



NEW FINDINGS FROM CLINICAL TRIALS IN THE TREATMENT OF POST-TRAUMATIC STRESS DISORDER

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L. DAVIS DISCLOSURES

Past 3 years as of May 27, 2026

- **Consulting Fees**
 - Otsuka
 - Boehringer Ingelheim
 - Signant Health
- **Research Funding**
 - VA
 - PCORI
 - DoD
 - Fisher Wallace
 - Social Finance
 - Alkermes

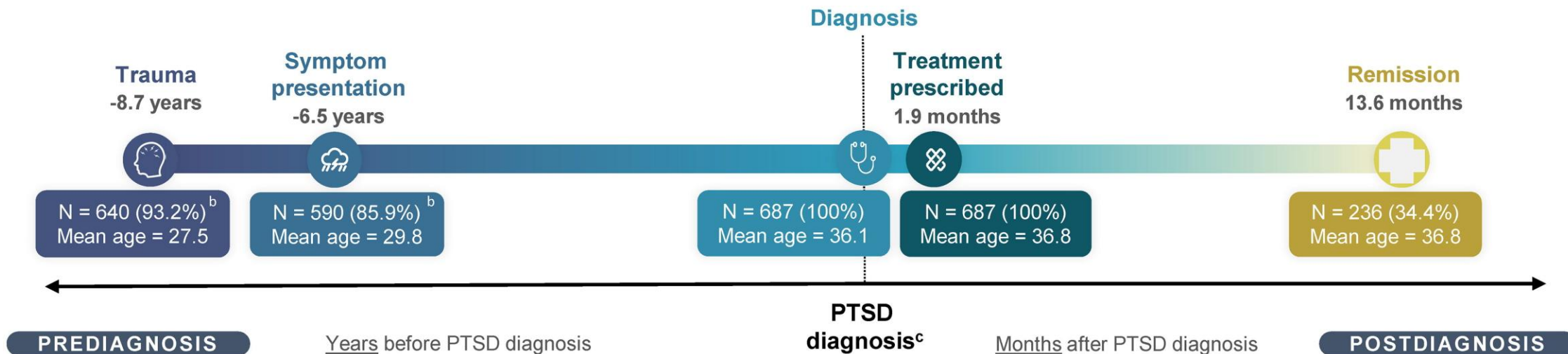


ONLY TWO MEDICATIONS ARE FDA-APPROVED FOR PTSD

- Sertraline (Zoloft)
- Paroxetine (Paxil)
- All other drugs discussed in this update are either off-label use or experimental research use under an IND

DELAY TO DIAGNOSIS AND TREATMENT FOR PTSD

273 psychiatrists contributed data on 687 patients with PTSD



Prior to PTSD diagnosis:

- Most patients receive pharmacotherapy (89%) or psychotherapy (50%)
- ~50% of patients receive SSRIs as first-line treatment, with a quarter receiving combination therapy
- ~25% of patients receive an atypical antipsychotic medication in combination or as monotherapy

Following PTSD diagnosis:

- The average time to first atypical antipsychotic prescription is ~6 mo
- 59% of patients with PTSD receive ≥2 distinct PTSD-related agents
- 79% have a treatment change during the first 2 yr
- 66% do not achieve remission within 2 yr of diagnosis

POSTTRAUMATIC STRESS DISORDER: HETEROGENEITY AND POLYPHARMACY

- At least 6 of 20 symptoms across reexperiencing, avoidance, alternations in mood and cognition, and hyperarousal categories.
- Mathematically = **636,120** potential clinical presentations of PTSD
- Of 3,511 participants (Army STARRS) positive for PTSD on self report (PCL-5), there were 2181 different patterns of symptoms; 89% occurred only once, i.e., **55% who met criteria for PTSD had a unique pattern of symptoms**
- High prevalence of psychotropic polypharmacy (36%, 95 % CI: 23-49 %) among active-duty military personnel and veterans; **veterans with PTSD had a higher prevalence of polypharmacy (48%) than those without PTSD (22%).**

Galatzer-Levy IR, Bryant RA. 636,120 ways to have posttraumatic stress disorder: the relative merits of categorical and dimensional approaches to posttraumatic stress. *Perspect Psychol Sci.* 2013;8(6):651-662.

Bryant RA, Galatzer-Levy I, Hadzi-Pavlovic D. The Heterogeneity of Posttraumatic Stress Disorder in DSM-5. *JAMA Psychiatry.* 2023;80(2):189-191. doi:10.1001/jamapsychiatry.2022.4092

Raut S, Mellor R, Meurk C, et al. Prevalence and factors associated with polypharmacy in military and veteran populations: A systematic review and meta-analysis. *J Affect Disord.* 2025;369:411-420. doi:10.1016/j.jad.2024.10.025

CAN WE PREVENT THE ONSET OF PTSD AFTER ACUTE TRAUMA?

