CLINICIAN'S TRAUMA UPDATE

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TREATMENT

Effects of EBPs for PTSD in routine VA care

A team led by investigators at the San Francisco VA Health Care System recently reported on the outcomes of Veterans who received PE or CPT in VHA between 2007 and 2017. The investigators reviewed electronic health records from Veterans with PTSD who initiated mental health treatment (N = 265,566) during this interval. They identified Veterans who initiated CPT (n = 636) or PE (n = 272) and had PCL scores available at baseline and 24-week follow-up. These groups were matched with Veterans who did not receive an EBP for PTSD but had similar PTSD severity, demographic, and comorbidity characteristics. Compared to those who did not receive an EBP, Veterans who engaged in ≥8 sessions of CPT showed a 6.4-point greater improvement on the PCL. Veterans who received ≥8 PE sessions showed a 9.7-point improvement greater improvement than non-EBP patients. Amount of improvement did not differ between PE and CPT (8.3 v. 7.0 points) among those who received ≥8 sessions of either treatment. These results suggest that improvements in routine care are more modest than in randomized controlled trials, but the comparison should be made with caution given factors such as the lack of measurement standardization in routine care. The importance of the study is that it demonstrates benefits of VA's investment in evidence-based psychotherapy for Veterans with PTSD.

Read the article: https://www.ptsd.va.gov/professional/articles/article-pdf/id1569506.pdf

Maguen, S., Madden, E., Holder, N., Li, Y., Seal, K. H., Neylan, T. C., . . . Shiner, B. (2021). Effectiveness and comparative effectiveness of evidence-based psychotherapies for posttraumatic stress disorder in clinical practice. *Psychological Medicine.* Advance online publication. PTSDpubs ID: 1565906

Deep transcranial magnetic stimulation following brief exposure is ineffective for PTSD

Increased activity in the medial prefrontal cortex (mPFC) may contribute to extinction of fear memories. Deep transcranial magnetic stimulation (dTMS) is a form of TMS that can broadly stimulate the mPFC. Based on an earlier pilot study, Brainsway, Inc. sponsored a multicenter, double-blind, sham-controlled trial of dTMS of the mPFC (to enhance extinction) combined with a brief exposure procedure. Participants with PTSD (n = 125) were randomized to receive active versus sham dTMS combined with Script Driven Imagery (SDI) based on a personalized script of a traumatic event. Three treatment sessions were delivered per week for four weeks. At each session, the SDI was performed, followed by active or sham dTMS. The primary outcome was change in CAPS-5 score from baseline to 1 week after the last treatment. The study was stopped after a planned interim analysis showed that the sham group had a significantly greater change in CAPS-5 score versus the active group (21-point vs. 16-point decrease). It is possible this resulted from using a different type of dTMS coil compared to the pilot study that may have affected brain regions involved in reconsolidation versus extinction. Additionally, dTMS might have been more effective delivered before the SDI; a previous study showed efficacy for TMS provided prior to weekly sessions of CPT. Combining TMS with behavioral interventions for PTSD is worth continued study, although these results do not support the use of dTMS following brief exposure.

Read the article: https://doi.org/10.1016/j.biopsych.2021.04.019

Isserles, M., Tendler, A., Roth, Y., Bystritsky, A., Blumberger, D. M., Ward, H., . . . Ressler, K. J. (2021). Deep transcranial magnetic stimulation combined with brief exposure for post-traumatic stress disorder – A prospective multisite randomized trial. *Biological Psychiatry.* Advance online publication. PTSDpubs ID: 1572922

Predicting response to PTSD treatment

Some people respond better to evidence-based treatments for PTSD than others. A series of new studies examined clinical and demographic factors that predicted response to different psychotherapies and medications for PTSD.

A team led by investigators at Flinders University in Australia explored whether clinical information that is typically available when starting CPT could predict likelihood of improvement. The investigators combined data from 4 RCTs of CPT among women who had experienced interpersonal trauma ($N = 179$). They used machine learning to examine patient-level demographic and clinical characteristics and session-level symptom information to predict treatment outcomes. The authors found four trajectories of response: clear responders (52.5%, $n = 94$), delayed responders (29.1%, $n = 52$), partial responders (9.5%, $n = 17$), and non-responders (8.9%, $n = 16$). Clear responders could be reliably detected at session 6. However delayed responders and non-responders could not be differentiated early in treatment—specifically, not until session 10. Notably, variables associated with clinical complexity like comorbidities and extent of past trauma were not predictive of outcome.

