

Acupressure as a Model for Complementary and Alternative Medicine (CAM) Treatment Following Acquired Brain Injury: Translating Lessons from the Laboratory

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Abstract

Background: Acquired brain injury (e.g., stroke and traumatic brain injury or TBI) and associated sequelae are highly prevalent in the United States (U.S.), impacting both civilians and military populations. Because conventional treatments can be limited and functional recovery incomplete, complementary and alternative medicine (CAM) is often sought out. The popularity of CAM exists despite inconclusive research findings for CAM treatments for injury-associated sequelae. Apparent methodological limitations in CAM studies include issues related to experimental design, control groups, sample size, blinding and disparities in outcome measures. Overcoming these limitations poses challenges, but not insurmountable ones.

Objective: Delineate and describe the necessary evidence-based infrastructure so that efficacious CAM treatments can be identified and this information disseminated to individuals seeking CAM therapies. With the full information of both risks and benefits, there is a increased likelihood of resources being invested in treatments that will achieve outcomes of interest.

Design: The present review of a published body of work will describe, step-by-step, the fundamental framework within which researching the CAM intervention acupressure for two types of acquired brain injury (traumatic brain injury/TBI and stroke), can be accomplished using the highest methodological rigor.

Results: Included is a review and description of the "choice points" encountered in the decade-plus of published research from the CAIRR (Clinical Assessment of Injury, Recovery and Resilience) Neuroscience Laboratory, the methodological framework underlying these choice points, and how decisions at each choice point were made to optimize rigor.

Conclusions: Cogent scientific research is essential for identifying effective treatments for acquired brain injury, regardless of whether the treatments are conventional or CAM-based. In terms of CAM, such work will provide the opportunity to characterize both efficacy and limitations of CAM treatments, so that CAM may be fully understood and accessed appropriately by both treatment teams and those engaged in rehabilitation.

Keywords: Acupressure; Traumatic brain injury; TBI; Stroke; Placebo-control; Blinded trial; Adults

Introduction

No longer the "silent epidemic" [1] first labeled as such 30 years ago, traumatic brain injury (TBI) is now more likely to be referred to as a "signature wound" of recent conflicts [2]. From this increased awareness is the reinforced recognition of TBI's often-chronic impact across the lifespan. Among civilian populations in the U.S., there are approximately 1.7 million TBIs sustained annually [3]. 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 [4]. Such injuries have resulted in a host of sequelae, that can individually or in combination negatively impact psychological health, cognition, stress sensitivity and quality of life [4-7].

There are also certain barriers to the effective treatment of TBI and associated comorbidities, including stigma [8,9] and the limited, effective treatments available [10-15]. Given the prevalence of TBI and its potential burden on the individual, family members and health care systems, identifying an effective, accessible and self-sustaining treatment strategy would be of significant benefit to those living with brain injury, their families and health care systems.

Complementary and alternative medicine (CAM) is such a treatment strategy, and one that shares many health care systems' emphasis on patient centered care [16], independence and agency. 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" [17], examples of CAM include acupuncture, acupressure, chiropractic manipulation, yoga and meditation [18]. In terms of access, CAM use among civilian, including U.S. and European cohorts [19,20], as well as U.S. military and Veteran populations [21-23] is comparable on average at approximately 30%. This level of use can be a risky endeavor if the CAM treatment has not been studied appropriately or at all, and if the treatment provider is unaware of concurrent CAM usage, which studies suggest, occurs 60-75% of the time [23-26]. Further contributing to this potential risk is that CAM's actual effectiveness for many conditions remains unsubstantiated. This, at least in part, stems from variations in experimental design, sample size and the use of controls. And while unequivocal support for CAM may seem distant, there is consensus regarding the need for additional studies, if done with experimental rigor [27].

While the focus of the present review is on acupressure, it is worth noting that multiple types of CAM have been studied following acquired brain injury, with the overall findings being mixed and some not replicated. A brief synopsis is presented to depict the current landscape, as well as areas of opportunity for future scientific study. Persons with TBI reported significantly improved quality of life scores after a 10-week pilot of mindfulness-based stress reduction techniques [28] or a 12-week series encouraging the use of mindfulness techniques [29]. In the latter study, this was maintained at a one-year follow-up [30]. Mindfulness based cognitive therapy (MBCT) after TBI was found to reduce symptoms of depression [31], though because this was a feasibility study, the single group, pre- vs. post-intervention design did not include a control group for comparison. In contrast, a randomized, controlled trial of mindfulness meditation after TBI found no such benefit [32], failing to replicate the promising pilot study that had preceded it.

