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TREATMENT

First dose-response study of MDMA for PTSD

The FDA recently designated MDMA-assisted psychotherapy (MDMA-AP) a “breakthrough therapy,” which supports expedited research and development. Investigators at the Medical University of South Carolina extended previous work (e.g., see the [December 2012 CTU-Online](#)) by addressing issues of blinding and dose response in MDMA-AP. This phase 2 pilot RCT used a 1:1:2 randomization scheme to assign Veterans and first responders to one of three MDMA doses added to non-directive psychotherapy: active control (30 mg; $n = 7$), 75 mg ($n = 7$), or 125 mg ($n = 12$). Participants receiving 75 and 125 mg had greater improvements in PTSD symptom severity, sleep, depressive symptoms, and suicidal ideation than those receiving 30 mg. After the primary endpoint (1 month post-2nd MDMA-AP session), those in the active control and 75 mg groups were offered 3 additional MDMA-AP psychotherapy sessions with MDMA doses between 100-125 mg. Patients initially randomized to the active control (30 mg) had significant improvement, whereas those originally given 75 mg did not show additional benefit. Active doses of MDMA (75 and 125 mg) were well tolerated and resulted in long-term clinical improvement ($\geq 30\%$ improvement on CAPS-IV for $\sim 85\%$ of the participants) at 12-month follow-up. Findings from this study suggest that MDMA-assisted psychotherapy is a potential strategy for enhancing treatment outcome in PTSD.

Read the article: [https://doi.org/10.1016/S2215-0366\(18\)30135-4](https://doi.org/10.1016/S2215-0366(18)30135-4)

Mithoefer, M. C., Mithoefer, A. T., Feduccia, A. A., Jerome, L., Wagner, M., Wymer, J., . . . Doblin, R. (2018). 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: A randomised, double-blind, dose-response, phase 2 clinical trial. *The Lancet Psychiatry*, 5, 486-497. PILOTS ID: 50277

Patients with dissociative subtype of PTSD respond to PE

Evidence suggests that individuals with PTSD who have dissociative symptoms respond well to Prolonged Exposure (PE), although to a somewhat lesser extent than individuals who do not have dissociation (see the [August 2015 CTU-Online](#)). An RCT led by investigators at Case Western Reserve University examined how patients with the dissociative subtype of PTSD ($N = 200$) responded not only to PE, but also to sertraline, an evidence-based medication for PTSD. Using latent transition analyses, the investigators identified four patient profiles before treatment: notable avoidance, dysphoria, general pathology, and dissociation-reexperiencing symptoms. Patients in the dissociation-reexperiencing group responded well to PE, although they did not respond as well compared to the other groups. A key finding was that the dissociative patients had a much better response to PE (67%) than to sertraline (17%), which suggests that PE is a preferred option for treating the dissociative subtype of PTSD.

Read the article: <https://doi.org/10.1037/ccp0000297>

Burton, M. S., Feeny, N. C., Connell, A. M., & Zoellner, L. A. (2018). Exploring evidence of a dissociative subtype in PTSD: Baseline symptom structure, etiology, and treatment efficacy for those who dissociate. *Journal of Consulting and Clinical Psychology*, 86, 439-451. PILOTS ID: 50275

Take NOTE

Update on psychological and pharmacological treatments for PTSD

The Agency for Healthcare Research and Quality released an update to their 2013 research synthesis report on effective treatments for PTSD.

Read the report: <https://doi.org/10.23970/AHRQEPCCER207>

Forman-Hoffman, V. L., Middleton, J. C., Feltner, C., Gaynes, B. N., Weber, R. P., Bann, C., . . . Green, J. (2018). Psychological and pharmacological treatments for adults with posttraumatic stress disorder: A systematic review update (Comparative Effectiveness Review No. 207). Rockville, MD: Agency for Healthcare Research and Quality. PILOTS ID: 50247

Special journal issue on PTSD

The most recent issue of *Harvard Review of Psychiatry* focuses on scientific advances in understanding and treating PTSD. Topics include fear processing, emotion regulation, resilience, neurobiology, and evidence-based treatment.

Read the issue: <https://journals.lww.com/hrpjournal/Pages/currenttoc.aspx>

Ressler, K. J. (Ed.). (2018). Recent advances in understanding and treatment of posttraumatic stress and trauma-related disorders [Special issue]. *Harvard Review of Psychiatry*, 26. PILOTS IDs: 50197, 50198, 50199, 50200, 50201, 502023

Report on the needs of male Servicemembers who experienced sexual assault

RAND released a report summarizing research on male sexual assault victims in the U.S. military. RAND investigators also conducted interviews about sexual assault victims' needs with service providers and civilian experts. The team offers suggestions for how the U.S. Department of Defense can more effectively address the needs of this population.