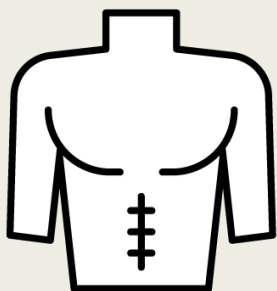
Perhaps by manipulating the HPA and noradrenergic cascade of neuroinflammatory stress hormones.
Dexmedetomidine - a highly selective alpha-2 receptor agonist - inhibits the release of norepinephrine.

Used as an IV sedative analgesic and pain treatment.

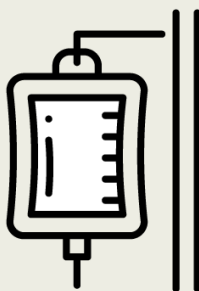
Now available as sublingual film (Igalmi) for agitation associated with schizophrenia or bipolar

RCT: Effect of Dexmedetomidine on Posttraumatic Stress Disorder in Patients Undergoing Emergency Trauma Surgery

Highly selective alpha-2 receptor agonist – analgesic and pain – inhibits release of NE

POPULATION**179 Men, 131 Women**

Adults aged 18-60 y undergoing emergency trauma surgery

Mean (SD) age, 40.2 (10.3) y**INTERVENTION****310** Patients randomized and analyzed**154 Normal saline group (placebo)**

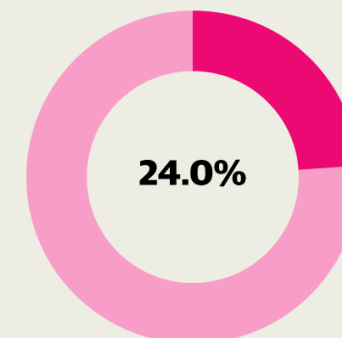
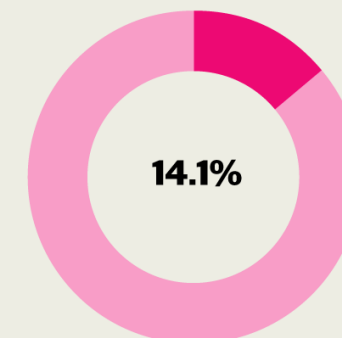
Maintained at a rate of 0.1 µg/kg/h during surgery and after surgery (9 PM to 7 AM on days 1-3)

**156 Dexmedetomidine group**

Maintained at a rate of 0.1 µg/kg/h during surgery and after surgery (9 PM to 7 AM on days 1-3)

FINDINGS

Incidence of PTSD was significantly lower for the dexmedetomidine group compared with the normal saline group 1 month after surgery

**Incidence of PTSD:
normal saline
group****Incidence of PTSD:
dexmedetomidine
group****Group 1:** 24.0%**Group 2:** 14.1%aOR, 0.51; 95% CI, 0.27-0.94; *P* = .03**SETTINGS / LOCATIONS****4 Hospitals in
Jiangsu, China****PRIMARY OUTCOME**

Incidence of posttraumatic stress disorder (PTSD), according to the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), defined as the number of participants with 4-symptom clusters divided by the number of participants in each group



CAN WE ADDRESS PTSD IN
THE PRIMARY CARE SETTING?

RCT: Pragmatic Comparative Effectiveness of Primary Care Treatments for Posttraumatic Stress Disorder

POPULATION

368 Males, 212 Females



Adults meeting clinical criteria for posttraumatic stress disorder (PTSD) with established primary care
Mean (SD) age, 45.1 (15.4) y

SETTINGS / LOCATIONS



15 Primary clinics in 11 US states

INTERVENTION

700 Patients randomized



295 Selective serotonin reuptake inhibitors (SSRIs)
Sertraline, paroxetine, or fluoxetine



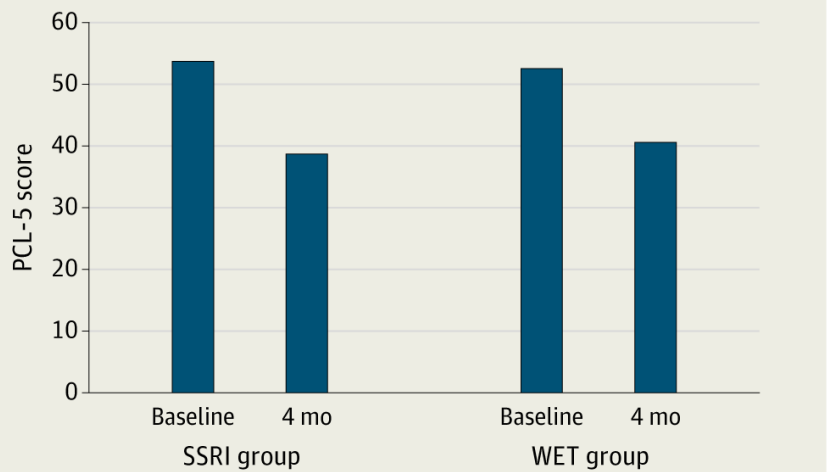
295 Written exposure therapy (WET)
Written exposure therapy is a trauma-focused therapy where patients write about their traumatic experience