Relaxation techniques reduced the number of symptoms and improved performance on cognitive tests in college students with mild TBI [33]. A review of the literature assessing biofeedback (with or without relaxation training) following TBI suggests that further study using larger sample sizes is necessary to determine its efficacy [34]. A placebo-controlled, blinded trial of homeopathy for mild TBI showed significant symptom reduction in the treatment group vs. control [35], though a later review of this study from a WHO Task Force on TBI withheld recommending homeopathic treatment for TBI because of need for and challenge inherent in replication, given the individualized nature of homeopathy [36]. Studies of acupuncture [37-39] have noted significant support for its use in the treatment of TBI, for a range of TBI severities and symptoms. Tai Chi has also been studied, using a wait-list or social-interaction control, and the initial results appear promising in terms of outcome measures related to mood and self-esteem [40,41].

Still, enthusiasm for CAM treatment for TBI has been tempered, because of issues related to experimental design, sample size and controls. Indeed, extensive reviews of the literature have concluded that no high quality, randomized clinical trials exist to-date that genuinely could support the use of acupuncture in treating TBI [42] and that there is an "urgent" need for research in this and other areas

of CAM for TBI [43]. Continued study in this area is called for, albeit with markedly increased rigor.

Optimizing CAM Research

Experiences of the CAIRR Neuroscience Laboratory

A purpose of the present review is to describe, step-by-step, a methodological strategy utilized to study the effects of CAM interventions in civilians and Veterans with acquired brain injury, specifically TBI and stroke, using the utmost scientific rigor. The overarching goal being that, if and when CAM is selected as a treatment strategy, it can be done with full knowledge that the treatment's potential efficacy, safety, and appropriateness have been characterized in the most methodologically rigorous way. With its emphasis on and detailed description of our decade-plus study of acupressure, this translation of Lessons from the Laboratory provides a step-by-step guide for future research studies evaluating acupressure or other CAM interventions.

Suggested best practices for conducting CAM research use a wise and logical progression to guide CAM intervention study designs [44]. First, a clinical observation or case history/report, identifies an interesting clinical observation and often builds upon an anecdotal observation. Second, case reports/studies provide effective novelty detection [45], but not proof of cause. Third, a case series, when it replicates the case report/studies' observation, supports that the finding is not a one-time occurrence. Fourth, an uncontrolled trial confirms the finding in a "reasonable number of patients" [44]. And fifth, a controlled trial shows the effect is treatment-associated and not due to chance, time, natural disease progression or expectation. And within this logical progression are additional research design considerations. These include feasibility, estimates of compliance, optimizing retention, minimizing participant burden, and determining the optimal effective dose, as well as the sensitivity and specificity of the primary outcome measure. There are also issues related to the composition of the control condition, which is extremely important, as it is one of the ways in which to assess for the "active ingredient/s" in the intervention [46]. Maintenance of treatment fidelity is equally critical so that treatment effects may be appropriately interpreted as being due to the intervention, rather than other factors [47]. Such fidelity is a direct path to replicable results [47] that can be built upon with confidence in subsequent studies. Finally, given the importance of observations when conducting clinical research, it is essential to have systems in place that can capitalize on anecdotal findings, which might in fact be critical components of the active ingredient. In this way, it may be possible to convert the anecdotes into data through subsequent studies.

From Anecdote to Controlled Trial

Acupressure after Acquired Brain Injury

Described here is the experimental process and "lessons learned" over a period of approximately 13 years in the development of an evidence-based infrastructure for the study of CAM treatments, acupressure specifically, following acquired brain injury, including TBI and stroke. Emphasis on these two types of brain injury stems from need (e.g., chronic symptoms associated with the post-acute period for which there is little relief) and expertise (e.g., research focus of several co-authors, TDH/GR/LAB). Together, these have provided a

fertile milieu for the series of studies described here, that assess the potential impact of acupressure on TBI and stroke.

