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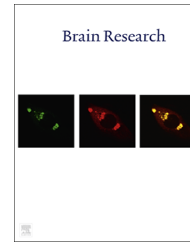

Review

Complementary and alternative medicine (CAM) following traumatic brain injury (TBI): Opportunities and challenges

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ABSTRACT

Traumatic brain injury (TBI) is highly prevalent and occurs in a variety of populations. Because of the complexity of its sequelae, treatment strategies pose a challenge. Given this complexity, TBI provides a unique target of opportunity for complementary and alternative medicine (CAM) treatments. The present review describes and discusses current opportunitites and challenges associated with CAM research and clinical applications in civilian, veteran and military service populations. In addition to a brief overview of CAM, the translational capacity from basic to clinical research to clinical practice will be described. Finally, a systematic approach to developing an adoptable evidence base, with proof of effectiveness based on the literature will be discussed. Inherent in this discussion will be the methodological and ethical challenges associated with CAM research in those with TBI and associated comorbidities, specifically in terms of how these challenges relate to practice and policy issues, implementation and dissemination.

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Contents

1. Background

The complexity inherent in traumatic brain injury (TBI), from its mechanisms of injury through to its neurobehavioral sequelae render it a promising target of opportunity for complementary and alternative medicine (CAM) treatment approaches. Indeed, the lack of a “silver bullet” with which to treat TBI-related symptoms supports that a multi-faceted approach is required, and even called for (Marguiles and Hicks, 2009; Rosenbaum and Lipton, 2012). And given the multi-facted nature of many CAM treatments and modalities, there should be potential for an evidence base to develop in the treatment of TBI. That said, such an evidence base would require methodologically rigorous studies, with good control procedures in order to yield unequivocal support of a particular CAM treatment. To this end, this review will describe the developing evidence base from studies of promising CAM treatments (i.e., acupressure, mindfulness-based stress reduction (MBSR), a CAM-augmented residential treatment program, and the Mantram Repetition Program (MRP) for TBI-associated sequelae.

Over the past 30 years, TBI has transitioned from a “silent epidemic” (Klein, 1982), to a highly publicized “signature wound” (Robertson, 2006) of operational conflicts. TBI no longer flies under the radar. Indeed, this increased awareness has led to the recognition of TBI’s often persistent sequelae, and the recommendation to treat it as a chronic health condition across the lifespan (Malec et al., 2013). In civilian populations, there are approximately 1.7 million TBIs sustained annually (Faul et al., 2010). Estimates among the 2 million U.S. military personnel deployed to Afghanistan and Iraq since 2001 show an even greater prevalence. In some cohorts, the data suggest up to one-quarter of individuals have sustained a TBI (Terrio et al., 2009) and the rate of disability associated with TBI has been on the rise (Gubata et al., 2014). Over the past decade, sports-related TBI has become a public health concern with the growing number in emergency department (ED) visits (3.42 million visits to the ED between 2001 and 2012 for sports or recreation related TBI) (Coronado et al., 2015). Across all of these populations and including the full range of severity, a TBI can result in a host of sequelae that can individually or in combination negatively impact a variety of important functional domains in the short-term, as well as chronically (Brenner et al., 2009; Ponsford et al., 2014; Kashluba et al., 2008; Rosenbaum and Lipton, 2012).

There are certain barriers to the effective treatment of TBI and associated comorbidities, including misconceptions and stigma (Redpath et al., 2010; Zhou et al., 2014), in addition to the limited, effective treatments available (Maas et al., 2010; Marguiles and Hicks, 2009; Tolias and Bullock, 2004). Given the prevalence of TBI and its potential burden, identifying effective, accessible and self-sustaining treatment strategies would be of significant benefit. Equally important is that potential strategies share an emphasis on patient-centered care, independence and agency, each of which can contribute to good outcome (Lukow et al., 2015). Lastly, and of essential importance, is developing a strong evidence base for such strategies.

2. Improving TBI outcome: the role of CAM

The treatment of and recovery from TBI are similarly vulnerable to the heterogeneity of the injury and contextual factors (Marguiles & Hicks, 2009); a likely contributor to the fact that even with the multitude of pre-clinical and clinical studies to date (Margulies and Hicks, 2009), uniformly promising neuroprotective agents have not been identified acutely or post-acutely (Warden et al., 2006). This lack of uniformity in response is also evident for certain non-pharmacologically based treatments. For example, cognitive rehabilitation therapy may be effective for certain TBI-associated deficits, but its efficacy can be variable in sometimes unpredictable ways (Institute of Medicine, 2011). Because of these limitations and the increasing availability of CAM treatments, individuals with chronic neurological conditions frequently seek CAM treatment modalities as an adjunct to ongoing conventional medical care. This enhanced visibility and increased use resulted in the American Psychological Association Monitor (April 2013) devoting a cover and an entire section to the importance of CAM in Psychology. This section also highlighted the limitations of current research on CAM efficacy and underlying mechanisms (Barnett and Shale, 2013).