PRIMARY OUTCOME

PTSD Checklist *DSM-5* (PCL-5): range, 0-80; cutoff score for probable diagnosis, 33

FINDINGS

WET was not superior to serotonin-norepinephrine reuptake inhibitors



Change in PCL-5 score between baseline and 4 mo:

SSRI group: 53.00 (95% CI, 51.82-54.17) to 38.95 (95% CI, 36.97-40.94)

WET group: 52.63 (95% CI, 51.68-53.58) to 40.52 (95% CI, 38.42-42.62)

Adjusted mean difference: 1.79 (95% CI, -0.76 to 4.34); *P* = .17



A Psychopharmacologic Treatment
That Came Very Close To FDA
Approval In 2025

BREXPIPIRAZOLE

Brexpiprazole (REXULTI) is an atypical antipsychotic indicated for:

- Adjunctive therapy to antidepressants for treatment of major depressive disorder (MDD) in adults
- Treatment of schizophrenia in adults and pediatric patients ages 13 years and older
- Treatment of agitation associated with dementia due to Alzheimer's disease

Receptor affinity

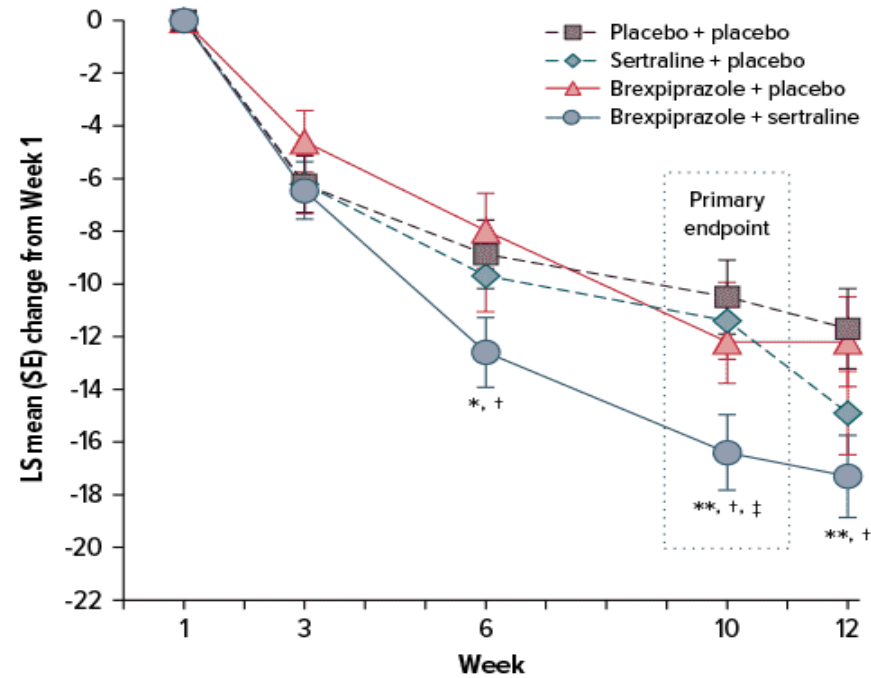
NE α_{1B} antagonism	 = 
NE α_{2C} antagonism	 = 
5-HT _{1A} partial agonism	 = 
5-HT _{2A} antagonism	 = 
D ₂ partial agonism	 = 

Limitations of Use: Not indicated as an as needed (“prn”) treatment for agitation associated with dementia due to Alzheimer's disease

Figure 2.

