CLINICIAN'S TRAUMA UPDATE

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TREATMENT

More evidence on MDMA-assisted psychotherapy for PTSD

A new study on psychedelic treatment represents an important step in an effort by the Multidisciplinary Association for Psychedelic Studies to obtain an indication from the Food and Drug Administration (FDA) for MDMA-assisted psychotherapy (MDMA-AT) for PTSD. The study, the second of two that will be used to seek FDA approval, replicated the findings of the prior study in showing benefits of MDMA-AT (see June 2021 *CTU-Online*).

The investigators randomized 104 men and women (12.5% Veterans) with PTSD to receive 3 8-hour sessions of MDMA or inactive placebo along with 12 90-minute psychotherapy sessions to help patients prepare for and integrate the medication sessions. Treatment lasted approximately 3 months, and outcomes were assessed 18 weeks after baseline. The MDMA group had greater improvement than the placebo group in CAPS-5 scores (d = .7) and Sheehan Disability Scale scores (d = .4). The MDMA group (86.5%) also was more likely than the placebo group (69.0%) to have at least a 10-point reduction in CAPS-5 scores. Dropout was low: 1.9% in MDMA and 15.7% in placebo. However, unblinding was high: 94.2% of the MDMA group and 75.0% of the placebo group correctly guessed their treatment assignment. The findings suggest the MDMA-AT is a promising treatment for PTSD, but studies that use active placebo to enhance blinding and have longer-term follow-up are needed in order to fully understand the effects of MDMA-AT on PTSD. Studies in VA patients are also needed in order to generalize findings to VA settings.

Read the article: https://doi.org/10.1038/s41591-023-02565-4

Mitchell, J. M., Ot'alora, G. M., van der Kolk, B., Shannon, S., Bogenschutz, M., Gelfand, Y., . . . Yazar-Klosinski, B. (2023). MDMA-assisted therapy for moderate to severe PTSD: a randomized, placebo-controlled phase 3 trial. *Nature and Medicine, 29,* 2473-2480, PTSDpubs: 1624623

Efficient exposure treatment is not inferior to PE

A previous trial of 5-session Written Exposure Therapy (WET) found it to be noninferior to CPT (see February 2022 *CTU-Online*). A team led by investigators from the National Center for PTSD conducted the first trial of WET comparing it to another exposure-based treatment, PE.

The 178 participants were Veterans (75.3% men) with PTSD who were randomized to either WET or PE. Participants received an average of 6.2 sessions in WET (range: 5-7) versus 12.5 in PE (range: 8-15). PTSD symptoms were measured at baseline and at 10, 20 and 30 weeks using the CAPS-5. While improvement in both treatments was modest (WET = 8.3 points; PE = 10.4 points at 20 weeks), the difference in PTSD severity between WET and PE was below the non-inferiority margin (10 points). Between-group effect sizes at all timepoints were very small (d's = -.02 - 0.02) and gains in WET were maintained several months after treatment. More patients completed an adequate dose of WET (87.5%) than PE (64.4%).

These results suggest that WET is comparable to PE in reducing PTSD symptoms and has lower dropout, although more data is needed on the durability of treatment effects in WET. WET may be a good treatment option for those who are interested in exposure treatment for PTSD but who prefer a shorter treatment.

Read the article: https://www.ptsd.va.gov/professional/articles/article-pdf/id1624550.pdf

Sloan, D. M., Marx, B. P., Acierno, R., Messina, M., Muzzy, W., Gallagher, M. W., . . . Sloan, C. (2023). Written exposure therapy vs prolonged exposure therapy in the treatment of posttraumatic stress disorder: A randomized clinical trial. *JAMA Psychiatry.* Advance online publication. PTSDpubs ID: 1624550

A randomized trial of Interpersonal Psychotherapy for PTSD in Veterans

Interpersonal Psychotherapy (IPT) is an effective treatment for depression. The only prior randomized trial of individual IPT for PTSD found that IPT was not inferior to PE for treating PTSD in civilians (see the April 2015 *CTU-Online*). A team led by investigators from the Providence VA Medical Center has reported the first randomized trial of IPT for Veterans.