Two studies investigated the amount of time since trauma exposure, which is typically thought to be associated with poorer treatment outcome. In the first study, investigators examined predictors of response to PE, sertraline and their combination using data from the PROGrESS trial in which 223 Veterans with PTSD were randomized to PE plus placebo, sertraline plus enhanced medication management (as a psychotherapy control condition), or PE plus sertraline. The original study found improvements in PTSD in all three groups but no differences among them (see the December 2018 *CTU-Online*). In this analysis, the investigators examined the effects of time since trauma, pain, alcohol use, and baseline symptoms and demographic characteristics on PTSD symptoms measured with the CAPS among the 196 Veterans with valid time since trauma data. Across conditions, more time since trauma (range 0.5 to 14.9 years) predicted greater reduction in PTSD symptoms; more pain (but not alcohol use) predicted less improvement in PTSD. Hispanic Veterans improved more than non-Hispanic Veterans. No other predictors emerged. Further analysis of the treatment conditions revealed that time since trauma most strongly predicted outcome in the PE plus sertraline group.

Investigators at the University of Copenhagen teamed up with the Otsuka Pharmaceutical company to examine predictors of response to paroxetine and sertraline, the SSRIs that are FDA-approved for treatment of PTSD. The sample was composed of 390 patients whose trauma occurred within the past 15 years and who did not have co-occurring depression, anxiety, or substance use disorder. Patients received open-label sertraline or paroxetine during the prospective phase of a trial to test a new medication for SSRI non-responders. They also received a double-blinded placebo in preparation for the second phase in which the new medication would be added. Overall, patients improved (baseline CAPS for *DSM-IV* $M = 86.3$, week 12 CAPS $M = 44.6$), with no difference between paroxetine and sertraline. There were three classes of responders: fast responders (16.2%, $n = 63$), responders with low baseline symptom severity (67%, $n = 260$) and responders with higher baseline symptoms (16.8%, $n = 65$). Patients with less time since trauma were more likely to belong to the responders with low symptom severity class, whereas more time since trauma increased the likelihood of membership in the fast responders group. They also found that women, patients who experienced childhood sexual trauma, and patients who identified sexual assault as their index trauma had more improvement in PTSD.

Lastly, investigators at the VA San Diego Healthcare System tested whether sleep quality predicted response to trauma-focused psychotherapy among 100 Iraq/Afghanistan Veterans with PTSD and history of mild to moderate TBI. Veterans had been randomized to either CPT or CPT combined with Cognitive Symptom Management and Rehabilitation Therapy—SMART-CPT. Poorer sleep quality was associated with less reduction in PTSD symptoms and cognitive concerns. Additionally, self-reported sleep quality did not improve in either treatment. The investigators suggested that targeting sleep before trauma-focused therapy could increase the likelihood of a good outcome.

Taken together, these studies illustrate the challenges of predicting who will and will not improve during PTSD treatment. Importantly, they suggest that some patient characteristics often assumed to predict poor outcome, such as alcohol use and comorbid psychiatric conditions, are not associated with less improvement, and some, like time since trauma, are associated with greater or faster improvement—at least among patients whose trauma occurred within the past 15 years. But, some difficulties like poor sleep and pain do predict poorer outcome. More research on predictors of treatment outcome like these studies may lead to a better understanding of which treatments work best for which patients.

Read the articles:

https://www.ptsd.va.gov/professional/articles/article-pdf/id1572921.pdf

Nixon, R. D. V., King, M. W., Smith, B. N., Gradus, J. L., Resick, P. A., & Galovski, T. E. (2021). Predicting response to cognitive processing therapy for PTSD: A machine-learning approach. *Behaviour Research and Therapy, 144,* Article 103920. PTSDpubs ID: 1572921

https://doi.org/10.1016/j.psychres.2021.113964

Nøhr, A. K., Eriksson, H., Hobart, M., Moltke, I., Buller, R., Albrechtsen, A., & Lindgreen, S. (2021). Predictors and trajectories of treatment response to SSRIs in patients suffering from PTSD. *Psychiatry Research, 301,* Article 113964. PTSDpubs ID: 1570071

https://www.ptsd.va.gov/professional/articles/article-pdf/id1571521.pdf

Rauch, S. A. M., Kim, H. M., Lederman, S., Sullivan, G., Acierno, R., Tuerk, P. W., . . . Baker, A. W. (2021). Predictors of response to prolonged exposure, sertraline, and their combination for the treatment of military PTSD. *Journal of Clinical Psychiatry, 82,* Article 20m13752. PTSDpubs ID: 1571521

https://www.ptsd.va.gov/professional/articles/article-pdf/id1571000.pdf

Sullan, M. J., Crocker, L. D., Thomas, K. R., Orff, H. J., Davey, D. K., Jurick, S. M., . . . Jak, A. J. (2021). Baseline sleep quality moderates symptom improvement in veterans with comorbid PTSD and TBI receiving trauma-focused treatment. *Behaviour Research and Therapy, 143,* Article 103892. PTSDpubs ID: 1571000