Read the report: <http://dx.doi.org/10.7249/RR2167>

Matthews, M., Farris, C., Tankard, M., & Dunbar, M. S. (2018). Needs of male sexual assault victims in the U.S. armed forces (RR-2167-OSD). Santa Monica, CA: RAND. PILOTS ID: 50210

Systematic review of RCTs of mind-body interventions for PTSD

In a systematic review of 22 clinical trials, a team led by investigators at the National Center for PTSD concluded that

mindfulness, yoga, and relaxation have positive effects. They provide recommendations for designing future trials to address the existing studies' methodological limitations.

Read the article: <https://www.ptsd.va.gov/professional/articles/article-pdf/id50274.pdf>

Niles, B. L., Mori, D. L., Polizzi, C., Pless Kaiser, A., Weinstein, E. S., Gershkovich, M., & Wang, C. (2018). A systematic review of randomized trials of mind-body interventions for PTSD. *Journal of Clinical Psychology*. Advance online publication. PILOTS ID: 50274

Systematic review of interventions for PTSD and TBI that involve or support families

A team led by investigators at the Durham VA reviewed 13 studies of psychological or rehabilitation interventions for PTSD, TBI, or polytrauma that involve families and caregivers. They found positive effects on patients' PTSD symptoms and mental health service use and some support for PTSD caregivers' psychological symptoms

Read the article: <https://doi.org/10.1007/s11606-018-4417-7>

Shepherd-Banigan, M. E., Shapiro, A., McDuffie, J. R., Brancu, M., Sperber, N. R., Van Houtven, C. H., . . . Williams, J. W. (2018). Interventions that support or involve caregivers or families of patients with traumatic injury: A systematic review. *Journal of General Internal Medicine*. Advance online publication. PILOTS ID: 50279

Systematic review and meta-analysis of early interventions after traumatic injury

A team led by investigators at Monash University in Australia conducted a systematic review of 26 studies and a meta-analysis of 12 studies focused on the effectiveness of interventions delivered within 3 months post-injury for treating PTSD, anxiety, and depression symptoms. CBT interventions were most effective; risk-stratified, stepped care approaches had the most reach.

Read the article: <https://doi.org/10.1016/j.cpr.2018.05.001>

Giummarra, M. J., Lennox, A., Dali, G., Costa, B., & Gabbe, B. J. (2018). Early psychological interventions for posttraumatic stress, depression and anxiety after traumatic injury: A systematic review and meta-analysis. *Clinical Psychology Review*, 62, 11–36. PILOTS ID: 50276

Novel statistical strategies help predict response to PTSD treatment

Although a number of treatments have been proven effective in treating PTSD, patients vary substantially in their response to these treatments. As a result, there is growing interest in understanding which patients are more likely to benefit from one therapy over another (see the [December 2017 CTU-Online](#)). Three new studies employed novel statistical techniques in order to match patients to their optimal treatment.

A study led by investigators from VA Puget Sound Healthcare System re-examined data from a randomized clinical trial comparing PE and virtual reality exposure (VRE) in a sample of 108 active duty U.S. Army Soldiers. Results of the main study found no differences between PE and VRE at posttreatment, but PE was superior to VRE for PTSD symptom reduction at follow-up (see the [October 2016 CTU-Online](#)), with some Servicemembers benefiting more from one treatment than the other. A composite moderator approach was used to identify which Soldiers would have better PTSD symptom reduction in PE or VRE according to the Clinician-Administered PTSD Scale. The technique used a combination of participants' baseline characteristics to predict optimal outcomes in each treatment condition. Of 18 potential moderators, 4 were included in the composite moderator. Participants predicted to have greater PTSD symptom reduction in VRE compared to PE (37% of the sample) were likely to be younger, have higher hyperarousal symptoms, have greater than minimal suicide risk, and not be taking antidepressant medications. The advantage of obtaining predicted treatment was 6.7 points on the CAPS in VRE and 17.8 points in PE. A next step is further replication in other samples and with other potential moderators in order to identify generalizable predictions.

Read the article: <https://doi.org/10.1002/da.22751>

A study by investigators from Duke University Medical Center used a classification tree method to derive an actuarial model of risk of dropout from PTSD treatment. Data were collected from clinical records of 124 returning Veterans seen in a VA PTSD outpatient clinic. A total of 51 unique patient, therapist, and system characteristics were entered into a model predicting the number of sessions completed by patients referred for psychotherapy for PTSD. The single best predictor of completed psychotherapy sessions was the number of days elapsed between the completion of an introductory information session and the invitation to enter psychotherapy. Those who had to wait fewer than 68 days to be invited to initiate treatment completed an average of 8 therapy sessions, compared to less than 3 sessions for those who had to wait more than 68 days. Other factors related to retention in therapy were higher levels of readiness to change, no history of previous counseling for PTSD, and presence of a traumatic brain injury. These findings suggest that rapid access to care and motivation for treatment are important factors to address when engaging returning Veterans in treatment for PTSD.