The study included 109 veterans (95% men; 64% White; age *M* = 49) with military-related PTSD and significant relationship dysfunction who were randomized to PE or IPT (12 weekly 50-minute sessions). IPT is not trauma-focused and instead focuses on improving social support and relationships. Investigators hypothesized that IPT would be equivalent to PE on CAPS-5 change and superior to PE on changes in interpersonal functioning. Neither hypothesis was supported. Average changes on the CAPS-5 were comparable in both groups—and even appeared a bit larger in IPT—and the IPT group was not statistically equivalent to the PE group. The IPT group did not show better improvements in interpersonal functioning.

Combined with the findings of the civilian trial, the data present an unclear picture about the benefits of IPT for Veterans. The similarity of improvements in PTSD in both groups suggest that IPT may be a good non-trauma-focused treatment option, but more definitive data are needed.

Read the article: https://www.ptsd.va.gov/professional/articles/article-pdf/id1624624.pdf

Shea, M. T., Krupnick, J. L., Sautter, F. J., Mete, M., Green, B. L., Norman, S. B., . . . Eaton, E. (2023). A randomized clinical trial comparing interpersonal psychotherapy with prolonged exposure for the treatment of PTSD in veterans. *Journal of Anxiety Disorders, 99,* Article 102770. PTSDpubs ID: 1624624

N-acetylcysteine is not effective for treating PTSD

Neuroinflammation and oxidative stress have been implicated in the pathophysiology of PTSD. N-acetylcysteine (NAC) may increase the production of glutathione, an antioxidant that may help ameliorate effects of oxidative stress. A pilot trial showed promising effects of NAC combined with cognitive behavioral therapy for Veterans with PTSD and substance use disorders (see October 2016 *CTU-Online*). Now a team led by investigators from the University of Melbourne, Australia has conducted a multisite, randomized, double-blind, placebo-controlled trial of NAC as an adjunct to treatment as usual for the treatment of PTSD.

Participants (*n* = 105) with treatment-resistant PTSD (defined as continuing to have PTSD despite completing a course of trauma-focused psychotherapy or 6 weeks of an SSRI or SNRI) were randomized to receive 12 weeks of NAC versus placebo. Change in CAPS-5 score from baseline to 12 weeks was the primary outcome, with additional assessments at 16 and 64 weeks. There was no difference in the change in mean CAPS-5 score from baseline to endpoint (or secondary endpoints) between the groups. NAC was well tolerated, and there were no differences in serious adverse events between the groups. Based on this well-powered study, NAC does not appear to be a potential treatment for PTSD.

Read the article: https://doi.org/10.1016/j.psychres.2023.115398

Kanaan, R. A., Oliver, G., Dharan, A., Sendi, S., Maier, A., Mohebbi, M., . . . Berk, M. (2023). A multi-centre, double-blind, 12-week, randomized, placebo-controlled trial of adjunctive N-Acetylcysteine for treatment-resistant PTSD. *Psychiatry Research, 327,* Article 115398. PTSDpubs ID: 1623513

Combination buprenorphine-naltrexone is not effective for treating PTSD and comorbid alcohol use disorder

Blocking kappa opioid receptors may be uniquely effective in treating patients with comorbid PTSD and substance use disorder. Buprenorphine is a kappa opioid antagonist but has partial agonism of mu opioid receptors. Naltrexone is a mu opioid antagonist, such that the combination of buprenorphine and naltrexone could achieve selective kappa opioid receptor blockade. A multisite study led by investigators at the Tuscaloosa VA assessed the efficacy of a buprenorphine-naltrexone combination for patients with comorbid PTSD and alcohol use disorder (AUD).

In a randomized, double-blind, placebo-controlled trial, participants with both PTSD and AUD (*n* = 75; 85% Veterans) were randomized to receive 12 weeks of placebo or a combination of naltrexone and buprenorphine at either 2 mg or 8 mg. The primary outcome was defined as both a decrease of ≥10 points on the CAPS-5 *and* a reduction of ≥1 of past month alcohol risk level. The combination buprenorphine-naltrexone was well-tolerated, and there were no differences in adverse events versus placebo. The drug combination showed no benefit over placebo on either the primary outcome or on PTSD or AUD severity separately. These results suggest that combination buprenorphine-naltrexone is not effective for the treatment of PTSD comorbid with AUD. However, other approaches to target this potential mechanism (kappa opioid antagonism) may be worth pursuing.