CAM is defined as “a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine” (NCCAM/NCCIH, 2011). Examples of CAM include acupuncture, acupressure, chiropractic manipulation and yoga, with deep breathing, relaxation, and meditation serving as examples of the more commonly utilized practices (Barnes et al., 2008). CAM surveys and clinical trials in the U.S. from 1990 through to present have generated a wealth of information about patterns of use and effectiveness (Eisenberg et al., 1993; Eisenberg et al., 1998). Most typically, CAM is used in conjunction with conventional treatment for chronic medical conditions for which there are not, as of yet, effective treatments (Astin, 1998; Barnes et al., 2008; Eisenberg et al., 1993; Mitchell, 1993; Perelson, 1996). This includes musculoskeletal issues and pain (Astin, 1998, Barnes et al., 2008; Carlson and Krahn, 2006; Eisenberg et al., 1998), as well as a variety of health-related conditions (Jacobson et al., 2009) and stress (Baldwin et al., 2002) or dissatisfaction with conventional medicine's emphasis on prescription medication (Kroesen et al., 2002). CAM is accessed at comparable rates (30% or more) among civilian, military and veteran populations (Astin, 1998; Astin et al., 2000; Barnes et al., 2004; Micek et al., 2007; White et al., 2011), which supports survey results indicating veterans are receptive to CAM modalities (Baldwin et al., 2002; Betthauser et al., 2014; Denneson et al., 2011; Elwy et al., 2014; Libby, et al., 2013; McEachrane-Gross et al., 2006).

Promotion of independence, self-efficacy and taking an active role in recovery are important and foundational cornerstones of the rehabilitation process (Dixon et al., 2007). These cornerstones are shared with CAM, in its focus on relationship-centered care, self-reflection and self-care, as well as its emphasis on facilitating health via agency, rather than curing disease (Rakel et al., 2008). Similarly to rehabilitation–based strategies (e.g., compensatory techniques, exercise), many CAM treatments (e.g., relaxation techniques, types of meditation, yoga, and acupressure) are portable. Once learned, these modalities can be self-administered, thereby becoming self-sustaining and part of the individual's routine which carries the potential for other vital health benefits, including reduced hospitilization rates (Smith et al., 2008).

A challenge in this self-utilization of CAM occurs when the primary treatment provider is unaware of concurrent CAM usage, which is estimated to occur 60-75% of the time (Micek et al., 2007; Eisenberg et al., 1998; Murphy et al., 2008; Saydah and Eberhardt, 2006). Adding to this potential risk is that CAM's efficacy and effectiveness for many conditions remains unsubstantiated. This, at least in part, stems from variations in experimental design, sample size, and the use of controls. That said, further study is supported *if* done with experimental rigor (Wahbeh et al., 2008).

The need for effective treatments for the variety of TBI sequelae, be it with conventional or CAM, is well-established (Flanagan et al., 2008; Wong et al., 2011). Though multiple types of CAM have been studied following TBI, the findings have generally been mixed and some not replicated. As well, the studies to date described here are predominately aimed at post-acute *mild* TBI, so the potential utility of CAM interventions for moderate to severe injuries remains an empirical question to be studied. To begin summarizing the published findings, mindfulness-based approaches have been examined in individuals with a TBI history. Individuals with a TBI history who received a 10-week pilot of MBSR (Azulay et al., 2013) or a 12-week series encouraging the use of other mindfulness techniques (Bedard et al., 2003) reported significantly improved quality of life scores after these programs. In the latter study, improvements were maintained at a one-year follow-up (Bedard et al., 2005). Mindfulness based cognitive therapy (MBCT) after TBI was found to reduce symptoms of depression (Bedard et al., 2012), though because this was a feasibility study, the single group, pre-post intervention design did not include a control group for comparison. In contrast, a randomized, controlled trial of a type mindfulness (e.g., attentional control training) after TBI found no such benefit (McMillan et al., 2002), failing to replicate the promising pilot study that had preceded it.

