Complementary and alternative medicine and traditional Western research methods have not always had the friendliest of relationships. This has spilled over beyond academic debate.

The poem “Storm” by the comedian Tim Minchin is often quoted by

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critics of complementary and alternative medicine (CAM): “By definition, alternative medicine … has either not been proved to work, or been proved not to work. You know what they call alternative medicine that’s been proved to work? Medicine.”

Conversely, Senator Tom Harkin (D-Iowa) has publically criticized the National Center for CAM (NCCAM) at the National Institutes of Health (NIH) for slowing the use of CAM by requiring methodologies that are overly complicated and inherently skeptical: “Quite frankly, I must say it’s fallen short … I think quite frankly that in this center, and previously in the office before it, most of its focus has been on disproving things, rather than seeking out and proving things.”

While one can understand the positions asserted by Mr. Minchin and Sen. Harkin, the nature of CAM is less binary. The evidence for CAM falls on a spectrum ranging from novel ideas with little to no empirical support, to rigorously established interventions accepted as standard practice.

Despite these differences, advocates and critics agree that there has been a prolific amount of research into CAM. In 2011, NCCAM alone had an annual budget of nearly $108 million and many other branches of the NIH have substantial budgets for CAM research.

A PubMed search on July 25, 2012, with the terms “alternative medicine” and “posttraumatic stress disorder” (PTSD) yielded more than 700 publications, 46 of which were randomized controlled trials.

Researching CAM treatments for mental health conditions like PTSD is both fertile and problematic. Interventions such as eye movement desensitization and reprocessing (EMDR), once thought of as a CAM modality, are now endorsed by mainstream reviewing bodies such as the Department of Defense/Veterans Affairs Clinical Practice Guidelines and the National Institutes for Clinical Excellence.

Nevertheless, critics charge that mental health conditions are too susceptible to placebo effect for CAM interventions to be appropriately tested and that PTSD is particularly difficult due to high dropout rates and issues of secondary gain.

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In this paper we will review issues pertaining to the design and implementation of CAM trials for the treatment of PTSD, the types of trials that have been conducted, and the impact, or lack thereof, that scientific studies have on the practice and perception of CAM.

ESTABLISHMENT OF A REASONABLE HYPOTHESIS

The mechanism of CAM modalities can be broadly divided into three categories: 1) modalities that fit within the modern conceptualization of medical science; 2) modalities that do not fit within this conceptualization but do not directly challenge it; and, 3) modalities that challenge established scientific principles.

Interventions such as herbal medications and exercise belong to the first category. Although the specific chemical or chemicals that are active within a plant may not be known, most scientists would accept that such a compound could exist. Similarly, the idea that exercise affects physiology and disease processes is a generally accepted scientific fact. In testing such interventions it is not unreasonable to postulate a specific mechanism of action, though this is not necessary.

Acupuncture, chiropractic, and some meditation techniques fall within the second category. These techniques are based on concepts such as “chi,” particular religious/spiritual beliefs, or traditions of medical practice not supported by the majority of the scientific community. However, one need not accept the concept of chi to accept that sticking a needle into the body might alter physiology, nor need one accept that the spinal column controls all aspects of health to test whether its manipulation may impact a health outcome like PTSD. In formulating hypotheses to test these types of CAM modalities, it is important not to assume that a positive result necessarily validates the proposed mechanism.

The third category includes concepts that violate basic laws of physics and chemistry. Some forms of homeopathy would fall into this category, as would alchemical interventions, and the idea that prayer has an effect in those unaware they are being prayed for.

In the case of homeopathy, the administered medication, if prepared as described, should be indistinguishable from purified water. Thus, if the homeopathic remedy was truly superior to placebo, it would say something not just about treatment for PTSD, but also that our current understanding of chemistry is in error. Considering the multiple ways a clinical experiment could be flawed, a positive result should more reasonably be interpreted as experimental error than as a true effect of homeopathy on the disease process.

Some might argue that physical conventions have been overturned before. While this may be true, such radical paradigm shifts in physics and chemistry would be exceedingly unlikely based on a study of psychological out-
come. Nevertheless, negative studies appear to do little to convince proponents of such techniques. Studies of this type of PTSD intervention are best avoided because they can have no useful outcome.

PTSD PROPERLY DEFINED

Although it is common to experience some PTSD symptoms following trauma, most individuals will not develop the full syndrome. Early or mild symptoms often resolve without the need for treatment. However, when the full constellation of symptoms chronically persists, spontaneous remission is unlikely. The fact that PTSD frequently self-remits can be a significant confound if chronicity is not explicitly established. If an intervention is evaluated in a population constituted primarily by those with early PTSD symptoms, efficacy may be artificially inflated, whereas a population with chronic treatment-resistant PTSD may skew the data negatively.