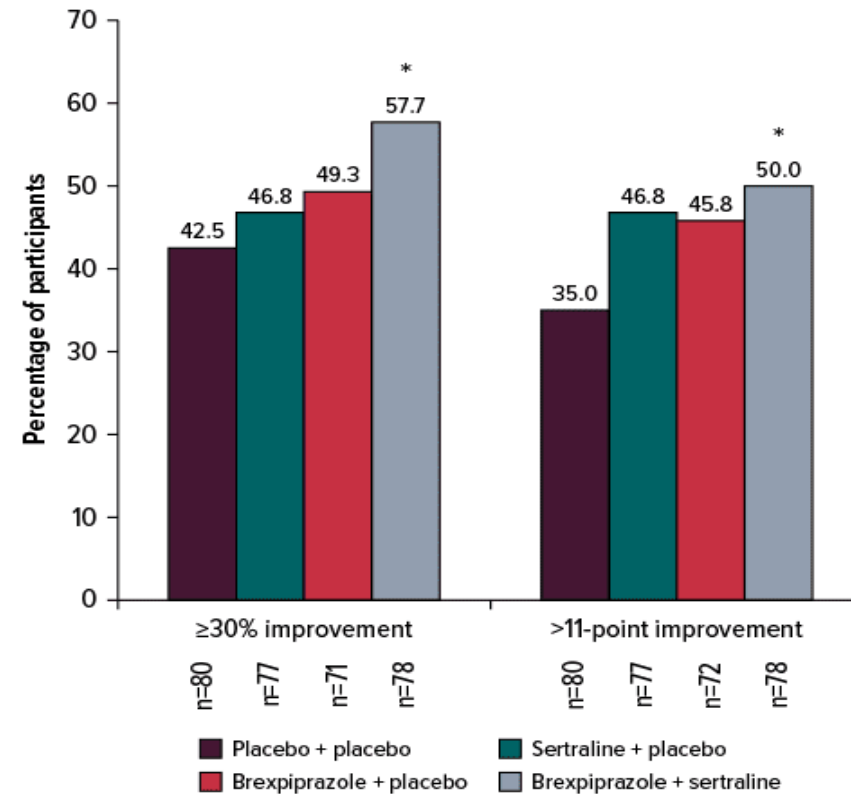
(A) Change in CAPS-5 Total Score (Primary Endpoint) and (B) CAPS-5 Response Rates^a

A. CAPS-5 total score (primary endpoint)



Plac + plac, n=	78	77	70	62	61
Sert + plac, n=	75	74	62	58	58
Brex + plac, n=	69	66	58	48	48
Brex + sert, n=	77	74	64	59	57

B. CAPS-5 response by two definitions at Week 10 (other endpoint)



^aCAPS-5 total score at randomization (Week 1): brexpiprazole + sertraline, 35.7; brexpiprazole + placebo, 33.9; sertraline + placebo, 36.5; placebo + placebo, 35.1. CAPS-5 total score was analyzed with a mixed model for repeated measures. CAPS-5 response was analyzed using last observation carried forward data and the Cochran–Mantel–Haenszel general association test. *P* values are nominal with no adjustment for multiplicity. All analyses were performed in the efficacy sample. **P* < .05 vs placebo + placebo. ***P* < .01 vs placebo + placebo. †*P* < .05 vs brexpiprazole + placebo. ‡*P* < .05 vs sertraline + placebo. Abbreviations: CAPS-5 = Clinician-Administered PTSD Scale for DSM-5, PTSD = posttraumatic stress disorder.

RCT: Brexpiprazole and Sertraline Combination Treatment in Posttraumatic Stress Disorder

POPULATION

106 Men, 310 Women



Adult outpatient participants with posttraumatic stress disorder (PTSD)

Mean (SD), 37.4 (11.9) y

INTERVENTION

416 Participants randomized



214 Brexpiprazole + sertraline
Oral brexpiprazole, 2-3 mg/d (flexible dose), and sertraline, 150 mg/d



202 Sertraline + placebo
Oral sertraline, 150 mg/d, and placebo

SETTINGS / LOCATIONS



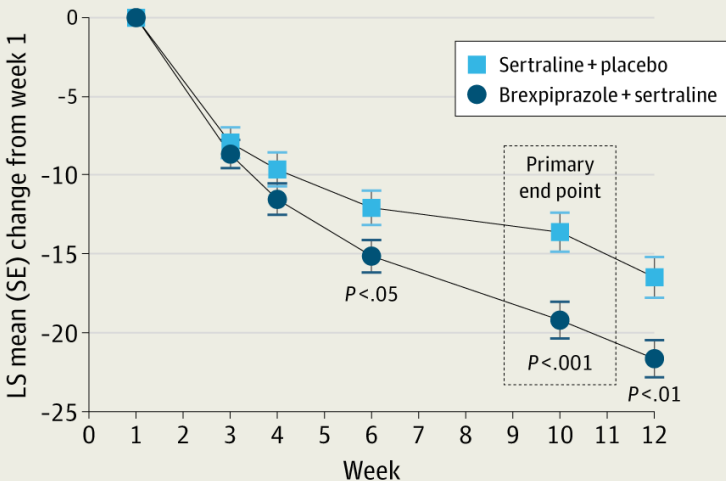
86 Trial sites in the US

PRIMARY OUTCOME

Change in Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5) total score (range: 0 [absent] to 80 [extreme or incapacitating]) from randomization (week 1) to week 10 for brexpiprazole + sertraline vs sertraline + placebo