Acupressure, including Jin Shin acupressure, makes contact with the body using only the tips of the fingers [48-53] and does not rely on needles as does acupuncture. Initially acupressure can be administered by a practitioner and then can be easily learned through classes or manuals. It can be simply and discreetly administered any time and any place and has the potential for self-directed maintenance treatment long-term. Indeed, because of this accessibility and portability, acupressure is an exceptional candidate intervention for individuals with chronic health conditions and limitations, who would particularly benefit from the ability to independently, or semi-independently, augment their own health practices. While ours were the first published data on acupressure following stroke or TBI to our knowledge, there are data in the literature that support acupressure's potential benefits following stroke or TBI, even though the data are from other populations. Indeed, the published work in other populations provided sufficient background and rationale for many of our outcome measures of interest, specifically those related to the psychological and physiological benefits of acupressure [51,54-59].

A theme of the studies described from our laboratory is the systematic, logical approach to rigorous experimental design using the following set of guiding principles that comply with an evidence-based medicine (EBM) perspective, e.g., improved controls--particularly placebo controls, randomization, blinding and multiple, disorder-specific outcome measures. To our knowledge, ours are the first series of studies of acupressure after TBI or stroke published in the English language and using a placebo-control.

A series of five studies that were performed in our laboratory and have been published elsewhere, will be reviewed and described here with citations included. From the original articles or published abstracts it is possible for the reader to gain additional detail on specific methods and results. The present review of the studies describes the steps or choice points at which each study built upon its predecessor both systematically and sequentially to enhance the methodological rigor, validity and reliability. As will be delineated, when there were anecdotal reports of a treatment effect that were not a part of our primary outcome measures, we used those as a choice point to measure it in the next study. This is because even though it is true that "the plural of anecdote is anecdotes, not data" [60], building upon anecdotal reports is a reasonable and effective means of progression within scientific inquiry [45].

The Uncontrolled Trial: Acupressure after Stroke

Study 1: Feasibility

A feasibility study was undertaken to determine whether a series of acupressure treatments in an elderly, post-acute stroke population would be well tolerated and acceptable, so as to be associated with good retention (Table 1). Because there was no published literature, at least in the English language that the investigators were aware of, stating the optimal number of acupressure treatments in post-acute stroke patients, this issue needed to be addressed. Lastly, decisions needed to be made in selecting optimal measures of stroke-associated functional impairment, and in particular, those that might be sensitive to intervention. Beginning with the post-acute stroke population stemmed from anecdotal evidence in our university stroke clinic: research study and clinic participants reported acupuncture, and to

some degree acupressure, had been effective at decreasing fatigue and improving speech (Ramsberger, personal communication). Yet acupressure, had yet to be systematically studied following stroke. To this end, a feasibility study of acupressure in a post-acute stroke population with speech impairment was designed.

Choice point #1: Participants received active treatment only, and differences between pre- and post-intervention outcome measures were assessed. A variety of considerations fed into the decision to not include a control group in this first study. This type of study had not been done before, the treatment was novel, and the target population was elderly. It was important to first determine if the treatment was well tolerated, acceptable and was associated with within-subject change in selected outcomes.

Choice point #2: Participants receive a total of four 40 minute treatments as the intervention. With no published data to guide us, the issue of "optimal" dose (treatment number and duration) for post-acute stroke was discussed with acupressure practitioners in the community. Based on this, four treatments were hypothesized to be the minimal number of treatments required to elicit functional change. Standard acupressure treatments in the community can range from 40-60 minutes. Treatment duration of 40 minutes was selected to allow time for additional measures pre- and post-treatment (which can take minutes) and to keep the entire treatment session duration to 60 minutes. Again, given the expected age range of the target population and the potential novelty of the treatment, it was thought this should both minimize study participant burden and be sufficient to yield treatment effects.

Choice point #3: Participants were a homogeneous sample of chronic stroke survivors with non-resolving aphasia and hemiplegia. Beginning with a homogeneous sample, with similar speech deficits was chosen to aid sensitivity in detecting treatment effects.