Read the article: https://doi.org/10.1111/acer.15155

Davis, L. L., Petrakis, I. L., Pilkinton, P. D., Nolen, T., Vandergrift, N., Hirsch, S., . . . Kosten, T. R. (2023). Comorbid alcohol use disorder and post-traumatic stress disorder: A proof-of-concept randomized placebo-controlled trial with buprenorphine and naltrexone combination treatment. *Alcohol: Clinical and Experimental Research, 47,* 1756-1772. PTSDpubs ID: 1623191

Session spacing and clinic policies facilitate consistent engagement in trauma-focused psychotherapies

A team led by Minneapolis VA investigators has reported how dropout and therapy effectiveness were affected by patient characteristics,

therapist effects, and clinic organizational factors such as session spacing and leadership support for CPT and PE implementation.

The study included 180 VA providers across 137 VAs and 1735 Veterans receiving CPT or PE. On average, therapists achieved similar rates of clinically meaningful improvement and recovery but had vastly different rates of treatment completion (27.0-78.8%). The differences between therapists were largely accounted for by session spacing (average number and consistency of days between sessions) and implementation climate (i.e., staff perceptions that clinic policies facilitate effective EBP implementation). These findings suggest that dropout is affected by clinic policies and by therapists, and not only by veteran characteristics. A new meta-analysis also showed that more frequent psychotherapy sessions improved treatment completion (see Take Note, below). Providers are encouraged to offer EBP sessions consistently and as often as the patient can participate in treatment. Clinic leaders may improve engagement in CPT and PE by facilitating more frequent sessions, demonstrating their understanding of EBPs, and reinforcing expectations of EBP delivery to their staff. Future research should explore barriers to increasing the frequency of EBP sessions and how to address these barriers.

Read the article: https://www.ptsd.va.gov/professional/articles/article-pdf/id1624068.pdf

Sayer, N. A., Wiltsey Stirman, S., Rosen, C. S., Kehle-Forbes, S., Spoont, M. R., Eftekhari, A., . . . Nelson, D. B. (2023). The role of therapy delivery and clinic organizational factors in explaining therapist effects for trauma-focused psychotherapies in the Veterans Health Administration. *Journal of Consulting and Clinical Psychology, 91,* 665-679. PTSDpubs ID: 1624068

Attending more PE sessions is linked to improved outcomes

Attending more CPT sessions has been linked to better outcomes, consistent with a dose-response model of treatment (see December 2019 *CTU Online*). National Center for PTSD investigators recently compared this model to the "good-enough level" model, which hypothesizes that patients who improve more quickly will end treatment faster, by performing secondary analysis of a trial comparing PE to a non-trauma-focused psychotherapy (Present-Centered Therapy, PCT).

Participants included 284 female Veterans and service members with PTSD who were randomized to 10 sessions of PE or PCT. Participants self-reported PTSD symptoms on the PCL before treatment and every other session. The investigators examined dropout patterns in each condition and found that PE participants had the greatest dropout risk between Sessions 3 and 4, when imaginal exposures are introduced. PCT participants were at greatest risk before treatment and between Sessions 8 and 9. Although improvement occurred steadily in both treatments, completing more sessions was linked to clinically significant improvement only in PE (*OR* = 1.6).

The findings suggest that the dose-response model applies in PE, like CPT in the prior study, but not in the non-trauma-focused PCT. Helping PE patients remain engaged in treatment, especially after introducing imaginal exposures, seems critical to optimizing their outcomes.

Read the article: https://www.ptsd.va.gov/professional/articles/article-pdf/id1623175.pdf

Thompson-Hollands, J., Lunney, C. A., Sloan, D. M., Wiltsey Stirman, S., & Schnurr, P. P. (2023). Treatment length and symptom improvement in prolonged exposure and present-centered therapy for posttraumatic stress disorder: Comparing dose-response and good-enough level models in two manualized interventions. *Journal of Consulting and Clinical Psychology, 91,* 596-605.PTSDpubs ID: 1623175

ASSESSMENT

Two studies explore differences in scores on PCL-5 and CAPS-5

The CAPS-5 and PCL-5 are the gold-standard instruments for assessing clinician-rated and self-reported symptoms of PTSD, respectively. Both measures are scored on a 0 to 80-point scale, but the CAPS-5 measures severity and the PCL-5 measures distress (how much a symptom bothers a person). Despite high correlations between the scales, there are often discrepancies in total and symptom-level scores between the measures. Two recent studies explored the source of these differences.