Disappointing findings on cyclobenzaprine for military-related PTSD

Cyclobenzaprine is FDA-approved for the adjunctive treatment of muscle spasms in musculoskeletal conditions. This medication also impacts several neurotransmitter systems implicated in PTSD. Tonix Pharmaceuticals sponsored a multicenter, double-blind, placebo-controlled trial assessing the efficacy of a sublingual formulation of cyclobenzaprine in military-related PTSD.

Participants were randomized in a 2:1:2 fashion to 12 weeks of 2.8 mg cyclobenzaprine (n = 101), 5.6 mg cyclobenzaprine (n = 50) or placebo (n = 94). CAPS-5 was performed at baseline then after 2, 4, 6, 8 and 12 weeks of treatment. The primary outcome was change in CAPS-5 score from baseline to week 12 in a modified intent-to-treat (mITT) sample, defined as the 225 participants who had at least one post-baseline CAPS-5 assessment; 77.5% (n = 179) completed 12 weeks of treatment. There was no difference in CAPS-5 change from baseline to week 12 with 2.8 mg cyclobenzaprine compared to placebo. The corresponding change with 5.6 mg cyclobenzaprine was 4.5 points greater than placebo (effect size = 0.4). Although this difference verged on statistical significance, it has uncertain clinical significance. With analysis restricted to participants with greater PTSD severity (CAPS-5 ≥ 33), the effect size increased to 0.5. Cyclobenzaprine was safe, although adverse events were greater in the two active drug groups compared with placebo. The most common adverse event was oral hypoaesthesia (numbing). Overall, these data support the safety of cyclobenzaprine but do not provide strong evidence for efficacy in PTSD.

Read the article: https://www.ptsd.va.gov/professional/articles/article-pdf/id1569175.pdf

Sullivan, G. M., Gendreau, R. M., Gendreau, J., Peters, P., Peters, A., Engels, J., . . . Lederman, S. (2021). Randomized clinical trial of bedtime sublingual cyclobenzaprine (TNX-102 SL) in military-related PTSD and the role of sleep quality in treatment response. *Psychiatry Research, 301*, Article 113974. PTSDpubs ID: 1569175

Investigating providers' role in CPT, PE retention

Efforts to understand engagement in EBPs for PTSD have largely focused on patient-level characteristics (see the April 2019 *CTU Online*), but differences among therapists may also be important. A new study by investigators from the Minneapolis VA Health Care System sought to quantify the effect therapists play in EBP engagement and retention. The investigators examined data from 2,709 therapists who delivered CPT or PE to 18,461 Veterans across 140 VHA facilities in 2017. The primary outcomes included early dropout (<3 sessions) and adequate dose (≥8 sessions). The investigators used multi-level modeling to calculate how much variability in these outcomes could be attributed to the therapists versus the facilities. For CPT, differences between therapists accounted for 10.9% of the variability in early dropout and 8.9% for adequate dose. Therapist effects accounted for 6.0% of early dropout and 8.8% of adequate dose for PE. Facility-level differences had less impact, with variability in early dropout and adequate dose ranging from 1.1% (early dropout in CPT) to 3.1% (adequate dose of PE). Therapist gender, discipline, and EBP workload did not explain the variability among therapists. Understanding which therapist-level factors account for their effects (e.g., adherence), as well as the role of clinic-level factors (e.g., focus on general mental health or PTSD), represent key next steps. This study demonstrates the importance of looking beyond the patient to understand treatment engagement.