Choice point #4. Primary outcome measures included a speech assessment (pre- and post-four week intervention), as well as a weekly diary of quality of life measures (e.g., energy, tiredness, happiness, frustration) in the form of a visual analogue scale (VAS). Not only were these outcome measures chosen because anecdotally speech and fatigue had been reported as improving with acupuncture or acupressure, but also because of the relevance of these functions (or impairment therein) in post-acute stroke.

Results and lessons learned: There was a trend towards improved function on the VAS, as well as communication success [61]. Anecdotally, participants perceived an increase in hemiplegic arm sensation and warmth during the intervention period, though this was not measured. The strengths of the study included clinically relevant, repeated measures, blinded data analyses and 100% retention. The limitations to this study were the lack of placebo control, that data acquisition was not fully blinded and the small sample size (n=3).

The Controlled Trials: Acupressure after Acquired Brain Injury

Study 2: Case Reports, Controlled Trial (Stroke)

The second study [62] utilized a placebo-controlled, crossover design, with an eight-treatment sessions intervention in post-acute stroke survivors with aphasia and hemiplegia to address and overcome the limitations of its predecessor, feasibility study (Table 1).

Choice point #1: A Placebo (control) group would be compared to the Active acupressure treatments. 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 placebo treatments [62]: a total of 17 places on the body were identified that were not on any established acupressure point charts and 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 flow. For example, there is a Placebo Gall Bladder Flow that matches the Active Gall Bladder Flow for number of steps and hand placement sequences. Two placebo points at a time were contacted, just as was done with active treatments. Importantly, prior to their use in the study, placebo treatments were tested on advanced acupressure practitioners to determine whether the placebo treatments were “inert” compared to active point activation; indeed, the practitioners reported that contact at placebo vs. active points were distinct.

Choice point #2: A total number of 8 treatments would be utilized. The total number of treatments in the intervention was doubled to eight, since there was only a trend towards treatment effects using four treatments in Study 1 and it was decided that doubling this to eight treatments should be more than sufficient to detect treatment effects if there were any.

Choice point #3: Random assignment to treatment condition was not utilized, but crossover design was. Participants were assigned to 8 weeks of Placebo acupressure treatments, followed by an 8 week washout period, followed by crossover into 8 weeks of Active acupressure treatments. This methodology was selected to determine how stable the repeated measures were over time in a chronic stroke population receiving an “inert” (e.g., placebo) treatment.

Choice point #4: Multiple and repeated measures of post-acute stroke outcome were utilized, as were measures related to anecdotal participant reports from the preceding feasibility study. Multiple measures of speech were utilized before and after each phase of the study, as were forearm skin surface temperature and heart rate (pre- and post-treatment session).

Choice point #5: An indirect assessment of treatment credibility was added. Because treatment credibility can affect outcome, individuals were asked (at the very end of the study) to state during which treatment period they thought they received the Active vs. the Placebo acupressure treatments.

Results and lessons learned: As reported in full detail elsewhere [62], active acupressure treatments were associated with a significantly greater increase in hemiplegic forearm skin surface temperature compared to Placebo treatments. Though both treatment types significantly reduced heart rate, Active treatments did so significantly more than did Placebo treatments. Lastly, Active treatments were associated with improvements in communication measures in three-fourths of the participants, while one-fourth improved more so in these measures following Placebo treatments. Two of the four participants accurately identified the active treatment phase, one identified it incorrectly and the other was uncertain. The strengths of the study were use of placebo control, crossover design, the clinically relevant, repeated measures, blinded data analyses, indirect measures of credibility, and the 100% retention rate. Limitations of the study include the small sample size (n=4), the lack of random assignment, and that data acquisition was not fully blinded.

Table 1: Experimental Design Progression: Acupressure after Acquired Brain Injury in Civilian and Veteran Populations.

Design	Uncontrolled Trial: Feasibility ⁶¹	Case Reports: Controlled Trial ⁶²	Controlled Trial ⁶³	Controlled Trial ⁷²	Controlled Trial ⁸⁵
Random Assignment			✓	✓	✓
Single Blind			✓	✓	✓
Placebo Control		✓	✓	✓	✓
Crossover Design		✓	✓		
Repeated Measures	✓	✓	✓	✓	✓
Blinded Analyses	✓	✓	✓	✓	✓

Study 3: Controlled Trial (Stroke)

The third study [63] utilized a placebo-controlled, 8 treatment intervention, single-blind, crossover design with random assignment to address some of its predecessor’s limitations and replicate or extend the findings (Table 1).