Other mind-body approaches have also been examined for individuals with a history of TBI. For example, relaxation techniques reduced the number of symptoms and improved performance on cognitive tests among college students with mild TBI (Hanna-Pladdy et al., 2001). A review of the biofeedback literature (with or without relaxation training, Laures and Shisler, 2004) or in relationship to heart rate variability enhancement (Conder and Conder, 2014)) suggests it may hold promise for TBI-related treatment, though further study is necessary to determine efficacy and mechanisms. A placebo-controlled, blinded trial of homeopathy for mild TBI-related related symptoms showed significant symptom reduction for individuals in the treatment group as compared to the control group (Chapman et al., 1999); though a later review of this study from a World Health Organization (WHO) Task Force on TBI withheld recommending homeopathic treatment for TBI-related symptoms because of the need for and challenge inherent in replication, given the individualized nature of homeopathy (Borg et al., 2004). Studies of acupuncture (Donnellan, 2006; He et al., 2005; Zollman et al., 2012) have yielded significant support for its use in the treatment of symptoms across the range of TBI severity. Tai Chi has also been studied, using a wait-list or social-interaction control, and the initial outcome results appear promising related to mood and self-esteem (Blake and Batson, 2009; Gemmell and Leathem, 2006). Finally, the most recent reviews of yoga (Coeytaux et al., 2014; Jeter et al., 2015) failed to identify studies of yoga as a stand alone intervention for TBI-related symptoms.

Enthusiasm for CAM treatment for TBI has been tempered however, because of issues related to experimental design, sample size, and lack of control conditions. Indeed, literature reviews challenge the state of the science pertaining to CAM interventions and have concluded that no high quality, randomized clinical trials exist to-date that genuinely could support the use of acupuncture in treating TBI (Wong et al., 2011), which arguably has been one of the more studied CAM approaches. As a result, there is an "urgent" need for research in this and other areas of CAM for TBI (Flanagan et al., 2008). Continued study in this area is called for, albeit with markedly increased rigor. It is unfortunate that pre-clinical studies of CAM in animal models may not be an optimal means by which to inform the clinical science and enhance the rigor. Indeed, the challenge of generating relevant pharmacotherapeutic data from animal models of TBI pre-clinical work to inform subsequent clinical trials has been recently highlighted (Watzlawick et al., 2015). These types of challenges would only be compounded given the nature of CAM interventions, which are sufficiently complex in human studies, and would therefore be even more so in animal models. As such, the most parsimonious and promising path for developing an evidence base for CAM treatments after TBI is with methodologically rigorous clinical studies of CAM in humans with TBI.

3. Optimizing CAM research for traumatic brain injury: lessons from the laboratory and the clinic

Acupressure: A Portable, Accessible, Non-pharmacological Efficacious Tool for Acquired Brain Injury. As mentioned, systematic reviews and meta-analyses of CAM research have consistently identified methodological weaknesses that preclude unequivocal endorsement of certain CAM treatments. Examples of these weaknesses include control procedures (or lack thereof), small sample sizes, limitations in research design and inconsistencies in outcome measures. To overcome these issues and potentially yield conclusive, replicable results, our laboratory has utilized the following methodologies to study the efficacy of the CAM modality of acupressure in the treatment of stroke and TBI. As such, acupressure will be discussed here in even greater detail (i.e., TBI and stroke; see McFadden et al., 2011; McFadden and Hernández, 2010; Hernández et al., 2015) with the hope that these studies may serve as a template from which to design and implement subsequent studies of other CAM therapies for conditions such as TBI.

Acupressure, including Jin Shin-acupressure used in our laboratory, makes contact with the body using only the tips of the fingers (Burmeister and Monte, 1997; Mines, 1982; Teegaurden, 1978) and does not rely on needles as does acupuncture. These points are focal areas that have been reported to have significantly reduced electrical resistance (approximately 1/100 of the surrounding area; Teegaurden, 1996). Jin Shin, which has been practiced since 712 AD (Higgins, 1988), was introduced to the U.S. via Japan in the mid-1900s and now is practiced and taught world-wide (Burmeister and Monte, 1997; Mines, 1996; Sempell, 2000; Teegaurden, 1996, 1978). Acupressure theory assumes a relatively direct connection between the site of stimulation (i.e., points) and the site of the illness (Burmeister and Monte, 1997; Teegaurden, 1996). It is thought that energy travels throughout the body via meridians or pathways. When energy becomes stuck, it creates energetic imbalances that can lead to illness. Stimulation at points along the meridians is said to unblock the energetic pathways. In doing so, this leads to energetic balance, healing, and health. Though not placebo-controlled studies, published reports suggest acupressure reduces anxiety and depression in patients waiting for heart transplant (Sempell, 2000), decreases perceived stress in nurses (Lamke, 1996; Lamke et al., 2014) and was beneficial in a case study of multiple myeloma (Shannon, 2002). Controlled studies of acupressure have shown it to impact the cardiovascular system (Felhendler and Lisander, 1999) and pulmonary rehabilitation (Maa et al.,1997, 2003), such that pressure at acupoints evoked statistically significant reductions in blood pressure and heart rate compared to light stimulation at non-acupoints (Felhendler and Lisander, 1999). In addition to these physiological effects, acupressure treatment (in comparison to "sham" acupressure treatment or a routine care control) has been associated with a reduction in distress, stress or challenge-associated anxiety, as well as improvement on several sleep indices (Agarwal et al., 2005; Hmwe et al., 2015; Kober et al., 2003; Shariati et al., 2012).