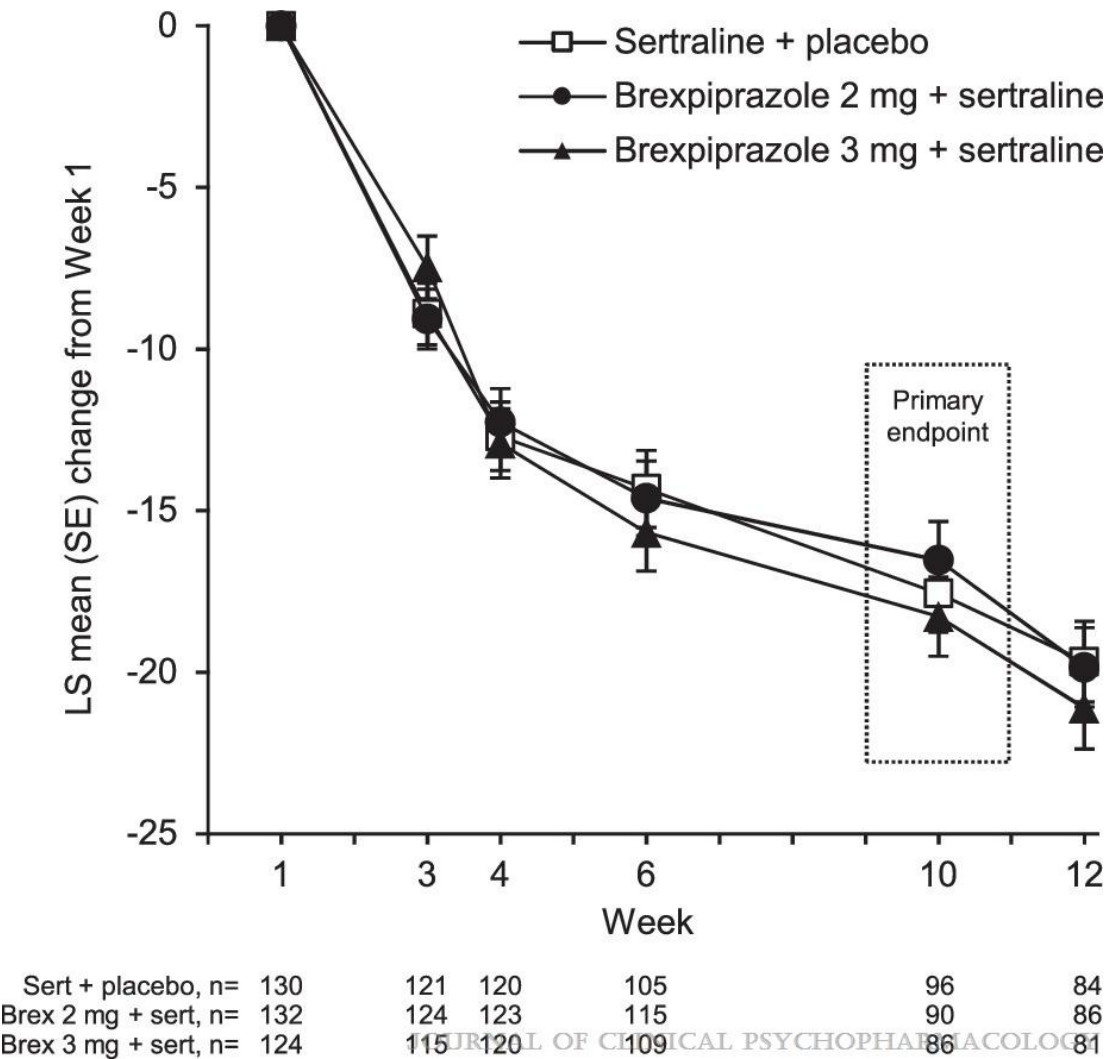
FINDINGS

Brexpiprazole + sertraline demonstrated significantly greater improvement than sertraline + placebo in change in CAPS-5 total score from randomization (week 1) to week 10



Least-squares (LS) mean (SE) change,
brexpiprazole + sertraline, -19.2 (1.2) points
LS mean (SE) change,
sertraline + placebo, -13.6 (1.2) points
Between-group difference,
-5.59 points (95% CI, -8.79 to -2.38); $P < .001$

Fixed Dose Brexpiprazole and Sertraline Combination for the Treatment of PTSD



Mean change in CAPS-5 total score (primary endpoint). CAPS-5, Clinician-Administered PTSD Scale for DSM-5; LS, least squares; MMRM, mixed model for repeated measures. All comparisons had $P > 0.05$ versus sertraline + placebo; MMRM, efficacy sample. Mean CAPS-5 total score at randomization (Week 1): brexpiprazole 2 mg + sertraline, 38.8; brexpiprazole 3 mg + sertraline, 37.9; sertraline + placebo, 39.3.

