EDITORIAL

# When Does Meta-analysis of a Network Not Work?
## Fishing for Answers

Murray B. Stein, MD, MPH; Sonya B. Norman, PhD

**Just as bluefin tuna** are high on the aquatic food chain, systematic reviews and meta-analyses are at the top of the evidence hierarchy. Tuna swallow up smaller fish that have eaten minnows, which have eaten plankton and so on, accumulating the nutrients—and the toxins (eg, mercury)—of their prey. Meta-analyses, too, acquire and filter data and the misinformation (eg, biases) from the studies they aggregate. Indiscriminate consumption of tuna or meta-analyses can be hazardous to brain health.

Related article

As clinician-scientists who work on posttraumatic stress disorder (PTSD) clinical trials and treat patients with PTSD and associated disorders, we value and rely on systematic reviews and meta-analyses to guide our research and patient care. As consumers of those studies, we do our best to understand what they are saying and the extent to which we should believe them.[1] It is from this perspective that we couch these comments.

In their network meta-analysis of 12 randomized clinical trials that compared pharmacological, psychotherapeutic, and/or combination treatments for PTSD, Merz et al[2] found that all approaches demonstrated similar results at the end of short-term treatment, but psychotherapy and combined pharmacotherapy and psychotherapy were more effective than pharmacotherapy alone at so-called long-term follow-up (an approach incorporated in 6 studies with highly variable follow-up durations). Meta-analyses compile, digest, and compare data from head-to-head trials (ie, ones comparing treatment A vs treatment B) to provide an integrated assessment of their relative efficacy. Network meta-analyses go a step further to compare the reported effectiveness of interventions that may or may not have been evaluated directly against each other. In other words, trials of treatment A vs treatment B and trials of treatment B vs treatment C may enable inferences about the effectiveness of treatment A vs treatment C.

Because there are so few available direct comparisons of pharmacological, psychotherapeutic, and combination treatments for PTSD, Merz et al[2] included all available studies in their network meta-analysis. In so doing, they amalgamated data from studies that had vastly differing objectives (eg, proof of principle, confirmation of efficacy, comparative effectiveness). Deciding which studies to include in a network meta-analysis—or whether the available studies are suitable for network meta-analysis at all—is a crucial undertaking that involves consideration of factors such as sample size, likelihood of bias, and heterogeneity.[3] Researchers conducting network meta-analyses must carefully select their trials based on numerous assumptions inherent to this approach, and it has been argued that these assumptions have often not been met in mental health studies comparing pharmacological and nonpharmacological interventions.[4]

Merz et al[2] followed established procedures in choosing which trials to include (and share a comprehensive set of documents in the Supplement to provide detail about those decisions). Yet their decision, for example, to include a trial with 14 patients (9 in one arm and 5 in the other) highlights the subjectivity and user variability involved in conducting meta-analyses, even when following recommended procedures (eg, ones for assessing risk of bias in a study).[5]

The approach of including all available studies has strengths and limitations. A principal strength of being extremely inclusive is maximizing power by using all available evidence. A downside is that this approach is likely to catch many different kinds of fish in its net, resulting in confusion about which of these ichthyological specimens are palatable and can be reasonably consumed and compared. For example, numerous studies have found specific trauma-focused psychotherapies (eg, prolonged exposure, cognitive processing therapy) to be effective,[6] and these treatments have the highest recommendation across all clinical practice guidelines for PTSD.[7] Yet this network meta-analysis made no distinction between trauma-focused or other psychotherapies, which may explain why it failed to see differences between pharmacotherapy and psychotherapy at the end of treatment. By the same token, this network meta-analysis did not distinguish between established, US Food and Drug Administration–approved pharmacological treatments administered at therapeutic dosage and duration (eg, sertraline at 100-200 mg for 8-12 weeks) from augmentation trials for patients who did not respond to treatment (eg, addition of atypical antipsychotics to selective serotonin reuptake inhibitors) from one-time administration of experimental agents (eg, 3,4-methylenedioxymethamphetamine [MDMA]). These considerations are not mere nuances; they are crucial to interpreting and contextualizing the data from the individual trials. Treating all psychotherapies as one modality and all pharmacotherapies as another and then comparing them, directly and indirectly, risks serving up (to continue with the marine life metaphor) a hard-to-swallow homogenized fish patty of inferences instead of the sushi-grade information we crave.

The network meta-analysis by Merz et al[2] does the field a great service in that it makes clear how few PTSD trials there have been and clarifies that more are needed. For a disorder widely acknowledged as an important public health problem, the lack of PTSD trials, particularly ones evaluating pharmacotherapies,[8] is troubling.[9] Equally concerning is the

size of the trials that have been funded, ranging from tiny (eg, with tens of participants) to small (eg, with fewer than 300 participants) by the standards of clinical trials in other serious disease states (eg, cardiovascular disease, cancer, Alzheimer disease). A study with 200 to 300 patients with PTSD might well be sufficient to permit the determination of efficacy for a new treatment vs matched placebo in the case of a pharmacotherapy trial or an already established intervention in the case of a psychotherapy trial. However, such a modestly sized study is extremely unlikely to provide insight into which individuals are most likely to benefit from the treatment.

To advance a goal of precision medicine in PTSD, the field needs not only more randomized clinical trials but rather larger trials that will enable the intelligent parsing of patient heterogeneity to develop guidelines for personalized treatment. To succeed in that effort, researchers also need to look beyond PTSD diagnosis to examine individual and disease characteristics that may contribute to PTSD symptom severity and persistence. Targeting factors known to affect posttraumatic distress may open new avenues of treatment. For example, having guilt and shame in association with a traumatic event is associated with greater severity of multiple negative posttraumatic reactions, including PTSD, depression, and suicidal ideation[10]; directly targeting guilt and shame could hypothetically lead to improved outcomes for affected individuals. Advances in the understanding of the relevance of fear systems, fear extinction, and memory reconsolidation mechanisms to PTSD, in concert with improved understanding of phenotypes and genetic risk for PTSD,[11] promise to accelerate drug discovery and treatment personalization for PTSD. But sufficient trials of substantial size are necessary to enable these advances in understanding disease processes to be translated into therapeutically beneficial interventions.

At this juncture, some evidence exists that patient preference (for the options of selective serotonin reuptake inhibitors [sertraline] vs prolonged exposure) matters in the initial selection of treatment.[12] But clinicians have no idea what to do when that first treatment fails. The field needs to get beyond the trope of asking "Which is better, psychotherapy or pharmacotherapy?" and ask clinically meaningful questions, such as, "What do you do after a patient with PTSD has not experienced improvement with their first evidence-based treatment? Do you add a second treatment? (Which one?) Do you switch to another evidence-based treatment?" What is most needed to help break through this therapeutic impasse is a monumental effort to prioritize and fund PTSD clinical trials and trial consortia, so that the size, quality, and number of trials can feed a robust set of quality meta-analytic results to the whale shark of evidence-based medicine—the systemic review of meta-analyses.[13]

## ARTICLE INFORMATION

**Author Affiliations:** Department of Psychiatry, University of California San Diego, La Jolla (Stein, Norman); Department of Family Medicine and Public Health, University of California San Diego, La Jolla (Stein); VA San Diego Healthcare System, San Diego, California (Stein, Norman); National Center for PTSD, White River Junction, Vermont (Norman).

**Corresponding Author:** Murray B. Stein, MD, MPH, Department of Psychiatry, Altman Clinical and Translational Research Institute, University of California San Diego, 9452 Medical Center Dr, La Jolla, CA 92037 (mstein@ucsd.edu).

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