Hypothesized mechanisms underlying acupressure's effects include peripheral nerve stimulation and centrally-mediated autonomic adjustment (Felhendler and Lisander, 1999). Other potential mechanisms include this treatment's ability to induce the "relaxation response" – a physiological response that includes reduced respiration, heart rate, and blood pressure (Benson et al.,1974). The relaxation response may be used to treat disease (Lazar et al., 2000), possibly by counteracting or protecting against stress, the stress response, and even against stress-related disease pathology (Esch et al., 2003) via alterations in the central nervous system (Jacobs et al.,1996; Jacobs and Lubar, 1989; Lazar et al., 2000) and sympathetic nervous system arousal (Hoffman et al., 1982).

Acupressure has been the focus of the Clinical Assessment of Injury, Recovery and Resilience (CAIRR) Neuroscience laboratory because of its accessibility as a treatment that can be initially administered by a practitioner and then, with education, can be learned and self-administered by the novice individual. Individuals with chronic health conditions and limitations would particularly benefit from the ability to independently, or semi-independently, augment their own health practices. Acupressure is easily learned through classes or manuals, can be simply and discreetly administered anytime and anyplace, and has the potential for self-administered maintenance treatment long-term.

Combining the highest scientific rigor with a systematic, logical and iterative progression approach to experimental design has yielded promising results with little ambiguity in interpretation of findings. The following set of guiding principles were used in the acupressure studies that comply with an evidence-based medicine (EBM) perspective by containing factors that strengthen CAM research rigor (e.g., improved controls—particularly placebo controls, randomization, blinding and multiple, disorder-specific outcome measures). To our knowledge, these were the first series of studies of acupressure post-stroke or TBI published in the English language and using a placebo-control.

A series of five studies (for review see Hernández et al., 2015) have been performed, each with an ever increasing level of methodological rigor, validity and reliability. A feasibility study showed that a series of four acupressure treatments in an elderly, post-acute stroke population were well-tolerated, associated with good retention, and showed a trend towards improved quality of life and communication success (Hernández et al., 2002). The second study (Hernández, et al., 2003) utilized a placebo-controlled, crossover design, with an eight-treatment series in post-acute stroke survivors with aphasia and hemiplegia. Important was the development of the placebo control, which would be compared to the active acupressure treatment series. The placebo treatments were designed to fully control for physical contact, attention and time associated with the active treatments. Because there were no established placebo points for acupressure reported in the literature, placebo acupressure points were developed by the lead author (TDH) to be used in all placebo treatments

(Hernández et al., 2003): a total of 17 locations on the body were identified that were not on established acupressure point charts. These 17 placebo points were assigned a number and using a random number generator, each was placed into a matching sequence for the customary (active) acupressure meridian and point flows. For example, there is a placebo spleen flow that matches the active spleen flow for number of steps and hand placement sequences. Two placebo points at a time were contacted, just as was done with active treatments. It was found that the active acupressure treatment series was associated with a significantly greater increase in hemiplegic forearm skin surface temperature compared to the placebo treatment series. Though both treatment series (active and placebo) significantly reduced heart rate, the active treatment series did so significantly more than did the placebo treatment series. Lastly, the active treatment series was associated with improvements in communication measures in the majority of the participants. Treatment credibility was also assessed: two of the four participants accurately identified the active treatment phase, one identified it incorrectly and the other was uncertain.

In the third study (McFadden and Hernández, 2010), a placebo-controlled, eight treatment series intervention, single-blind, crossover design with random assignment was utlized. The eight treatment series was sufficient to significantly reduce heart rate and enhance the relaxation response in comparison to the placebo treatment series (McFadden and Hernández, 2010). While blood pressure was significantly reduced, the amount of reduction did not differ between active and placebo treatment series. The active treatment series was associated with significantly more weekly hours of physical activity than the placebo treatment series. None of the treatment effects could be accounted for by intervening variables such as assigned treatment order, expectancy, credibility, age, time since stroke, etc. Active and placebo treatments were rated as equally credible and expectancy was equivalent prior to each intervention period. The significant treatment-associated elevation in hemiplegic forearm skin-surface temperature was not replicated in this study. A serendipitous finding in this study was one of *stress resilience* (e.g., a treatment-associated reduction in the stress response). Specifically, heart rate was monitored before, during and after forearm blood flow was measured using venous occlusion plethysmography (VOP). Forearm blood flow using VOP was assessed four times over the course of the study: before and after each intervention period. Although there were no differences among participants in initial heart rate obtained at the baseline forearm blood flow assessment point (prior to their being randomly assigned to the active or placebo treatment arm), it was striking that when forearm blood flow was measured again after the 8 treatment series, heart rate was elevated in those who had completed the placebo treatment series (suggesting anticipatory anxiety about the upcoming VOP measure), while heart rate was *not elevated* in those who had just completed the active treatment series. The finding that active treatments significantly reduced or *buffered* the heart rate elevation associated with blood flow measurement suggests that active acupressure promotes *stress resilience*.