Investigators from the STRONG STAR Consortium used data from four PTSD clinical trials with active duty military personnel and Veterans (*N* = 739, 85.3% men) to examine the relationship between scores on the CAPS-5 and PCL-5. The total scores of the two measures were highly correlated (*r* = .8 and *r* = .9 at baseline and posttreatment). All baseline scores were higher on the PCL-5 compared to the CAPS-5, with a total score mean difference of 13.9; differences at posttreatment were smaller (*M* = 7.4). There were notable item-level scoring differences. PTSD symptoms were most commonly rated as 0 (*absent*; 32.0%) or 2 (*moderate/threshold*; 34.2%) on the CAPS-5, whereas 3 (*quite a bit*; 29.7%) or 4 (*extremely*; 22.6%) were the most common ratings on the PCL-5. Differences in the anchors of each scale (e.g., *extreme/incapacitating* on the CAPS-5 vs. *extremely* on the PCL-5) may partially contribute to these discrepancies.

Another study led by investigators from the University of Cincinnati College of Medicine examined discordance between scores on the CAPS-5 and PCL-5 in a cross-sectional sample of 60 trauma-exposed undergraduates (88.3% women, 51.7% had PTSD per CAPS-5). Participants completed the CAPS-5 and PCL-5, then participated in a qualitative interview on why they responded differently across the two measures. The PCL-5 and CAPS-5 symptom-level scores were significantly and positively correlated (*rs* = 0.4-0.8), but mean PCL-5 scores were significantly higher than mean CAPS-5 scores for most items. Qualitative responses indicated reasons for the discrepancies included difficulties understanding and differentiating between symptoms (such as intrusive memories versus flashbacks), having more time to reflect on symptoms during the CAPS-5, responding to the PCL-5 based on general distress, and trauma-related attribution error (e.g.,

attributing pre-existing symptoms to the trauma). Whereas the CAPS-5 allows for the clarification of many of these issues, the PCL-5 does not. Clinicians may find it helpful to preemptively cue patients to the need to identify trauma-related symptoms in the past month when completing the PCL-5.

Both studies report similar findings of acceptable correlations between both measures but found that scores on the PCL-5 are generally rated higher than the CAPS-5. However, because the two measures are assessing separate constructs, perfect concordance between these measures may not be necessary or expected. Rather, clinicians and researchers should weigh the benefits and limitations of each measure (e.g., diagnostic accuracy vs. ease of administration) when considering their needs.

Read the articles:

https://www.ptsd.va.gov/professional/articles/article-pdf/id1622167.pdf

Resick, P. A., Straud, C. L., Wachen, J. S., LoSavio, S. T., Peterson, A. L., McGeary, D. D., . . . Mintz, J. (2023). A comparison of the CAPS-5 and PCL-5 to assess PTSD in military and veteran treatment-seeking samples. *European Journal of Psychotraumatology, 14*(2), Article 2222608. PTSDpubs ID: 1622167

https://www.ptsd.va.gov/professional/articles/article-pdf/id1597580.pdf

Kramer, L. B., Whiteman, S. E., Petri, J. M., Spitzer, E. G., & Weathers, F. W. (2023). Self-rated versus clinician-rated assessment of posttraumatic stress disorder: An evaluation of discrepancies between the PTSD Checklist for DSM-5 and the Clinician-Administered PTSD Scale for DSM-5. *Assessment, 30,* 1590-1605. PTSDpubs ID: 1597580

Take NOTE

Meta-analysis compares PTSD treatments delivered at standard or higher frequency

A meta-analysis of 160 RCTs compared PTSD symptom outcomes and dropout rates between psychotherapies offered at standard frequency (less than 1.5 sessions per week) versus more intensive frequency (more than 1.5 sessions per week). PTSD symptom outcomes did not differ between different frequencies, but dropout was lower for more intensively offered treatments.

Read the article: https://doi.org/10.1016/j.janxdis.2023.102684

Hoppen, T. H., Kip, A., & Morina, N. (2023). Are psychological interventions for adult PTSD more efficacious and acceptable when treatment is delivered in higher frequency? A meta-analysis of randomized controlled trials. *Journal of Anxiety Disorders, 95,* Article 102684. PTSDpubs ID: 1616615

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