Choice point #1: Participants were post-acute stroke survivors with hemiplegia who were not engaged in any other type of stroke-specific physical therapy that might influence the results. Because the largest effects in the preceding study were physiological and not necessarily speech-related, participants were recruited who had significant hemiplegia-associated temperature asymmetry (hemiplegic forearm was at > 1 degree Celsius cooler than the non-hemiplegic side). If participants meeting these criteria also had aphasia, they were not excluded from the study. The present study’s design necessitated a clear exclusion criteria for individuals engaged in stroke-specific physical therapy (e.g., constraint-induced movement therapy), but did not exclude individuals engaged in extracurricular activities in general, not aimed at stroke specific symptoms. This was an important criteria to allow us to differentiate between treatment effects due to the acupressure intervention vs. another stroke-targeted intervention outside of the study.

Choice point #2: Continuous physiological assessment in multiple domains was conducted. To determine the nature and time course of physiological change associated with treatment effects, continuous measurement of skin surface temperature and heart rate were assessed throughout each treatment. Given the concordance of heart rate with breathing and blood pressure, these latter measures were done as well.

Choice point #3: Additional measures were added to identify potential mechanism underlying improved forearm skin surface temperature. Forearm blood flow and self-reported physical activity were assessed before and after each intervention period.

Choice point #4: Pulse diagnosis, rather than a predetermined set of treatment points, was utilized to determine acupressure treatments.

Because there are insufficient data from which to derive uniformly agreed upon acupressure treatments for stroke (e.g., a single point or a predetermined set of points), pulse diagnosis was utilized to determine the “greatest need” and therefore which acupressure treatments to administer. This methodology and expertise is not unlike that relied upon in the numerous (and often NIH-funded) studies of acupuncture and acupressure where it is accepted that highly trained practitioners are able to reliably utilize their skills in working with pulses and points on the body, based on both anatomical markers and recognition of the unique indicators of locating a point [64-69]. While the method of pulse diagnosis had been utilized in the Feasibility Study and Case Reports, it was here in Study 3 (Controlled Trial) that the procedure was systematized.

Choice point #5: All pulse diagnoses, selected treatments and treatment duration were documented. In order to provide data identifying those treatments or individual points most associated with improved outcome, we meticulously recorded pulse diagnoses, resultant treatment sequences and duration for all Active and Placebo treatments.

Choice point #6: Credibility and expectancy were measured. To account for the important variables of credibility and expectancy, we added a well-documented measure of each before (expectancy) and after (credibility) each intervention period.

Choice Point #7: Measures related to fidelity were included. To assure intervention fidelity and as is standard in many studies of specialized treatment interventions [57,70,71], the same practitioner was used to administer the Active and Placebo treatments, allowing us to hold constant any possible effects due to the specific treatment provider. The practitioner was highly experienced in acupressure treatments and self-care education, and received extensive training in the Active and Placebo intervention protocols. Because the person administering the treatments (Active and Placebo) cannot be blind to condition, the following procedures were utilized to support treatment fidelity. Data acquisition and analyses were done blinded and any potential dialogue between the practitioner and study participant was scripted and monitored. Hence, the study was single-blind in that only the acupressure practitioner knew which treatment was being administered, yet the participant and all study-related personnel remained blinded to condition throughout data acquisition and analyses. Only at the very end of their study participation were participants and study-related personnel unblinded to treatment condition.

Results and lessons learned: Eight treatments were sufficient to significantly reduce heart rate and enhance the relaxation response in comparison to placebo treatments (as reported in the following [63]). While blood pressure was significantly reduced, the amount of reduction did not differ between Active and Placebo treatments. Active treatments were associated with significantly more weekly hours of physical activity than were Placebo treatments. None of the treatment effects could be accounted for by intervening variables such as assigned treatment order, expectancy, credibility, age, time since stroke and so on. 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.

