Starting From Something: Augmenting Exposure Therapy and Methods of Inquiry

In this issue of the *Journal*, Telch et al. (1) examine the ability of methylene blue to augment extinction learning in individuals with claustrophobic fear. The authors studied 42 individuals randomly assigned to double-blind administration of 260 mg of methylene blue or placebo following multiple extinction trials in an enclosed chamber over the course of one clinical session. The primary outcome is self-rated peak fear (scale: 0–100 points) upon re-entry into a similar enclosed chamber a month later. The authors correctly hypothesize extinction augmentation only for those who report low end-state fear subsequent to extinction training; the primary interaction and follow-up analysis effects are large and statistically significant. Marginally supportive evidence is also found for a hypothesized deleterious effect of the medication on those with high end-state fear subsequent to extinction training. The authors include a free-recall contextual learning test to examine the impact of medication on learning in general and find positive hypothesized effects. In other words, methylene blue improved recall of nonfear-related stimuli for the entire medication group but only improved outcomes for those with low end-state fear after exposure. The take-home message is that methylene blue is related to enhanced contextual learning in general. Accordingly, learning is enhanced regarding whatever takes place; if exposures are successful, the successful learning is enhanced, if unsuccessful, learning related to the negative experience is enhanced.

Telch et al. offer a rigorous study that builds on the literature with a highly controlled exposure paradigm, well-specified a priori hypotheses, and appropriate means to address those hypotheses. The study is not without limitations, which the authors adequately identify. I have been asked to comment, more generally, on the relative importance of extinction augmentation research, and Telch et al. provide a solid sounding board to do so.

In the past 5 years, over 20 studies have been published regarding pharmacological enhancement of extinction in humans, and there are at least 15 similar studies in the active-recruitment phase on clinicaltrials.gov. This growing body of research provides optimized environments to noninvasively investigate mechanisms of pathological anxiety and treatment in humans. The translational nature of extinction enhancement research necessitates investigation of interactions among pharmacological agents, human behavior, and psychotherapy protocols. Accordingly, translating animal extinction paradigms into appropriate analogs of exposure therapy for humans calls for, perhaps, more exacting methods than are typically employed in standard psychotherapy outcome studies. As a result, research related to exposure enhancement is significant not only because of the very real potential to improve evidence-based treatments for anxiety spectrum disorders but also because such research is spurring on the application and development of measurement paradigms and specified research designs that are healthy for and beneficial to the larger field of clinical research regarding evidence-based treatments.

Given an augmentation effect, detecting it can be challenging for a number of reasons, including already robust effect sizes for exposure-oriented interventions.

Meta-analyses indicate effects for exposure therapies close to or over 1 standard deviation for specific phobias (2), social phobias (3), obsessive-compulsive disorder (4), and posttraumatic stress disorder (PTSD) (5), which the balance of scientific evidence supports as an anxiety spectrum disorder. Moreover, effect sizes for individuals who complete treatment are often close to or over 2 standard deviations (6, 7). Comparatively, a meta-analysis of antidepressants for major depressive disorder evidenced a 0.20 standard deviation effect size (8). In other words, variations of exposure therapy for anxiety are associated with effects arguably five to 10 times larger than those of antidepressants for depression, the most widely accepted standard of care for the disorder. Of course, there is much room for improvement; dropout rates are substantial (although normative compared with other psychotherapies), and posttreatment diagnosis rates tell a more somber tale than effect sizes. However, casting the size of exposure effects in this comparative light underscores the importance of specificity in augmentation trials. For example, it may be difficult for augmentation trials to broadly improve posttreatment effects for treatment completers, as significant gains for completers in both conditions may wash out the ability to measure incremental benefits of a novel strategy. Regardless of the reason, a significant number of trials evidence an early augmentation benefit that diminishes with more treatment (9–13). In this context, initial slope of response over time is emerging as an important primary outcome (14). Accordingly, it is notable that Telch et al. utilize multiple exposures within just one session in their experiment. Providing multiple sessions may have obscured a positive/important finding. Under-dosing exposures might efficiently reveal how enhancing agents can be incorporated into a course of treatment and/or replace the need for additional sessions. Although the one-session claustrophobia protocol has been shown to be quite effective, a recent investigation of D-cycloserine for PTSD purposely under dosed the number of exposures to avoid ceiling effects for responders (15). This less-is-more strategy may be particularly helpful in translating animal-to-human effects, as unknowns regarding optimal timing and level of dosing for drugs imbedded within specific therapies render the task of isolating effects even more difficult.

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Augmentation studies also require careful thought about who the novel effects are meant to target. Extinction augmentation is not necessarily the same as treatment augmentation. In general terms, treatment augmentation may refer to reducing dropout, improving treatment efficiency, bolstering effects for responders, or bolstering effects for partial and nonresponders. These are four separate, not necessarily related, goals aimed at distinct populations of patients undergoing exposure therapy. Along these lines, Telch et al. build on the literature by demonstrating augmentation effects for subjects with "successful" exposures and poor effects for those with "unsuccessful" exposures. This finding, noted in previous D-cycloserine (16) and yohimbine (17) trials, represents an increasingly popular design strategy. Such designs move the field toward focusing stratified research questions on ideographic patient factors, therapy-specific reactions, and phenotypes, rather than on broad demographic stratifications, taxonomies (i.e., co-occurring diagnoses), or baseline severity of self-reported symptoms, which traditionally have yielded modest scientific progress regarding the explanation of variance in outcomes to exposure protocols.

A related point is that augmentation trials often identify outcomes that are more specified than standard patient-reported clinician interviews, which, for good or bad, have come to dominate the field. The translational nature of the research encourages testing mechanisms as one goes and differentiating subjects with measures that are dynamically relevant to their ongoing treatment. For example, Telch et al. use specific fear in response to a stimulus as the primary outcome, rather than a diagnostic interview. Data related to inhibitory learning models provide robust support for measuring decreases in exposure-related arousal as meaningful markers of future symptom decline (18), with predictive validity centering on between-exposure declines, rather than on within-exposure habituation. Objective measures, such as cortisol, startle, heart rate, and skin conductance, have also been employed (19, 20) and can be more sensitive to augmentation manipulations than subjective outcomes (15). Overall, there is a trend toward validating biological and physiological measures implicated in preclinical/laboratory-based anxiety studies as dynamic indices of effective exposure therapy (21). Establishing the predictive validity of objective measures in multiple exposure contexts not only assists in the identification of novel exposure/drug combinations but also builds an evidence base to enable future preselection of individuals with specific exposure-related response styles. Thus, augmentation research is playing multiple roles, not only in seeking to improve evidence-based treatments in general but also in helping to identify for whom and under what circumstances evidence-based treatments will be effective.

In summary, the translational nature of extinction augmentation research and the necessity of understanding individualized responses create the need for specificity and complexity in clinical trials. Yet the level of appropriate complexity is not prohibitive; rather, it is readily attainable with current and developing measurement paradigms and research designs. This literature has the potential to address crucial knowledge traditionally deemed as peripheral to the development of evidence-based treatments. Whether or not specific agents are eventually proven to be helpful, the augmentation literature on a whole is focusing on aspects of the clinical canvass that have often been out of the frame, and perhaps for too long.

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