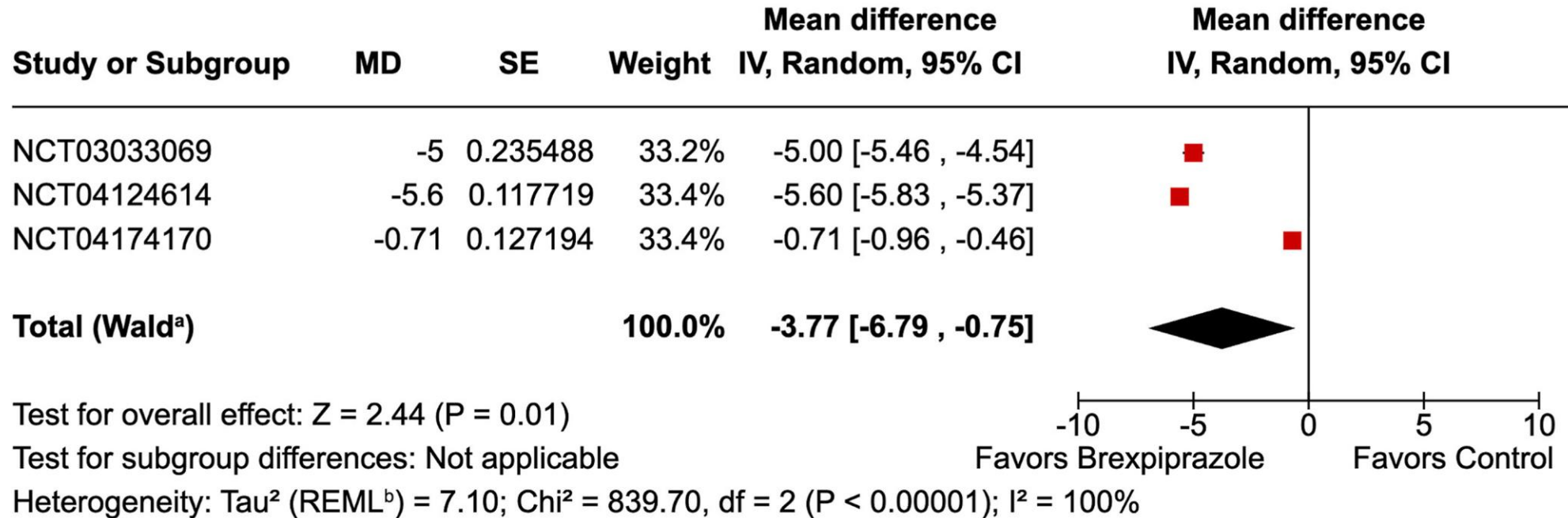
[Fixed-Dose Brexpiprazole and Sertraline Combination Therapy for the Treatment of Posttraumatic Stress Disorder: A Phase 3, Randomized Trial](#)

Davis, Lori L.; Behl, Saloni; Lee, Daniel; Zeng, Hui; Skubiak, Taisa; Weaver, Shelley; Hefting, Nanco; Larsen, Klaus Groes; Hobart, Mary

Journal of Clinical Psychopharmacology 45(6):580-589, November/December 2025.

doi: 10.1097/JCP.0000000000002076

CAPS-5



Footnotes

^aCI calculated by Wald-type method.

^b Tau^2 calculated by Restricted Maximum-Likelihood method.

Kotochinsky M, Alessi MR, Vieira GH, Balogun M, Sherpa NN, Lezana AG. Efficacy and tolerability of brexpiprazole augmentation of SSRI therapy in PTSD: A systematic review and meta-analysis of randomized controlled trials. *J Psychiatr Res.* 2026;192:237-244. doi:10.1016/j.jpsychires.2025.10.063

Summary: Brexpiprazole-sertraline combination

- FDA rejected as a new drug indication for PTSD - not convinced of “substantial evidence”.
- Adjunctive brexpiprazole has a place in the treatment of patients with PTSD (off label), many of whom have difficult to treat major depression (on label).
- Important to incorporate in Clinical Practice Guidelines for PTSD – as with other medications and psychotherapy treatments that have limited or mixed evidence of efficacy.



