CLINICIAN'S TRAUMA UPDATE

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TREATMENT

Recent randomized controlled trials fail to detect effect on primary outcome

Five newly published trials testing interventions to treat (or prevent) PTSD have one thing in common: they all failed to detect a difference between the treatment of interest and comparison condition(s) on the primary outcome. However, a closer look at the results of these studies suggests that some of the tested interventions may still hold promise, despite the negative findings. In the first three trials, positive treatment effects were detected within specific subgroups or on secondary outcomes. In the fourth trial, the interventions being compared (PE and imagery rehearsal) did not differentiate from one another—because both were effective. Only the fifth trial, which tested the medication ganaxolone, failed to find any treatment or moderation effect.

In the first trial, investigators at the University of Pennsylvania tested the hypothesis that combining trauma-focused psychotherapy with smoking cessation treatment would help people with PTSD quit smoking. The study enrolled 142 adults with nicotine dependence and PTSD. All participants received 2mg/day of varenicline (a first-line medication for nicotine dependence) and smoking cessation counseling. Half the sample (n = 72) was randomly assigned to also receive PE. As expected, those who received PE showed greater improvement in PTSD and depression. However, there were no differences between the two groups on smoking outcomes. Follow-up analyses revealed that PE resulted in superior smoking outcomes for participants who started treatment with more severe PTSD. Participants with higher baseline PTSD also made the greatest improvements in depression, and these depression gains contributed to reductions in smoking. Overall, results suggest that the effect of concurrent PE and smoking cessation treatment on smoking behavior depends on the patient's baseline symptoms – but there is clear evidence that regardless of initial severity, PE can help people with PTSD and nicotine dependence find relief from PTSD and depressive symptoms.

Read the article: https://doi.org/10.1037/ccp0000213

Led by investigators at the University of Washington, a second trial tested whether methylene blue, a drug shown to improve retention of extinction learning, enhanced response to a brief imaginal exposure intervention. Participants were 42 patients with chronic *DSM-IV* PTSD who were randomly assigned to 5 daily imaginal exposure sessions plus either methylene blue (n = 15) or placebo (n = 16), or to a waitlist that later received standard PE (n = 11). Both treatment groups showed greater improvement in PTSD than waitlist at one month follow-up. At 3-month follow-up, after the waitlist had received PE, the three groups did not differ significantly on PTSD outcomes. Methylene blue did improve PTSD outcomes for participants with better working memory, however. In addition, the methylene blue group showed a unique change trajectory; whereas placebo participants demonstrated linear change, methylene blue participants had slow initial gains that accelerated over treatment. The authors suggest that methylene blue may alter the course of treatment by increasing fear expression in earlier sessions—though in the end, methylene blue did not enahnce posttreatment and follow-up outcomes.

Read the article: https://doi.org/10.4088/JCP.16m10936

A third trial examined whether the SSRI escitalopram can prevent the onset of PTSD. Investigators at Chaim Sheba Medical Center in Israel recruited participants from a sample of over 25,000 patients referred to an emergency department following a traumatic event. Participants were randomized within 1 month of the event to receive 20mg daily escitalopram (n = 176) or placebo (n = 177). Only those who received treatment for at least 12 weeks and were available for follow-up at 56 weeks post-trauma were included in analyses (escitalopram: n = 102; placebo: n = 96). Escitalopram did not prevent the onset of PTSD, though it was associated with decreased PTSD symptom severity (d = .20) and improved sleep quality (d = .39) relative to placebo. These effects were even stronger in a subgroup of participants who experienced intentional (vs non-intentional) trauma (d = .58). Although the results did not support escitalopram as a preventative intervention overall, the fact that the analyses included only those participants who completed treatment and follow-up (56% of the sample) makes it difficult to interpret the results.

Read the article: https://doi.org/10.4088/JCP.16m10730

A fourth trial led by researchers from University of Oslo examined how PE compares with imagery rehearsal (IR) for reducing the non-fear emotions that are prevalent in PTSD (e.g., guilt, anger, shame). Sixty-five patients with PTSD (38 women, 27 men) enrolled in a community residential program were randomized to IR or PE delivered in 10 weekly 90-120 minute sessions. The IR condition included imagery-based cognitive restructuring in addition to in vivo and imaginal exposures. Because PE is often conceptualized as targeting fear-based emotions, it was hypothesized that patients with higher pretreatment non-fear emotion levels would respond better to IR and that IR would more effectively reduce non-fear emotions. However, the treatments were similarly effective at reducing PTSD symptoms (both had large pre-post effect sizes; g = .90 for IR and 1.24 for PE) and non-fear emotions (g's = .36-.72). In addition, pretreatment non-fear emotions did not predict response to either treatment. These findings refute the assumption that non-fear emotions are associated with poor response to PE and suggest that PE can successfully reduce a variety of distressing emotions.