The fourth study (McFadden et al., 2011) was based on accumulated basic and clinical research showing the adverse consequences of TBI can be exacerbated by stress (Hanna-Pladdy et al., 2001; Bohnen et al., 1992; Ewing et al., 1980) and mitigated by physical activity levels (Devine and Zafonte, 2009; Grealy et al., 1999; Griesbach et al., 2009). Given that the findings of Study 3 showed acupressure-associated enhancement of the relaxation response, improved physical activity and an anecdotal reduction in the stress response, results suggested that acupressure may hold promise and generalizability beyond stroke patients to individuals with a TBI history. As such, the 4th study utilized a randomized, placebo-controlled, eight treatment intervention, single-blind design with multiple, repeated measures of fidelity. The active acupressure treatment series significantly enhanced performance on the Digit Span Task (Lesak et al., 2004) and did so with a clinically meaningful effect size (Cohen's $d=0.68$). Active acupressure was also associated with a greater reduction in P300 latency and amplitude, as well as a reduced Stroop (Dyer, 1973) interference effect on accuracy, when compared to the placebo-treated group (McFadden et al., 2011). There were also marginal reductions in perceived stress and improvement in the composite score of the neuropsychological test battery in the active group compared to the placebo group. A trend emerged towards a significant active acupressure-associated enhancement of the relaxation response. There were no differences between the groups in measures of expectancy or credibility, so these and other variables could not account for treatment effects.

In the final study (Hernández and Brenner, 2013), we have utilized a randomized, placebo-controlled, eight treatment intervention, single-blind design to expand upon the predecessor study and determine if active acupressure minimizes the adverse effects of stress in veterans with co-occurring mild TBI and posttraumatic stress disorder (PTSD). It was hypothesized that stress resilience should be significant and apparent in a variety of domains, including psychiatric, psychological, cognitive, and physiological measures of function in the active acupressure treated group when compared to the placebo acupressure treated group. Although participant recruitment is closed, blinded data analyses are not complete, and results are not currently available.

MBSR (Mindfulness Based Stress Reduction): Efficacy and Effectiveness with Online Group Meetings. Fatigue is a major complaint following TBI and for many, mental fatigue may become an enduring symptom that has a substantial impact on the ability to resume work, studies, and social activities (Belmont et al., 2006). Currently, there is no effective treatment for mental fatigue. Generally, patients are advised to adapt to the decrease in available energy.

An alternative approach is the MBSR curriculum, which fosters an intention to cultivate awareness for the present moment in order to discover the connection with mind and body, experiencing new perspectives, moving towards acceptance, and stimulating growing compassion (Kabat-Zinn, 2001; McCown et al., 2011). MBSR has been shown to regulate autonomic arousal by enhancing parasympathetic tone (Bhatnagar et al., 2013). MBSR encompasses formal and informal practices, as well as group inquiry. The formal practices are a body scan to cultivate awareness of each area of the body; sitting meditation with an awareness of the breath; and a systematic widening of the field of awareness to include all four foundations of mindfulness, namely awareness of the body, feeling tone, mental states and mental contents, and mindful hatha yoga.

To promote potential acceptance and finding an appropriate balance between rest and activity, the MBSR program was evaluated for participants suffering from long-lasting mental fatigue after TBI or stroke. Participants attended eight weekly 2.5 hour sessions and one full-day session between the sixth and seventh sessions. Participants were encouraged to practice at home six days per week. Home practice was supported by guided instructions through video recordings on the website and CDs. Significant improvements were achieved for mental fatigue (Mental Fatigue Scale, MFS; Johansson and Rönnbäck, 2014) and on the neuropsychological tests measuring information processing speed and attention (Johansson et al., 2012). However, difficulty traveling to the locations where MBSR courses are held may prevent individuals from attending a mindfulness course.

In a following feasibility study, an MBSR program delivered live online, which includes the entire MBSR curriculum, was evaluated. For comparison, a face-to-face MBSR group and a control group who met for eight weekly walking meetings were included (Johansson et al., 2015). A significant reduction in mental fatigue (MFS) was found in the Internet group compared to the face-to-face and the control group. They also reduced their rating on depression and anxiety (Comprehensive Psychopathological Rating Scale; Svanborg and Åsberg, 1994). Individuals in the Internet and face-to-face MBSR groups also improved their ability to process two temporally-close targets (attentional blink task), while this was not detected in the control group. Results suggest that it is possible to deliver a live online MBSR program, including the entire MBSR curriculum, with positive results. The live online MBSR program, using web camera and microphones, also gives the attendees the sense of belonging to a group and learning from each other's perspectives. It also allows for access by individuals who live at a distance from in-person programs.