Read the article: https://www.ptsd.va.gov/professional/articles/article-pdf/id1570610.pdf

Sayer, N. A., Wiltsey-Stirman, S., Rosen, C. S., Bernardy, N. C., Spoont, M. R., Kehle-Forbes, S. M., . . . Nelson, D. B. (2021). Investigation of therapist effects on patient engagement in evidence-based psychotherapies for posttraumatic stress disorder in the Veterans Health Administration. *Journal of Traumatic Stress*. Advance online publication. PTSDpubs ID: 1570610

ASSESSMENT

Computerized adaptive diagnosis and testing can quickly screen for PTSD

Computerized adaptive testing is an automated technique for administering assessments in which questions are chosen by an algorithm that uses a particular patient's previous responses to select each subsequent question. This individualized approach can reduce the number of items needed for assessment. Investigators at the VA Rocky Mountain MIRECC tested this assessment approach in PTSD. A sample of 713 Veterans completed the PCL-5, Criterion A trauma assessment and a 211-item PTSD symptom questionnaire with items drawn from several PTSD assessments. A subset of 304 Veterans (those with a Criterion A event who endorsed at least one PTSD symptom) also completed the CAPS-5. Using advanced statistical methods, the investigators found that no more than 6 items from the item bank were needed to have diagnostic screening accuracy comparable to the CAPS-5 and ten items provided valid severity ratings equivalent to the PCL-5. The computerized adaptive approach may be a promising strategy for efficiently assessing PTSD, particularly in clinical settings in which screening for PTSD is appropriate.

Read the article: https://doi.org/10.1001/jamanetworkopen.2021.15707

Brenner, L. A., Betthauser, L. M., Penzenik, M., Germain, A., Li, J. J., Chattopadhyay, I., . . . Gibbons, R. D. (2021). Development and validation of computerized adaptive assessment tools for the measurement of posttraumatic stress disorder among US military veterans. *JAMA Network Open, 4,* Article e2115707. PTSDpubs ID: 1572666

Take NOTE

Long-term effects of psychotherapies for PTSD

In a systematic review and meta-analysis, a team led by investigators at Freie Universität Berlin in Germany examined long-term outcomes (i.e., 12 month follow-up) of psychological interventions for PTSD.

Read the article: https://doi.org/10.1017/s003329172100163x

Weber, M., Schumacher, S., Hannig, W., Barth, J., Lotzin, A., Schäfer, I., . . . Kleim, B. (2021). Long-term outcomes of psychological treatment for posttraumatic stress disorder: A systematic review and meta-analysis. *Psychological Medicine, 51*, 1420-1430. PTSDpubs ID: 1572385

Trauma-focused treatment during ongoing threat

Investigators at Ryerson University conducted a systematic review of studies of trauma-focused CBT for individuals experiencing ongoing threat of trauma re-exposure, such as those experiencing war-related violence, community violence and intimate partner violence.

Read the article: https://doi.org/10.1016/j.cpr.2021.102049

Ennis, N., Sijercic, I., & Monson, C. M. (2021). Trauma-focused cognitive-behavioral therapies for posttraumatic stress disorder under ongoing threat: A systematic review. *Clinical Psychology Review, 88,* Article 102049. PTSDpubs ID: 1571494

Study quality and PTSD treatment outcomes

Investigators at the University of Münster in Germany conducted a meta-analysis of the association between study quality and efficacy of psychological treatments for PTSD.

Read the article: https://doi.org/10.1017/s0033291721001641

Morina, N., Hoppen, T. H., & Kip, A. (2021). Study quality and efficacy of psychological interventions for posttraumatic stress disorder: A meta-analysis of randomized controlled trials. *Psychological Medicine, 51*, 1260-1270. PTSDpubs ID: 1570038

Effect of comorbid psychiatric conditions on response to psychotherapy for PTSD

In a new systematic review and meta-analysis, investigators at the Amsterdam University Medical Center examined the impact of comorbid personality disorders on outcomes in psychotherapy for PTSD.

Read the article: https://doi.org/10.1080/20008198.2021.1929753

Snoek, A., Nederstigt, J., Ciharova, M., Sijbrandij, M., Lok, A., Cuijpers, P., & Thomaes, K. (2021). Impact of comorbid personality disorders on psychotherapy for posttraumatic stress disorder: Systematic review and meta-analysis. *European Journal of Psychotraumatology, 12,* Article 1929753. PTSDpubs ID: 1572243

A team led by investigators at the Ralph H. Johnson VAMC and Medical University of South Carolina carried out a meta-analysis of 14 clinical trials of psychotherapy for PTSD among individuals with co-occurring severe mental illness (i.e., schizophrenia, bipolar disorder, and major depressive disorder).

Read the article: https://doi.org/10.4088/JCP.20r13584

Grubaugh, A. L., Brown, W. J., Wojtalik, J. A., Myers, U. S., & Eack, S. M. (2021). Meta-Analysis of the treatment of posttraumatic stress disorder in adults with comorbid severe mental illness. *Journal of Clinical Psychiatry, 82,* Article 20r13584. PTSDpubs ID: 1570655

Veterans Health Administration

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