Read the article: <https://doi.org/10.1037/ser0000139>

Researchers from the University of Trier in Germany led a study investigating treatment matching using a different approach to combine multiple variables for predicting treatment outcome. The Personalized Advantage Index (PAI) is the number of additional points of improvement on an outcome predicted for an individual who receives the treatment predicted as optimal (vs. not optimal) for them. The study used data from a sample of patients receiving EMDR ($n=75$) or trauma-focused CBT (TF-CBT; $n=242$) for PTSD in a primary care mental health service in England. The PHQ-9 measuring depressive symptoms was used as the primary outcome because a measure of PTSD was not available. Variables predicting optimal TF-CBT outcomes were older age, being employed, female gender, and lower baseline functional impairment. Variables predicting optimal EMDR outcomes were lower baseline depression symptoms and not being prescribed antidepressant medication. Participants were then classified as those who received their optimal treatment or suboptimal treatment based on the PAI. Of patients who received their optimal treatment, 63% had reliable improvement after treatment, compared with only 34% in the suboptimal group. These results add to growing evidence that matching patients to their optimal treatment based on the PAI model could improve treatment outcomes.

Read the article: <https://doi.org/10.1002/da.22755>

Taken together, these studies demonstrate the utility of advanced statistical techniques in predicting optimal treatment outcomes for patients with PTSD. Because each study examined different variables and used different patient populations, it is not yet possible to widely generalize these findings for treatment matching purposes. However, these strategies offer promise that precision medicine could become a viable option for psychotherapy.

Deisenhofer, A.-K., Delgadillo, J., Rubel, J. A., Böhnke, J. R., Zimmermann, D., Schwartz, B., & Lutz, W. (2018). Individual treatment selection for patients with posttraumatic stress disorder. *Depression and Anxiety, 35*, 541-550. PILOTS ID: 50159

Fleming, C. E., Kholodkov, T., Dillon, K. H., Belvet, B., & Crawford, E. F. (2018). Actuarial prediction of psychotherapy retention among Iraq-Afghanistan veterans with posttraumatic stress disorder. *Psychological Services, 15*, 172-180. PILOTS ID: 50256

Norr, A. M., Smolenski, D. J., Katz, A. C., Rizzo, A. A., Rothbaum, B. O., Difede, J., . . . Reger, G. M. (2018). Virtual reality exposure versus prolonged exposure for PTSD: Which treatment for whom? *Depression and Anxiety, 35*, 523-529. PILOTS ID: 50278

Fidelity of collaborative care predicts outcomes for depression but not PTSD

The STEPS-UP study found that stepped collaborative telecare led to increased access to mental health care and modest improvements in PTSD and depression symptoms among active duty Servicemembers (see [August 2016 CTU-Online](#)). Additional analyses by a team led by investigators at the Defense Health Agency examined whether treatment fidelity predicted changes in PTSD and depression symptoms over time. Participants were 666 male and female Servicemembers. The investigators collapsed data from the telecare group and the usual collaborative care group and defined fidelity as contact with the patient, symptom moni-

toring, and psychiatric consultation within the same month. Four fidelity categories over 4 timepoints in one year were examined: low, high, early, and late fidelity. The investigators controlled for treatment utilization, expected to vary across the two arms, in order to isolate the contribution of fidelity to outcomes. Relative to the early and low-fidelity groups, the high and late fidelity trajectories were associated with greater improvement in depression symptoms. Fidelity was unrelated to PTSD outcomes. A possible explanation for the lack of effect of fidelity on PTSD is the modest effect on PTSD in the study overall.

Read the article: <https://doi.org/10.1007/s11606-018-4451-5>

Belsher, B. E., Evatt, D. P., Liu, X., Freed, M. C., Engel, C. C., Beech, E. H., & Jaycox, L. H. (2018). Collaborative care for depression and posttraumatic stress disorder: Evaluation of collaborative care fidelity on symptom trajectories and outcomes. *Journal of General Internal Medicine*. Advance online publication. PILOTS ID: 50252