4. CAM use in conditions with TBI-symptom overlap: PTSD-focused interventions hold promise for TBI symptom reduction and improved outcome

CAM-augmented Residential Treatment Program. One factor that complicates the examination of effective interventions for TBI-related symptoms (particularly at the mild levels of TBI) is the overlap between symptoms often associated with TBI and those of PTSD and depression. For example, sleep disturbance, irritability/agitation, and concentration problems are non-specific symptoms that are associated with TBI, PTSD, and depression. Further confounding the symptom presentation is the fact that TBI, PTSD, and/or depression commonly co-occur (Hoge et al., 2008; Hibbard et al., 1998; Schell and Marshall, 2008) and may even result from the same traumatic event (e.g., motor vehicular accident, domestic violence, improvised explosive device). Due to the complexity in establishing the etiology of symptoms in individuals with a history of TBI, addressing presenting symptom concerns is recommended rather than focusing efforts on determining etiology (U.S. Department of Veterans Affairs & Department of Defense, 2009).

In following with recommendations to improve presenting symptoms and functional outcomes, a residential PTSD/TBI treatment program at the Cincinnati VA Medical Center was developed for male veterans that also serves active duty, guard, and reserve service members. In order to be eligible for the program, patients need to have a PTSD diagnosis from any traumatic event and have a history of TBI, ranging from mild to severe. The residential treatment program is an eight-week, interdisciplinary program in which approximately 8-10 individuals are admitted as part of a cohort. Comprehensive diagnostic and functional assessments are completed upon admission to and discharge from the program in order to assess treatment outcome.

The primary focus of the program includes cognitive processing therapy (CPT; Resick et al., 2014) and cognitive processing therapy-cognitive only (CPT-C; Resick et al., 2014), which are evidence-based treatments designed to reduce PTSD and related symptoms. CPT and CPT-C are both delivered twice weekly using the combined individual and group format. In addition to CPT and CPT-C, veterans receive other psychoeducation such as anger management, communication, and relapse prevention. CogSmart (Twamley et al., 2008), a cognitive compensatory intervention, is offered to teach compensatory strategies for cognitive impairments, regardless of the etiology. Furthermore, individualized speech/cognitive treatment is offered and is based on evidence-based interventions that include hierarchical attention training, environmental modifications, internal memory strategies, and the use of external memory aids (Helmick, 2010). Individual occupational therapy is provided and focuses on the unique goals of each patient in domains such as educational opportunities, coping strategies, social interaction, and self-regulation tools, which are to be exercised in a variety of environments. Finally, the program was augmented by several CAM interventions including a morning sensory regulation group, yoga, nutrition, art expression/therapy, and spirituality. Overall, although evidence-based PTSD treatment is emphasized in the program, a variety of interventions designed to address non-specific symptoms and functional impairments associated with a history of TBI, depression, and anxiety are incorporated into the program structure.

Several studies have examined clinical outcomes following treatment in the residential PTSD/TBI program. In the initial study, Chard et al. (2011) found that veterans and service members in the program experienced significant reductions in psychological symptoms (i.e., PTSD and depression) following residential treatment. As the program was designed to also address symptoms associated with a history of TBI, another study examined whether postconcussive symptoms decreased over the course of treatment and whether a change in postconcussive symptoms corresponded to a change in PTSD symptoms (Walter et al., 2012). Study results indicated that postconcussive symptoms significantly declined from pre- to post-treatment. Additionally, the study found that reductions in PTSD symptoms were associated with reductions in postconcussive symptoms, suggesting an interdependent relationship (Benge et al., 2009) where successful treatment of PTSD or postconcussive symptoms may decrease symptoms associated with the other condition. The study is novel in that it examined the relationship between PTSD and postconcussive symptoms over the course of a PTSD/TBI treatment program that utilized evidence-based and complementary interventions. However, symptoms were assessed at only two time-points, precluding evaluation of whether one set of symptoms affected change in the other and more fully investigating the hypothesis that reducing PTSD symptoms may reduce symptoms associated with TBI (Belanger et al., 2010). Assessing symptoms more frequently throughout treatment would yield valuable clinical information that could assist in identifying the mechanisms of change and thus, tailoring treatment more effectively.

Symptom reduction is an important outcome following clinical intervention, as are individual, functional goals of the patient. In an interdisciplinary effort, Speicher et al. (2014) investigated individualized, occupational therapy outcomes and their association with psychological symptoms outcomes following residential PTSD/TBI treatment. Veterans identified their target occupational areas for improvement and the most commonly reported areas were health management and maintenance, social participation, and rest. Study results demonstrated that occupational performance and satisfaction with occupational performance in these domains significantly improved over the course of treatment. As previously shown, findings revealed that PTSD and depression symptoms significantly decreased following residential treatment. Analyses examining the relationship among the outcome variables found that improvement in occupational satisfaction with performance was significantly negatively correlated with PTSD and depression symptoms. In other words, as occupational satisfaction with performance improved, symptoms of PTSD and depression lessened. The pattern emerged slightly different for occupational performance; where improvements in performance were significantly, negatively associated with depression, but not PTSD. Overall, this study highlights the importance of assessing psychological symptoms, especially PTSD and depression, which can affect functional and occupational goals.