The diagnosis of PTSD can be verified using structured interviews such as the Clinician-Administered PTSD Scale (CAPS), Structured Clinical Interview for Diagnosis (SCID), or Mini-International Neuropsychological Interview. Reports that fail to rigorously establish a PTSD diagnosis, or worse, describe improvement by appealing to vaguely defined notions like “trauma,” have little value.

Some advocates of CAM may prefer to investigate a different, related construct, perhaps due to perceived limitations of the standard medical definition of PTSD. In this case, the construct must be defined and operationalized with no less rigor than is demanded of PTSD.

IMPROVEMENT METRICS

Many validated scales exist to assess the severity of PTSD. The CAPS is widely considered the “gold standard,” but most PTSD scales are highly correlated for outcome. More important than which scale is used is that it be used correctly. Most PTSD scales assess the frequency and/or severity of PTSD symptoms over a specified interval of time. Naturally, it would be expected that some of these symptoms (nightmares, flashbacks, etc) are not present all the time. Yet, it is not uncommon to read reports of improvement based on PTSD scores taken immediately following treatment. Because symptoms such as nightmares presumably would not have occurred until after the individual went home to sleep, this indicates improper use of the scale.

Most scales are also highly dependent on the overall impression of the patient and the assessor. To avoid bias, it is important that those performing the assessment be separate from those administering the treatment, and blind to the treatment condition. Additionally, it is vital to evaluate the sustained benefits of any intervention. Research has shown improved mental health after a vacation, but that the benefit is relatively temporary. CAM interventions need to differentiate from vacation-like effects by evaluating symptoms for an extended interval after treatment, often multiple months of follow-up assessments.

EFFICACY VS. EFFECTIVENESS

In the world of clinical research, “effectiveness” refers to how well a treatment works in clinical practice; whereas “efficacy” refers to how well it works under highly controlled experimental conditions. A common criticism of traditional medical interventions is that efficacy proven in laboratory models and controlled clinical trials does not necessarily translate into real-world effectiveness. Criticism of CAM often follows the opposite path. Skeptics may concede that although some patients receiving CAM may improve, this does not necessarily mean there was an effect beyond placebo. For studies of CAM, even more so than with studies of traditional interventions, it is critical that proper controls be used.

STANDARDIZATION OF TESTS FOR CAM INTERVENTIONS

A requirement of any scientific finding is that it be reproducible. This can be a particular challenge for CAM modalities as, unlike most medication or surgical interventions, there may be little agreement of what constitutes a CAM treatment. Naturopathic medications may display great variability in formulation and dosage. For procedural interventions such as acupuncture or chiropractic treatment, there may be disagreement over what constitutes proper technique.

Also, most interventions of ancient medicinal traditions would be offered as part of a collection of rituals and treatments individualized to the patient. These all make drafting an explicit replicable protocol challenging. They also make truly disproving a CAM modality difficult, as it can always be argued that the intervention was unduly rigid.

RANDOMIZED, PLACEBO-CONTROLLED, AND BLIND TRIALS

Double-blind, randomized, placebo-controlled trials (RCT) are well-established and considered the gold standard for testing the efficacy of both traditional and alternative treatments. However, CAM modalities are often offered in a “whole person” manner as part of a collection of rituals and treatments individualized to the patient. These all make drafting an explicit replicable protocol challenging. They also make truly disproving a CAM modality difficult, as it can always be argued that the intervention was unduly rigid.

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standard of treatment. There are, however, special challenges in conducting an RCT of CAM for PTSD. The population with PTSD is difficult to recruit and attrition can be large. Most CAM modalities are already available to patients. Enticing participants who know they may be randomized to placebo may prove a challenge. Once enrolled, participants may attempt to break the blinding to obtain the active treatment should they suspect they have received the control.\textsuperscript{20,21}

It is notoriously difficult to design a properly blinded and placebo-controlled protocol for CAM modalities.\textsuperscript{22} Sham procedures used as controls may still include the active component of treatment. For example, sham acupuncture often involves either inserting needles at what are considered invalid acupuncture points or the superficial insertion of needles. However, there is not always agreement concerning the location of acupuncture points, nor the appropriate depth of needling.\textsuperscript{23} Even if a proper control intervention can be designed, blinding the person administering the treatment may be difficult. Greater enthusiasm for the CAM intervention may be subconsciously communicated to the patient, influencing the outcome.