One of our findings was anecdotal and serendipitous: a treatment-associated reduction in the stress response. Specifically, the measure of forearm blood flow, though not identified by participants as a

“stressor”, was nonetheless described as uncomfortable, unusual and not a favored measure. Heart rate is monitored before, during and after this procedure, which was done four times over the course of the study: before and after each intervention period. There were no differences among participants in initial heart rate taken at the baseline forearm blood flow time point prior to their being randomly assigned to the Active or Placebo treatment condition. However, when forearm blood flow was measured again after the 8 treatment series, initial heart rate was elevated in those who had completed the Placebo treatment series (suggesting anticipatory anxiety about the upcoming measure), while heart rate was not elevated in those who had just completed the Active intervention period. That active treatments significantly reduced the heart rate elevation associated with blood flow measurement suggests that active acupressure promotes stress resilience. The strengths of the study were the placebo-controlled, single-blind, crossover design with random assignment and that there was 100% retention. An additional strength included the efficacious eight-treatment intervention period, with treatments based on “greatest need.” While it could be argued that a sample size of 13 is small, the large effect size associated with the enhanced relaxation response seems to effectively counter this argument. Another potential limitation is in the crossover design. While this can be seen as a strength in terms of increased power associated with within-subject repeated measures, there are simultaneous limitations related to the potential for period effects and receiving both treatments affecting expectancy, as well as credibility. That said, the data did not show period effects or that expectancy or credibility contributed to treatment effects.

Study 4: Controlled Trial (TBI)

This study (see ref 72 for complete details) [72] utilized a randomized, placebo-controlled, 8 treatment intervention, single-blind design to expand upon the predecessor study and determine if Active acupressure exerts its effects in adults with a different type of acquired brain injury: TBI (Table 1). Studies in animals and humans have shown that the adverse consequences of TBI can be exacerbated by stress [33,73,74] and mitigated by physical activity levels [75-77]. Taken together with the basic research, the clinical research findings in Study 3 showing acupressure-associated enhancement of the relaxation response, improved physical activity and an anecdotal reduction in the stress response all showed promise for acupressure’s potential generalizability across acquired brain injury: from stroke to TBI.

Choice point #1: Participants were adults with mild TBI identified via the Brain Injury Screening Questionnaire [78], who were not engaged in any other cognitive rehabilitation program aimed at TBI-associated impairment. Again, this was important because it allowed for interpretation of positive results to be attributed to the acupressure intervention, as opposed to another type of intervention.

Choice point #2: A crossover design was not utilized. Because of the inherent challenges and limitations associated with a crossover design (described above in Study 3), consented individuals were randomly assigned to either the Active or Placebo treatment condition.

Choice point #3: The cognitive effects of the intervention were assessed. To determine if there were cognitive benefits of acupressure’s enhanced relaxation response, we assessed neuropsychological function using an abbreviated test battery.

Choice Point #4: Neurophysiological measures were added to delineate mechanisms underlying potential cognitive change associated with the treatment. Event-related potentials (ERPs) were used to assess attentional and neurophysiological resource allocation, because it has been shown that even mild TBI affects the amplitude and latency of this ERP marker [79-82].

Choice point #5: Maintain fidelity procedures, and measures of expectancy and credibility.

Results and lessons learned: Eight Active acupressure treatments significantly enhanced performance on the Digit Span Task (as reported [72]), and were associated with a greater reduction in P300 latency and amplitude, as well as a reduced Stroop [83,84] effect on accuracy, when compared to the Placebo-treated group. There was also a marginally significant reduction in perceived stress and a marginally significant improvement in the composite score of the neuropsychological test battery in the active group compared to the placebo group, as well as a trend towards a significant Active acupressure treatment-associated enhancement of the relaxation response. The strengths of this study include a strong effect size (Cohen's $d=0.68$ for digit span improvement) supporting clinical significance and relevance. Additional strengths were the multiple behavioral and physiological measures of treatment-associated change, as well as the 100% retention rate. Ongoing strengths of this program of research relate to the experimental design: placebo-controlled, random assignment, single-blind, fidelity procedures, and repeated measures of treatment expectancy and credibility. The potential limitations of this study include a relatively small sample size ($n=21$ /Placebo and $n=17$ /Active), though this can be countered somewhat by the strong effect size. Additional potential limitations include that the enduring nature of the acupressure treatment effects remains unclear, as follow-up measures were beyond the scope of the study. As well, individuals with mild TBI were identified via the Brain Injury Screening Questionnaire [78], which has good reliability and validity, but is still a self-report measure to detect TBI. That said, because acupressure appeared to be safe, well tolerated and acceptable, future studies could assess its efficacy in those with TBI and comorbidities, particularly those related to psychological health and the adverse consequences of stress.