Collectively, the clinical use and examination of interdisciplinary residential treatment programs for PTSD and TBI answer some questions while raising others. The aforementioned studies demonstrate statistically and clinically significant reduction of PTSD and depression symptoms. Furthermore, postconcussive symptoms and functional, occupational goals also significantly improved over the course of treatment. Importantly, these studies also showed that psychological symptoms were associated with not only reductions in postconcussive symptoms, but also to improvements in functional, occupational goals. This suggests that symptom reduction may serve as a proxy or representation of more general functional improvement. As a result, the variety of interventions provided yields treatment outcomes targeted by the program for veterans and service members with PTSD and a history of TBI. Interdisciplinary programs also raise questions as to which component yields the greatest therapeutic benefit? What is the minimal dose of an intervention to produce a clinically meaningful outcome? And does reducing psychological symptoms result in decreases in cognitive and somatic symptoms, or is separate intervention necessary (particularly with mild TBI)? The answers to these important questions will help shape the most effective and efficient interventions for individuals with TBI.

Mantram Repetition Program (MRP). The MRP is a psycho-spiritually based, meditation-like intervention designed to enhance symptom management by improving one's cognitive awareness of the thinking process, increasing one's ability to focus attention, and enhancing spiritual wellbeing (Bormann et al., 2012, 2014; Oman and Bormann, 2015). Unlike other meditation or mindfulness interventions described as secular or non-spiritual, the MRP teaches a set of portable, mental practices that incorporate and foster a potentially "value-added" component of spirituality for those who find comfort in the teachings from spiritual or religious traditions. There is a growing body of research that has shown a positive association between spiritual wellbeing and quality of life. (Bormann et al., 2005, 2006; Tsuang et al., 2007).

The MRP supports one's spiritual beliefs by having participants select a mantram—(more commonly known as mantra)—defined as a sacred word or phrase. A mantram is a positive, meaningful, and empowering mental phrase that is to be silently repeated (with as much concentration as possible) at numerous, intermittent times throughout the day with the goal of training attention (Easwaran, 2008) and initiating the relaxation response (Benson, 1993,1996). When the mind wanders, attention is brought back to the mantram to interrupt unwanted thoughts and redirect attention as a form of emotional self-regulation (Kemeny et al., 2012). This practice is portable and doesn't require any particular time or position. The other two MRP strategies involve intentionally slowing down thoughts and behaviors and developing one-pointed attention (i.e., doing one thing at a time; Easwaran, 2008). Slowing down may require quiet time for reflection, values clarification, and setting priorities. One-pointed attention is practiced inwardly by repeating the mantram and outwardly by focusing on one task at a time.

Over time and with consistent practice of all three MRP skills, one's ability to focus and concentrate becomes stronger as hypothesized by activating the neural networks in the brain that are involved with attention and arousal (Hölzel et al., 2011; Lazar et al., 2005; Manna et al., 2010). Brain imaging studies have further explained how the beneficial effects of repetitive speech result in psychological calmness (Berkovich-Ohana et al., 2015). Other mantra meditation techniques have resulted in slowing respiration and heart rates (Peng et al., 2004).

Research on the MRP has progressed in a systematic way similar to studies on acupressure described above. Initial studies utilized single group, pre- and posttest designs, qualitative methods, and increasely more rigorous studies used mixed methods and RCTs. Research that has been conducted in a variety of patient and caregiver populations over the past decade has shown significant reductions in a variety of symptoms such as perceived stress, depression, and insomnia, while also improving quality of life and spiritual wellbeing (Barger et al., 2015; Bormann et al., 2013; Bormann, Oman et al., 2014). In RCT's on the efficacy of the MRP in Veterans with PTSD (Bormann et al., 2008, 2013; Oman and Bormann, 2015), findings have shown significant and clinically meaningful reductions in PTSD symptom severity and, in particular, reductions in hyperarousal—a symptom cluster that has been linked to insomnia. Veterans with PTSD have also reported reduced emotional reactivity in a variety of situations and improved interpersonal relationships (Bormann et al., 2013), improved self-efficacy managing symptoms of PTSD (Oman and Bormann, 2015), improved mindful attention awareness (Bormann et al., 2015) and higher levels of spiritual wellbeing (Bormann, Liu, Thorpe et al., 2012). And although no studies have assessed the effect of MRP on memory or cognitive function, these are areas that may also be fruitful to explore.