Similar methodological issues have been addressed in studies of psychotherapeutic interventions.\textsuperscript{24} A number of psychotherapies such as cognitive-behavioral therapy (CBT) have achieved strong levels of evidence through well-executed research studies. One factor differentiating evidenced-based therapies from a number of the other psychotherapy interventions is manualization. Strictly formalizing the interactions between therapist and patient limits a number of possible confounds. The success of psychotherapeutic research that controls for such confounds is instructive for designing CAM interventions and would prove a significant step toward remedying the heterogeneity currently plaguing much of CAM research.

\textbf{STATISTICS AND INTERPRETATION OF RESULTS}

Extraordinary claims require extraordinary proof. It is important that researchers of CAM maintain a healthy skepticism, even in the face of encouraging preliminary results. For a CAM modality to be accepted as a mainstream treatment study, results must be reproducible, not due to placebo or random chance, and free from scores of other sources of error and fraud. A common criticism of any successful CAM trial is that it is nothing more than a type II statistical error (ie, a fluke that occurred because our standard for accepting a result as significant still allows the possibility that it be due to random chance). After all, the ubiquitous $P$ value of .05, by definition, sets the threshold whereby testing the same intervention 20 different ways or 20 different times will result in one positive outcome purely by chance.

Even if the results meet a higher statistical standard, one must not forget that scientists are not immune to their own biases or even the temptation to outright manufacture results.\textsuperscript{25,26} These are frequent criticisms of studies sponsored by pharmaceutical com-

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MILITARY-SPECIFIC ISSUES

Performing trials of CAM in military populations poses a unique set of challenges. The levels of political, command, and administrative approval required can be baroque. The culture of the armed forces may be particularly hostile to hypotheses involving mystic-sounding mechanisms and some have publically decried any and all use of CAM in the military.29 Even something as seemingly straightforward as properly defining PTSD may prove fraught with difficulty. For example, recent findings suggest that service members often do not experience, or at least do not endorse, the “fear, hopelessness, or horror,” that is currently the Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision (DSM-IV-TR) PTSD A2 criterion.30

Service members have only a limited time to recover before they face the possibility of a disability evaluation via the medical evaluation board system. Enrolling military subjects in placebo-controlled or wait-list control studies may be considered unethical, given the potential ramifications for service members. Specifically, military internal review boards (IRBs) may reject studies that include placebo-only arms or prohibit the simultaneous use of traditional treatments, though these are common practice in civilian clinical trials. Exclusion criteria such as the absence of outside financial incentives is not possible in active duty service members who are yet to receive a veterans’ disability rating.

Although the absence of such exclusion criteria may challenge the validity of symptom measurement, the use of measures to detect malingering may be perceived as demeaning.31 Although the military has a large medical system, including providers trained in CAM modalities, it is rare to find providers also proficient in research methods like the use of measurement scales or fixed protocols. However, civilian researchers coming on base may have a poor grasp of military culture and experience difficulty convincing service members to participate in clinical trials.32

In military trials, dropout rates can be quite high.33 Service member availability is variable as missions and roles change, and moves are frequent. A trial studying a unit of service members thought to be deploying to Afghanistan may discover that they have been assigned elsewhere. Service members often cannot be paid to participate in research and they usually have access to a wide variety of health care options beyond those offered in the study. Thus, researchers must devise means to motivate military participants to return for ongoing assessments, especially beyond the period when the intervention itself served as incentive.

Despite these additional complexities, research in military populations ought not to be held to any lower a standard. In fact, military institutions often require that potential scientific publications receive an internal review prior to submission for wider dissemination. Although this adds rigor, it can slow publication.

CONCLUSION

Performing studies of CAM for PTSD is challenging. Western science and CAM often start with different perspectives. Beyond the need for general scientific rigor, there are difficulties specific to the study of PTSD and the use of CAM. Performing these studies in the military may be particularly challenging. This does not mean that good science and CAM are incompatible. Many researchers have led trials of CAM for PTSD, and there is much important work left to do.34 New ideas for CAM interventions for PTSD continue to be postulated.35,36 Respected organizations such as the Department of Defense, the Department of Veterans Affairs, and the European Commission are funding CAM trials.37,38 With the ongoing epidemic of PTSD among service members returning from combat deployment, there is a dire need for new treatments. We need to know which interventions work and which do not (see Sidebar, page 41). Performing rigorously conceived scientific trials of CAM for PTSD is the only way to establish this.

REFERENCES

3. Complementary and Alternative Medicine...