

Q. What is low-intensity focused ultrasound?

A. Treatment of brain disorders using a growing number of physical modalities has been increasing for decades with varying degrees of success. Such modalities include the delivery of electrical current, exposure to magnetic fields, low-power laser light, and ultrasound. Ultrasound waves are sound waves with frequencies too high for the human ear to detect. Diagnostic ultrasound has been used for decades for clinical imaging. Functional ultrasound, or the therapeutic use of ultrasound, utilizes lower frequencies (kilohertz rather than megahertz) than diagnostic ultrasound, resulting in more focused beams of energy that target deeper brain structures with greater precision (Bowary & Greenberg, 2018). High-intensity functional ultrasound, specifically magnetic resonance-guided focused ultrasound (MRgFUS), is approved by the U.S. Food and Drug Administration (FDA) for treatment of essential tremor via removal of problematic tissue, or ablation (FDA, 2016). Unlike high-intensity functional ultrasound, which delivers a continuous wave that heats targeted tissue for ablation, low-intensity focused ultrasound (LIFUS) relies on non-thermal mechanical effects and is commonly delivered via pulses (Bowary & Greenberg, 2018). Terminology is varied across the literature, and the same approach is sometimes referred to as noninvasive focused ultrasound, ultrasound neuromodulation, or transcranial focused ultrasound (TFUS), just to name a few. This evidence brief is on noninvasive, low-intensity, transcranial ultrasound that targets specific deep-brain structures for treatment via neuromodulation rather than via ablation.

Q. What are the potential mechanisms of action of LIFUS?

A. LIFUS excites or suppresses neuronal activity in the areas targeted, with neuromodulation effects that could theoretically translate to desired behavioral changes. A number of preclinical studies have demonstrated the neuromodulatory effects of LIFUS (see Bowary & Greenberg, 2018, and Fomenko, Neudorfer, Dallapiazza, Kalia, & Lozano, 2018, for reviews of these studies). Despite a large body of research on the neuromodulatory effects of LIFUS, the mechanisms of action are not clear (see Fomenko et al., 2018, for a review of potential mechanisms).

A 2012 patent application put forward that non-invasive neuromodulation using LIFUS ultrasound can be used to treat posttraumatic stress disorder (PTSD) by upregulating or downregulating specific brain targets, including the amygdala, hippocampus, anterior cingulate cortex, orbito-frontal cortex, and the insula (Mishelevich, 2012). However, at this time there is a lack of evidence demonstrating that PTSD can be effectively treated via these mechanisms.

Q. Is LIFUS recommended in the Military Health System (MHS)?

A. **No.** The 2017 VA/DoD *Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder* does not include any ultrasound therapy.

The MHS relies on the Department of Veterans Affairs (VA)/Department of Defense (DoD) clinical practice guidelines (CPGs) to inform best clinical practices. The CPGs are developed under the purview of clinical experts and are derived through a transparent and systematic approach that includes, but is not limited to, systematic reviews of the literature on a given topic and development of recommendations using a graded system that takes into account the overall quality of the evidence and the magnitude of the net benefit of the recommendation. A further description of this process and CPGs on specific topics can be found on the VA clinical practice guidelines website.

Q. Do other guidelines and evidence reviews recommend LIFUS for PTSD?

A. **No.** Other authoritative reviews have not substantiated the use of LIFUS for treating PTSD.

Several other recognized organizations conduct systematic reviews and evidence syntheses on psychological health topics using similar grading systems as the VA/DoD CPGs. These include the Agency for Healthcare Research and Quality (AHRQ) and Cochrane.

- AHRQ: No reviews were found on LIFUS as treatment for PTSD
- Cochrane: No reviews were found on LIFUS as treatment for PTSD

Q. Is there any recent research on LIFUS as a treatment for PTSD?

A. A May 2019 literature search identified no studies on LIFUS for PTSD. Recent reviews have highlighted the promise of LIFUS for neuromodulation, including its potential to replace current therapies (such as transcranial magnetic stimulation and deep brain stimulation) due to its greater spatial resolution and depth penetration (Bowery & Greenberg, 2018; Baek, Pahk, & Kim, 2017), and its potential as a treatment for psychiatric disorders (Fini & Tyler, 2017; Tsai, 2015). However, research on the use of LIFUS for treating psychiatric disorders is in its infancy, and is largely limited to animal studies examining basic science questions related to psychiatric disorders (e.g., Min et al., 2011; Yang et al., 2012) and pilot studies in humans that assess mood (e.g., Hameroff et al., 2013; Sanguinetti & Allen, 2017).

Q. What conclusions can be drawn about the use of LIFUS as a treatment for PTSD in the MHS?

A. Because there is insufficient evidence that LIFUS is effective or safe in the treatment of PTSD, LIFUS is not recommended by current guidelines or authoritative reviews. At this time the use of LIFUS for treatment of PTSD remains investigational.

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