and veterans, with adverse effects rarely reported. A small number of studies and case studies which involved pharmacotherapy (prazosin, clonidine, citalopram), complementary (mindfulness, meditation, massage, acupuncture) and novel therapies (HBOT, neurotherapy, brain and vestibular rehabilitation) showed promising results in patients with chronic PTSD symptoms. Almost all studies and case reports/studies reported positive PTSD outcomes, however, their quality was mainly low.

Methodological limitations arose from weak study designs, as in case reports/studies and single-arm studies, or from the lack of control in group allocation. In several studies, the main treatment was part of an integrative program, or the effects were not separated from concurrent therapies: pharmacotherapy; cognitive and speech therapies and modifications of treatments aimed at compensation of neurocognitive deficits. Thus, it was not clear whether the treatments would be equally appropriate and effective, or too demanding, without those adjuncts and adjustments. Furthermore, in order to obtain non-biased measures of treatment outcomes, a blinded assessment with gold standard techniques and longer follow-up is required. Lastly, TBI assessment significantly varied between studies, and included direct hospital referrals in civilian studies, and in the military context self-report, military records and clinical examination were used. Prompt, corroborated and accurate assessment of TBI is difficult in combat conditions, and records frequently rely on self-reports (Davis et al., 2013). Nonetheless, to reduce bias, future studies could profit from usage of structured instruments for assessment of TBI.

Regarding generalizability, the evidence of treatment effectiveness remains unclear in the context of severe injuries. Positive changes in PTSD symptoms were reported across levels of TBI severity. However, patients who sustained a moderate to severe TBI were outnumbered or excluded. In addition, the majority of studies were conducted after a minimum of one year following a traumatic incident. Although two civilian studies suggested that an early intervention was not harmful but beneficial, it still cannot be concluded when it is optimal for interventions to be implemented after a trauma occurs, particularly involving severe TBIs, related pain and greater cognitive deficits.

The majority of studies involved male service members and veterans with high prevalence of multiple and blast-related injuries (Chapman & Diaz-Arrastia, 2014). Thus, it is unclear whether the results can be generalized to female and civilian patients. Nevertheless, the study with a low risk of bias (Bryant et al., 2003) and several case studies involving civilians provided results similar to results in the military population. In addition, there are some similarities between military and civilian populations. Although in lower percentages, other types of trauma than combat were present among service members and veterans, and unfortunately, blast-related injuries have recently become more common in civilians (Maas et al., 2017). There is some evidence that there are no major differences between blast and non-blast-related injuries (Belanger, Kretzmer, Yoash-Gantz, Pickett, & Tupler, 2009; Kennedy et al., 2010; Lamberty, Nelson, & Yamada, 2013; Lippa, Pastorek, Benge, & Thornton, 2010), but the issue remains under examination. Finally, the majority of studies involved comprehensive multidisciplinary treatments involving multiple types of therapies. While these might be common in military/VA and hospital settings, they could be less accessible for civilians who were not in residential care or for the veterans from countries other than the US. Based on the included studies, the efficacy of psychotherapies outside of integrative and multidisciplinary programs is unclear.

Studies of greater rigor are particularly needed for treatments that are not well-investigated in PTSD patients, with or without a history of TBI, namely HBOT (Harch et al., 2017; Weaver et al., 2018), neurotherapy (Nelson & Esty, 2012, 2015), LTMT (Davis et al., 2016), and vestibular and brain rehabilitation (Carrick, McLellan, et al., 2015;

Carrick, Pagnacco, et al., 2015). A small number of included studies and case studies suggested some improvements in patients with chronic PTSD symptoms. However, increases in symptoms (LTMT; Davis et al., 2016), and transient side-effects (HBOT; Harch et al., 2017) are also reported. For instance, HBOT remains a controversial treatment with insufficient evidence for effectiveness in the context of TBI (Bennett, 2018). Uncontrolled studies typically found some improvements in TBI and PTSD-related symptoms, whereas there was no difference in effectiveness of HBOT compared to inactive treatment (Bennett, 2018; Eve, Steele, Sanberg, & Borlongan, 2016). In this review, an uncontrolled study found short- and long-term improvements of PTSD following HBOT (Harch et al., 2009, 2017), whereas in a RCT the post-treatment improvements did not persist (Weaver et al., 2018). Moreover, evidence for brain and vestibular rehabilitation and neurotherapy was particularly scarce and based on uncontrolled studies of a single groups of authors (Carrick, McLellan, et al., 2015; Carrick, Pagnacco, et al., 2015).

