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HOT TOPICS

The promise of 3,4-methylenedioxymethamphetamine (MDMA) in combination with prolonged exposure therapy for posttraumatic stress disorder

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3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy is likely to be the next FDA-approved indication for PTSD. In a phase 3 trial, MDMA-assisted therapy resulted in significantly greater reductions in PTSD compared to placebo [1]. This non-directive therapeutic approach is time intensive (i.e., 42 therapist hours); research testing mechanisms of action and investigating models with fewer therapist hours is needed. The APA Clinical Practice Guidelines for the Treatment of PTSD strongly recommends four interventions as PTSD treatments: cognitive behavioral therapy, cognitive processing therapy (CPT), cognitive therapy, and prolonged exposure therapy (PE) [2]. MDMA has never previously been investigated in combination with any of these gold standard PTSD interventions.

PTSD can be understood using a translational fear extinction model in which exposure to a trauma represents an unconditioned stimulus (US) that elicits an unconditioned fear response (UR) [3]. The environmental cues present at the time of trauma are then associated with the US (trauma) and serve as conditioned stimuli (CSs) and acquire the ability to produce subsequent conditioned fear responses (CRs). In the laboratory, fear extinction training involves repeated presentations of the CS without the US, resulting in a decreased conditioned fear response. PE involves confronting feared trauma-related stimuli including the trauma memory and real-life reminders in a systematic approach under therapeutic conditions resulting in decreased fear responses over repeated repetitions of the exposure (i.e., fear extinction). PE being based, at least partially, on extinction learning is supported by psychophysiological experimental findings that PE responders maintain fear extinction learning whereas low PE responders demonstrate return of fear [4]. Translational research supports that MDMA facilitates the extinction of fear. In rodent models, MDMA enhances the extinction of both conditioned freezing and fear-potentiated startle, which is highly conserved across species [5]. In a randomized, placebo-controlled trial with healthy adults using the same experimental startle paradigm, significantly more participants in the MDMA group retained extinction learning compared to the placebo group ($\chi^2 = 7.29$, $p = 0.007$) [6]. Thus, translational evidence indicates PE could represent the optimal psychotherapy to be combined with MDMA for PTSD intervention. Pilot work is needed to explore possible challenges of this model, including best practice for integrating manualized treatments with a medicine with significant psychoactive effects and patient acceptability and tolerability of exposure therapy augmented with MDMA.

PE demonstrates advantages with regard to empirical support, efficiency, and dissemination. PE has a strong data base for its efficacy, requires approximately 10 sessions, has published manuals translated into multiple languages, and involves an efficient 2-day training. The Department of Veterans Affairs has nationally disseminated PE and CPT throughout the VA, as such there is a large quantity of trained PE providers. This dissemination potential and theoretical support for a synergistic mechanism of action for combining MDMA with PE indicate this combined treatment could represent a breakthrough in our ability to treat PTSD, and scientific understanding of therapeutic mechanism (i.e., fear extinction) of PE + MDMA could inform personalized medicine approaches.

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COMPETING INTERESTS

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ADDITIONAL INFORMATION

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