Read the article: https://doi.org/10.1016/j.brat.2017.06.007

In the fifth trial, investigators at the National Center for PTSD and Durham VA Medical Center were the first to test whether ganaxolone, a steroid shown to reduce anxiety in animal models, improves PTSD among Veteran and non-Veteran outpatients. The 8-site study included a 6-week, randomized, double-blind phase (ganaxolone: n = 59; placebo: n = 53) followed by a 6-week open-label phase during which all participants received ganaxolone. Participants had been exposed to trauma in the past 6 months and met criteria for *DSM-IV* PTSD. For the first 6 weeks of ganaxolone, dosage increased every 2 weeks, with most participants tolerating the maximum dose (1200 mg/day). On average, PTSD symptoms improved regardless of medication group. Analysis of blood plasma revealed that ganaxolone levels were lower than expected in most participants, possibly due to non-adherence or poor absorption. However, even when comparing adequately-dosed ganaxolone participants to control participants, there were no differences in outcomes except for more adverse events in the ganaxolone group.

Read the article: https://www.ptsd.va.gov/professional/articles/article-pdf/id48368.pdf

Take NOTE

Empirical review examines Prolonged Exposure mechanisms of change

A recent review by investigators at Case Western Reserve University evaluated the evidence behind a variety of proposed mechanisms (and mediators) of PE and identified those with the strongest research support.

Read the article: https://doi.org/10.1016/j.cpr.2017.07.003

Cooper, A. A., Clifton, E. G., & Feeny, N. C. (2017). An empirical review of potential mediators and mechanisms of prolonged exposure therapy. *Clinical Psychology Review, 56*, 106–121. PILOTS ID: 48568

Systematic review of the benefits and harms of marijuana for PTSD

Based on their review of published studies evaluating the effects of marijuana on PTSD, investigators from the VA Portland Health Care System concluded that the evidence was limited and inconclusive. The authors highlight the need for future randomized controlled trials in this area.

Read the article: https://doi.org/10.7326/M17-0477

O'Neil, M. E., Nugent, S. M., Morasco, B. J., Freeman, M., Low, A., Kondo, K., . . . Kansagara, D. (2017). Benefits and harms of plant-based cannabis for posttraumatic stress disorder: A systematic review. *Annals of Internal Medicine.* Advance online publication. PILOTS ID: 48681

When interpreting results from these trials, is important to remember that null findings do not necessarily mean that a treatment is ineffective. Even the ganaxolone trial should not be interpreted as definitive proof that ganaxolone is ineffective. Only trials designed specifically to test the hypothesis that two interventions do not differ—equivalence or non-inferiority designs—can conclusively be interpreted as indicating no difference. The bottom line: to have confidence in the results, trials need to be well-powered and rigorously designed.

Foa, E. B., Asnaani, A., Rosenfield, D., Zandberg, L. J., Gariti, P., & Imms, P. (2017). Concurrent varenicline and prolonged exposure for patients with nicotine dependence and PTSD: A randomized controlled trial. *Journal of Consulting and Clinical Psychology.* Advance online publication. PILOTS ID: 48569

Langkaas, T. F., Hoffart, A., Øktedalen, T., Ulvenes, P. G., Hembree, E. A., & Smucker, M. (2017). Exposure and non-fear emotions: A randomized controlled study of exposure-based and rescripting-based imagery in PTSD treatment. *Behaviour Research and Therapy, 97*, 33–42. PILOTS ID: 48570

Rasmusson, A. M., Marx, C. E., Jain, S., Farfel, G. M., Tsai, J., Sun, X., . . . Stein, M. B. (2017). A randomized controlled trial of ganaxolone in posttraumatic stress disorder. *Psychopharmacology.* Advance online publication. PILOTS ID: 48368

Zoellner, L. A., Telch, M., Foa, E. B., Farach, F. J., McLean, C. P., Gallop, R., ... & Gonzalez-Lima, F. (2017). Enhancing extinction learning in posttraumatic stress disorder with brief daily imaginal exposure and methylene blue: A randomized controlled trial. *Journal of Clinical Psychiatry.* Advance online publication. PILOTS ID: 48582

Zohar, J., Fostick, L., Juven-Wetzler, A., Kaplan, Z., Shalev, H., Schreiber, G., ... & Suliman, S. (2017). Secondary prevention of chronic PTSD by early and short-term administration of escitalopram: A prospective randomized, placebo-controlled, double-blind trial. *Journal of Clinical Psychiatry.* Advance online publication. PILOTS ID: 48583

Study examines whether patients with more severe PTSD can benefit from online interventions

As web-based interventions for PTSD and related disorders gain both popularity and research support, it is important to better understand which patients can benefit from this approach to treatment. Recently, investigators from the National Center for PTSD examined whether patients' PTSD severity or prior combat exposure impacts the effectiveness of VetChange, an online intervention targeting alcohol misuse. The investigators analyzed data from 523 Veterans who participated in VetChange as part of a larger randomized trial (see the August 2013 *CTU-Online*). All participants reported problematic drinking behavior and 65% had probable PTSD (PCL-5 score ≥ 33). At the start of treatment, greater PTSD severity and prior combat exposure were both linked to heavier alcohol use. Nonetheless, participants with high levels of PTSD and combat exposure still benefitted from VetChange, deriving comparable benefit—and in some cases, greater benefit—on drinking-related outcomes relative to participants with less severe PTSD and combat exposure. Although there may be other important patient characteristics that predict response to web-based treatment, these results are encouraging in that they suggest the benefits of this particular online intervention extend to those with trauma exposure and high levels of PTSD symptoms.