Another study of HBOT, but no definitive answers for PTSD

During hyperbaric oxygen therapy (HBOT), a patient breathes 100% oxygen delivered above atmospheric pressure. HBOT is effective for treating medical conditions such as decompression sickness in divers, and has been proposed as an intervention for PTSD and post-concussive syndrome. Three prior RCTs have failed to show that HBOT was effective for PTSD or TBI symptoms. A new RCT has reported positive results. Investigators at Intermountain Medical Center in Utah conducted an RCT of HBOT for persistent post-concussive symptoms in 71 military personnel, about half of whom had PTSD. Thirteen weeks of HBOT was associated with a greater reduction in post-concussive symptoms and PTSD symptoms compared with sham. On secondary measures, HBOT was associated with a greater reduction in post-concussive (but not PTSD) symptoms at 6-month follow-up. No efficacy differences between HBOT and placebo were seen at 12 months. It is difficult to interpret these findings conclusively because the HBOT and sham groups differed in multiple ways at baseline, despite randomization, and there is no discussion of how missing data were managed, which is important because some participants dropped out of the study before each of the assessment points. It also is difficult to reconcile these positive findings with the 3 prior negative trials, but taken together, the evidence

suggests that HBOT is not an effective treatment for PTSD or post-concussive symptoms.

Read the article: [Hyperbaric oxygen for post-concussive symptoms](#)

Weaver, L. K., Wilson, S. H., Lindblad, A. S., Churchill, S., Deru, K., Price, R. C., . . . Meehan, A. (2018). Hyperbaric oxygen for post-concussive symptoms in United States military service members: A randomized clinical trial. *Undersea & Hyperbaric Medicine*, 45, 129-156. PILOTS ID: 50280

Pilot evaluation of web-based peer educational campaign about PTSD

Stigma about having a mental health disorder is one of a range of barriers to treatment among individuals with PTSD. Peer-to-peer interventions may reduce stigma and promote readiness for treatment. A team led by investigators at the National Center for PTSD examined Veterans' impressions of [AboutFace](#), a website in which Veterans, clinicians, and family members share personal stories about PTSD and treatment, and whether exposing participants to AboutFace at the beginning of outpatient PTSD treatment affected beliefs about treatment. Twenty Veterans with PTSD explored the AboutFace website and answered questions about how they were using the site. Veterans reported that the website was helpful, that it normalized their experiences, and that they learned about PTSD symptoms, treatment, and effects on family members. In phase two, 49 Veterans were randomized to receive either written information about PTSD or to use AboutFace before starting treatment. Stigma and attitudes about mental health treatment were measured at baseline and two weeks later. Both groups reported more positive attitudes toward mental illness and treatment-seeking. The sample size was too small to detect differences between groups. Larger trials are required to determine if AboutFace can increase Veterans' engagement in evidence-based interventions for PTSD and whether this is due to reduced stigma about PTSD.

Read the article: <https://www.ptsd.va.gov/professional/articles/article-pdf/id50273.pdf>

Hamblen, J. L., Grubaugh, A. L., Davidson, T. M., Borkman, A. L., Bunnell, B. E., & Ruggiero, K. J. (2018). An online peer educational campaign to reduce stigma and improve help seeking in veterans with posttraumatic stress disorder. *Telemedicine and E-Health*. Advance online publication. PILOTS ID: 50273

New measure assesses PTSD-specific psychosocial functioning in Veterans

There are a number of measures available to assess psychosocial functioning in PTSD. These measures work well, but investigators from the National Center for PTSD used input from Veterans to create a new questionnaire, the Inventory of Psychosocial Functioning (IPF) to ensure that their measure comprehensively assesses Veterans' concerns. The IPF is an 80-item self-report measure of PTSD-related psychosocial functional impairment over the past 30 days. The measure includes 7 domains identified through 12 veteran focus groups: romantic relationship with spouse or partner, family relationships, work, friendships and socializing, parenting, education, and self-care. Items are scored on a 7-point Likert scale, with higher scores representing greater impairment in functioning. The IPF was tested in two independent samples of Veterans ($n_s = 285, 384$). The IPF overall score was strongly pos-

itively correlated with other measures of mental health impairment and weakly correlated with measures of physical health impairment. Participants with PTSD had higher levels of impairment on the overall scale and 6 of the 7 domain scales. These findings demonstrate that the IPF is a psychometrically sound measure of PTSD-related psychosocial functional impairment. Additionally, the extensive number of domains allows for a nuanced assessment of an individual's psychosocial functioning that may be useful in both clinical and research contexts, although validation with non-Veteran samples is warranted.

Read the article: <https://www.ptsd.va.gov/professional/articles/article-pdf/id50272.pdf>

Bovin, M. J., Black, S. K., Rodriguez, P., Lunney, C. A., Kleiman, S. E., Weathers, F. W., . . . Marx, B. P. (2018). Development and validation of a measure of PTSD-related psychosocial functional impairment: The Inventory of Psychosocial Functioning. *Psychological Services, 15*, 216–229. PILOTS ID: 50272



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