Study 5: Controlled Trial (TBI)

This study [85] utilizes a randomized, placebo-controlled, 8 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 PTSD to promote stress resilience. 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.

Choice Point #1: Recruited participants are adults with mild TBI and PTSD, identified via the OSU TBI-ID (Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID [86] and the SCID [87], respectively. These measurement tools have significant reliability and validity, and are considered the gold standard.

Choice Point #2: The effects of acupressure on cognitive function and psychological health, including suicidality, are being analyzed, as is the relaxation response using heart rate, during each treatment session.

Choice Point #3: Physiological and psychological measures of a laboratory stress task were included to delineate mechanisms underlying potential cognitive change associated with the treatment, as well as potential buffering of the stress response that may be due to an enhanced relaxation response.

Choice Point #4: Fidelity procedures were maintained, as were measures of expectancy and credibility.

Choice Point #5: To accommodate comfort level of participants with PTSD, acupressure treatments were administered in a recumbent position, rather than while supine and ambient light was raised.

Results and lessons learned: Though the study is currently active, recruitment is closed and results have yet to be compiled and published. That said, Lessons Learned thus far include the treatment parameter modifications described in Choice Point #5, as well as the recruitment and retention challenges related to conducting a long term study assessing the impact of a CAM intervention for promoting relaxation, in a population with challenges related to both cognitive function, psychological health and autonomic arousal.

Conclusions

The present Lessons from the Laboratory has outlined and described in a step-by-step manner, a fundamental framework within which researching acupressure has been accomplished using the highest methodological rigor. In its detailed descriptions, it may also provide valuable tools for future studies of CAM where experimental design may be a challenge. Indeed, this challenge in the field of CAM is not unfamiliar to the field of rehabilitation, where the value and therapeutic importance [88] of complex interventions is well recognized. Also recognized is the degree to which this complexity impacts the study of these interventions in a controlled manner [46]. As such, by definition, CAM research is currently best labeled "Generation I", defined as the earliest of stages of researching outcome in response to CAM therapies/intervention [89].

In the present paper we have reviewed and described more than a decade's worth of research in a sequential, step-by-step manner, identifying "choice points" encountered in a clinical neuroscience research setting from which decisions were made to optimize rigor. This fundamental framework includes the following basic characteristics: optimizing methodological rigor with repeated measures in a variety of domains; using an appropriate control group; building upon findings (those measured and those perceived as anecdotal) in the design of subsequent studies; utilizing blinding procedures and fidelity assessment throughout the study; and finally, systematically elevating methodological rigor in experimental design at each iteration of the research effort, such that each study is an expansion of and improvement upon its predecessor. It is hoped that this explicit description of and guide to the scientific research process provides pertinent background as to how a study's final design is achieved, particularly as it relates to CAM (where there is a need for such guidance). This guide may not only support investigators in their developing work, but may also lead to stronger scientific study.

More and more, CAM treatment modalities are being sought out following acquired brain injury. 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 brain injury is highly variable and often incomplete. With a sufficient evidence base, CAM could

benefit civilians, Veterans, family members and large health care systems by serving as a safe, portable, low-cost, efficacious and accessible treatment strategy. Acupressure, in particular, appears to hold real promise.

While there is potential for this to result in additional treatment benefits, it also carries the potential for failed, costly, and/or potentially risky treatment in the absence of rigorous, methodologically sound studies of CAM. As such, meticulous scientific research is essential for identifying potentially effective novel treatments for acquired brain injury and associated sequelae. Furthermore, such increasingly rigorous research provides the opportunity to simultaneously characterize both efficacy and limitations of CAM treatments. Only in this way can CAM be more fully understood and accessed appropriately by both the treating clinicians and the patients with whom they work.

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