Given these findings, the MRP may benefit those with TBI in a variety of ways, but one particular advantage is how simple it is to teach and learn. Although it can be taught in a formal eight-week course, the MRP has been taught in one 40-minute session to a group of homeless women to improve sleep quality. They were given rubber wrist-bands and small, daily flip-cards as reminders to practice. After one week of practice, women reported a significant reduction in insomnia. (Barger et al., 2015). Other types of reminders to practice can be posted in various locations at home or affiliated with specific activities such as daily hygiene, exercise, waiting for appointments, or at night before sleep.

MRP may also be taught to family and professional caregivers of patients with TBI. In one study of family caregivers of veterans with dementia, those completing the MRP reported significant reductions in caregiver burden, perceived stress, depression and rumination at 36-week follow-up (Bormann et al., 2009). The advantage of this portable practice is its convenience and accessibility compared to types of sitting meditation, body-scans, or movement meditation practices such as yoga, Tai Chi, or Qi-gong.

Based on these studies, one could argue that any means by which symptoms can be reduced would improve TBI outcome, regardless of it being via CAM treatments or other types of strategies. There are data to support that symptom reduction yields functional improvement (Brenner et al., 2009). Indeed, Brenner and colleagues (2009) highlight the importance of addressing symptoms of co-occurring mild TBI and PTSD regardless of etiology in a stepped manner. This is consistent with care models proposed by the Departments of Veterans Affairs/Department of Defense. In building upon work presented by Terrio (2009), Brenner and colleagues suggested that an important first step is to educate patients regarding the high likelihood of recovery. Next steps include addressing symptoms association with psychiatric conditions, while at the same time reinforcing the importance of self-care routines (e.g., diet, sleep hygiene). Addressing specific somatic complaints (e.g., headaches) is also consistent with the proposed stepped care model, particularly if the patient describes such symptoms as being particularly distressing. Perhaps most important, is addressing complaints with methods supported by scientific evidence. And while to date, this would include evidence-based psychotherapies, the developing evidence base for CAM therapies described in the present review hold real promise that symptom reduction and improved outcome can and will be associated with certain types of CAM.

Utilizing CAM treatments to augment rehabilitation practices may serve as an effective way to facilitate the impact of rehabilitation and improve patient outcome. Additional studies would need to be done and it would be important in these studies to determine which types of CAM were best paired with which types of condition-specific rehabliation. CAM practices' heterogeneity would not easily translate into a one-size-fits-all add-on for rehabilitation. It would depend on which areas of rehabilitation are the targets of CAM approaches. As examples, Tai Chi appears useful for post-stroke rehabilitation as a means of improving balance and controlled movement, and can be accessed in a community-based setting (Taylor-Piliae and Coull, 2012). Yoga could be important for TBI to promote autonomic regulation, strength and purposeful movement. Mantram repetition can be used to redirect attention away from negative thoughts and be practiced during physical therapy ot other painful procedures to help relax and manage hyperarousal.

5. Conclusions: CAM as a useful tool for chronic symptoms

This review highlights the potential utility of CAM, and the evidence base that exists thus far. Most promising are the studies, presented in greater detail here, which have sequentially and systematically utilized experimental methodologies that build upon prior studies to optimize the generalizability of the findings. Also promising are those CAM treatments that can be used independently, are self-sustaining and portable, and result in reductions in symptoms that are associated with or adversely impact outcome after TBI. Effective, evidence-based CAM treatment options hold real promise to enhance positive long-term outcomes and quality of life following TBI. Developing such an evidence base, as described here, is not without challenge and one that is not dissimilar from the field of rehabilitation, which has long recognized the therapeutic importance of and challenge inherent in complex interventions (Hart, 2009). Moreover, the very nature of these strategies impacts their ability to be studied in a controlled manner (Hart et al., 2008).

CAM treatments modalities are sought to meet many unmet needs in health care. This is in part because conventional medical care can be limited and accessing it may be associated with unintended consequences (e.g., perceived stigma, side effects, monetary costs). As well, recovery from TBI is highly variable and often incomplete. With a sufficient evidence base, CAM could benefit those sustaining a TBI, their family members, and large health care systems by serving as a safe, portable, low-cost, efficacious, effective and accessible treatment strategy. Even with this potential for CAM treatment benefits, there comes a note of caution related to the absence of rigorous, methodologically sound CAM studies. As such, meticulous scientific research that contributes to an evidence-base is essential for identifying potentially effective novel treatments for TBI and associated sequelae. Importantly, such increasingly rigorous research provides the opportunity to simultaneously characterize efficacy and effectiveness, as well as limitations of CAM treatments. Only in this way can CAM be more fully understood and accessed

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appropriately by both the treating clinicians and the patients with whom they work.

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