This review included only one study and two case studies targeting pharmacotherapy. Additionally, there was a relevant RCT (not completely meeting inclusion criteria regarding the sample and therefore excluded) of methylphenidate and galantamine in patients with PTSD, TBI or both by McAllister et al. (2016). It observed improvements in PTSD symptoms in association with methylphenidate. Available literature reviews suggest that medication targeting overlapping symptoms (e.g. selective serotonin reuptake inhibitors) can improve outcomes of both conditions, but many pharmacological treatments for one condition can aggravate the symptoms of the other (McAllister, 2009). Therefore, further research on psychopharmacology in this population is of pivotal importance.

Some important issues are beginning to be elucidated. It seems that CPT augmented with cognitive rehabilitation, compared to standard CPT, results in similar PTSD reductions, but substantial improvements in different cognitive domains (Jak et al., 2019). Nevertheless, the findings were obtained in patients who sustained mild to moderate TBIs a few years before the therapy, and it therefore remains unclear how important those adjuncts are for reducing symptoms in patients with more severe and more recent TBIs.

Some researchers emphasize the importance of neurocognitive disturbances and not historical TBI status when considering differential treatment outcomes. In a recent study by Scott et al. (2017), response to CBT for PTSD-related sleep difficulties was related to verbal memory but not to TBI status. Similarly, early dropout and response to CPT in patients with PTSD and a history of TBI was associated with poorer executive functioning, and not TBI characteristics (Crocker et al., 2018). However, in the majority of included studies, objective neuropsychological functioning was not measured, and it should be included in future studies as an important confounder. Other TBI characteristics, such as presence and duration of PTA and LOC, could also influence the treatment process and effects beyond TBI severity (Verfaellie, Amick, & Vasterling, 2012).

Finally, this review has some limitations. Literature search was restricted to English and articles were only partly screened by two researchers. However, in case of doubts in screening, articles were discussed with a second and third researcher. In addition, reference lists of included articles and a base of clinical trials were also inspected.

5. Conclusion

TBI history should not discourage the application of PTSD treatments, particularly PE, CPT and other CBT, which seem to result in reductions of symptoms and have no serious adverse effects. However, the quality of evidence is limited. Future studies should conduct controlled PTSD trials to obtain more conclusive evidence regarding the treatment effectiveness in this population. In recent years, there has been a growing number of articles discussing functioning and treatment of patients with PTSD and a history of TBI, as well as announced trials

that respond to some of the challenges in the field. Nevertheless, this review highlights the importance of improving several aspects of future studies: controlling for concurrent therapies; involving more female and civilian patients; investigating the impact of TBI severity and other TBI characteristics; using valid and reliable instruments for TBI and PTSD, and assessing neurocognitive deficits using objective measures. Finally, the same therapies may be appropriate and effective in this subgroup of PTSD patients, but the needs and limitations of individuals should be taken into account in the treatment process.

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Contributors

MC and AM designed the study and wrote the protocol. Screening and full text review were conducted by AM (100%) and IRH (10%). Data extraction and assessment of bias were performed by AM and checked (100%) by IRH. All steps were guided by MC, and SP supervised the project. AM wrote the tables and draft of the manuscript. SP, MC, IRH, JH critically commented on the manuscript and approved the final version.

Declaration of competing interest

All authors declare that they have no conflicts of interest.

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Ana Mikolić is a psychologist and works as a researcher at the Department of Public Health of the Erasmus Medical Center (MC) in Rotterdam. She is involved in the European project called Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI), where she studies prediction, outcome and gender differences in traumatic brain injury.

Suzanne Polinder (PhD) is a health economist and Associate Professor at the Department of Public Health, Erasmus MC in Rotterdam. She is an outcome expert involved in Health technology assessment & implementation and CENTER-TBI project.

Isabel R.A. Retel Helmrich is a researcher at the Department of Public Health of the Erasmus MC in Rotterdam. She is involved in the CENTER-TBI project, and studies development, validation and implementation of prognostic models in traumatic brain injury.

Juanita A. Haagsma (PhD) is an Assistant Professor at the Department of Public Health of the Erasmus MC in Rotterdam. She previously worked as a Clinical Assistant Professor at the Institute for Health Metrics and Evaluation, University of Washington, Seattle, USA, and Senior researcher at the Erasmus MC, Rotterdam.

Maryse C. Cnossen (PhD) is a psychologist and researcher. She currently works as a Researcher and Lecturer at the University of Applied Sciences, Rotterdam. She worked as a researcher and obtained her PhD at the Department of Public Health, Erasmus MC, Rotterdam, where she studied outcome, prediction and comparative effectiveness research in traumatic brain injury.