Read the article: https://www.ptsd.va.gov/professional/articles/article-pdf/id48173.pdf

Brief, D. J., Solhan, M., Rybin, D., Enggasser, J. L., Rubin, A., Roy, M., . . . Keane, T. M. (2017). Web-based alcohol intervention for Veterans: PTSD, combat exposure, and alcohol outcomes. *Psychological Trauma: Theory, Research, Practice, and Policy.* Advance online publication. PILOTS ID: 48173

MILITARY SEXUAL TRAUMA

MST associated with poor mental health, military career outcomes

Much of the research on the impact of MST among active duty servicemembers has relied on Veterans' retrospective reports, often many years after the event(s). A study led by investigators at the Harvard School of Medicine sought to address these limitations by examining Army administrative records containing information with closer proximity to the MST. Investigators reviewed records from 153,250 active duty women included in the Army Study to Assess Risk and Resilience in Servicemembers. Of these, 4,238 had an administrative record of MST and were matched to non-sexually victimized controls with similar risk characteristics, including psychiatric disorders, crime victimization/perpetration, young age, low rank, and short time in service. In the 12 months following MST (or a comparable date for controls), women with recorded MST had significantly greater likelihood of subsequent mental health treatment (*OR* = 2.5 to 7.7 depending on treatment type), suicide attempt (*OR* = 3.0), career demotion (*OR* = 2.1), and attrition (*OR* = 1.2) relative to controls. Victimization was related to suicidality for those with no treatment history during the evaluation period (OR = 6.2), but not those with previous treatment (OR = 1.3), a disparity emphasizing the critical need for psychiatric care following MST. These results enhance the validity of retrospectively-reported findings on the detrimental impact of MST on mental health and military outcomes, and importantly, highlight the magnitude of problems within the first year following trauma.

Read the article: https://www.ptsd.va.gov/professional/articles/article-pdf/id47686.pdf

Rosellini, A. J., Street, A. E., Ursano, R. J., Chiu, W. T., Heeringa, S. G., Monahan, J., . . . Kessler, R. C. (2017). Sexual assault victimization and mental health treatment, suicide attempts, and career outcomes among women in the US Army. *American Journal of Public Health, 107*, 732–739. PILOTS ID: 47686

Compared with *DSM* definitions, ICD-11 criteria may underestimate PTSD prevalence

The proposed criteria for PTSD in the forthcoming ICD-11 look quite different from *DSM-5* criteria. The number of ICD-11 symptoms has been reduced to 6, compared with 17 in *DSM-IV* and 20 in *DSM-5*, in an effort to improve diagnostic accuracy and reduce comorbidities. But do these distinct conceptualizations result in comparable diagnostic prevalence? Investigators from the University of North Carolina Greensboro and the National Center for PTSD examined this question. Two nationally representative Veteran samples completed a web survey assessing PTSD symptoms according to *DSM-IV* (PCL-S; n = 3,517) and *DSM-5* (PCL-5; n = 1,484). PTSD diagnoses were obtained using the criteria for *DSM-IV*, *DSM-5*, and ICD-11. Comorbidities (depression, substance use disorders, and social phobia) were assessed using the MINI Neuropsychiatric Interview adapted for self-report. Compared to ICD-11, significantly more Veterans met *DSM-IV* (6.9% vs. 5.0% lifetime and 4.0% vs. 2.7% past month, $ps < .001$) or *DSM-5* (6.8% vs. 5.7% lifetime, $p = .002$ and 3.9% vs. 3.1% past month, $p = .008$) criteria. Furthermore, 22%-36% of those who met *DSM-IV* or *DSM-5* criteria did not meet under ICD-11. Conversely, only 2.4%-7.1% of those who met ICD-11 criteria did not meet for one of the *DSM* criteria. Notably, there were no significant differences in comorbidities between *DSM* and ICD-11. These more stringent ICD-11 criteria may have implications affecting receipt of benefits and treatment among Veterans who would have met criteria under *DSM*.

Read the article: https://www.ptsd.va.gov/professional/articles/article-pdf/id48567.pdf

Wisco, B. E., Marx, B. P., Miller, M. W., Wolf, E. J., Krystal, J. H., Southwick, S. M., & Pietrzak, R. H. (2017). A comparison of ICD-11 and *DSM* criteria for posttraumatic stress disorder in two national samples of U.S. military Veterans. *Journal of Affective Disorders, 223*, 17–19. PILOTS ID: 48567

Veterans Health Administration

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