PUBLISHED POSITIVE RESULTS IN PTSD TREATMENT

RCT: Efficacy and Safety of the Neuroplastogen TSND-201 for the Treatment of PTSD

POPULATION

26 Men, 39 Women



Adults with severe posttraumatic stress disorder (PTSD)
(CAPS-5 score ≥ 35)

Mean (SD) age, 43.7 (10.5) y

SETTINGS / LOCATIONS



**16 Clinics
(US, UK, Ireland)**

INTERVENTION

65 Patients randomized and analyzed



32 TSND-201

(30 Included in efficacy analysis,
32 included in safety analysis)
Monoamine releaser and
rapid-acting neuroplastogen



33 Placebo

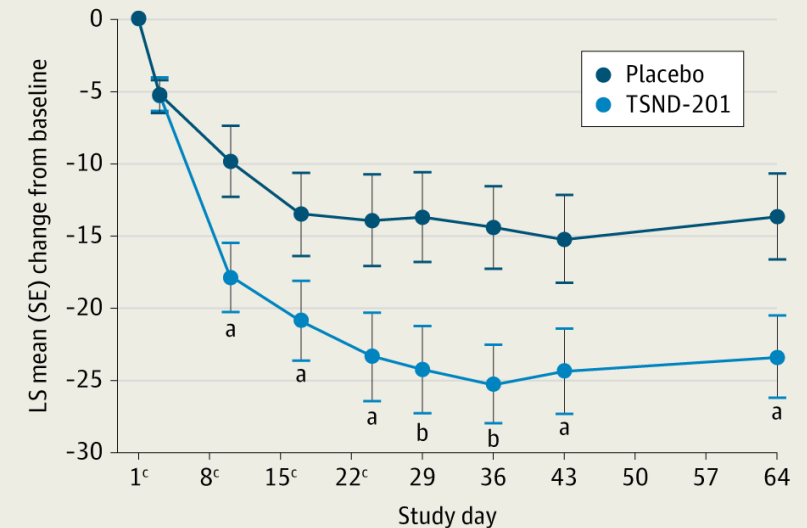
(30 Included in efficacy analysis,
33 included in safety analysis)
Inert placebo

PRIMARY OUTCOME

The primary outcome was the mean change in Clinician-Administered PTSD Scales for *DSM-5* (CAPS-5) from baseline to day 64 (week 10) compared with placebo. The CAPS-5 total score ranges from 0 to 80 points, with higher scores indicating greater PTSD symptom severity.

FINDINGS

TSND-201 demonstrated statistically significant improvement from baseline to day 64 in CAPS-5 total score



Change in CAPS-5 score, LS mean (SE):

TSND-201 group: -23.28 (2.84)

Placebo group: -13.64 (2.95)

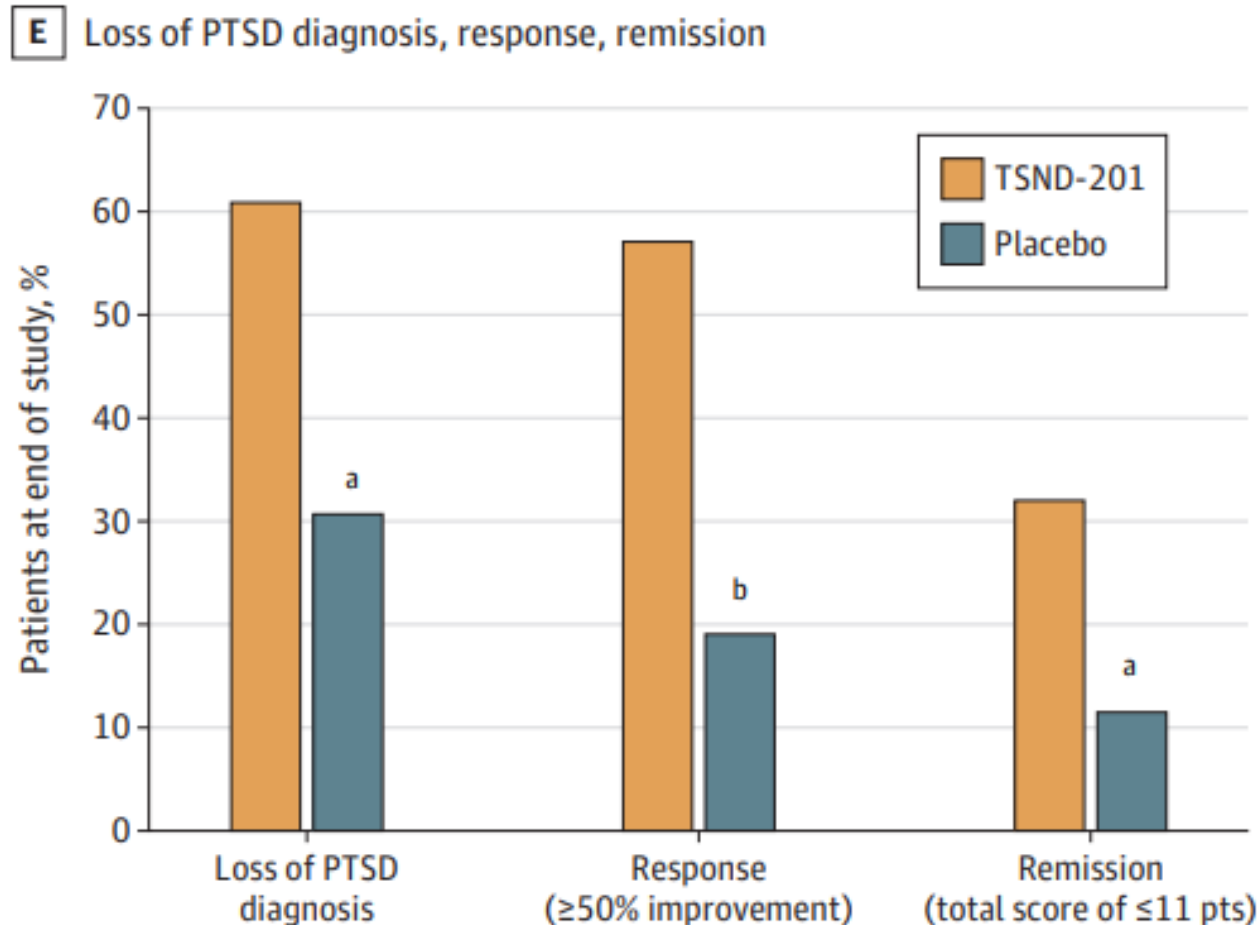
Between-group LS mean difference:

-9.64; 90% CI, -16.48 to -2.80; $P = .01$

Efficacy and Safety of the Neuroplastogen TSND-201 for the Treatment of PTSD

A Randomized Clinical Trial

Amanda Jones, PharmD; Jennifer Warner-Schmidt, PhD; Hannah Kwak, MHS; Martin Stogniew, PhD; Blake Mandell, MA; Terence H.W. Ching, PhD; Murray B. Stein, MD, MPH; Benjamin Kelmendi, MD



TSND-201 (methyllone)

RCT: Virtual Reality and Transcranial Direct Current Stimulation for Posttraumatic Stress Disorder

POPULATION

51 Men, 3 Women



Adults meeting *DSM-5* criteria for chronic PTSD with warzone trauma
Mean age, 45.7 y

INTERVENTION

55 Patients randomized



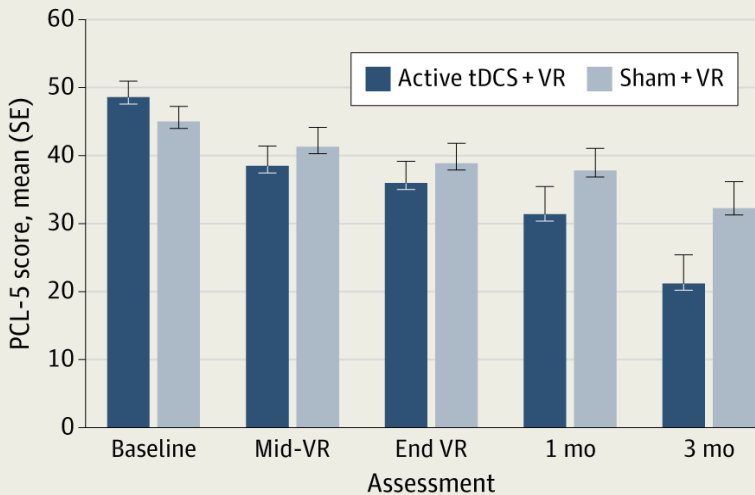
29 Sham stimulation plus virtual reality (VR)
Sham transcranial direct current stimulation (tDCS) plus VR



26 Active stimulation plus VR
Active tDCS plus VR

FINDINGS

Active tDCS plus VR significantly improved PTSD symptoms at 1 mo compared with sham tDCS plus VR



PCL-5 change at 1 mo
Sham tDCS plus VR: -7.1
Active tDCS plus VR: -17.2
Cohen $d = -0.82$; $P = .02$

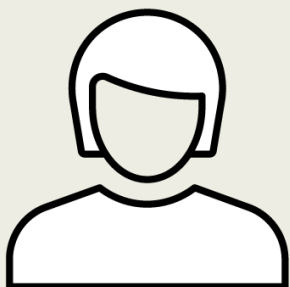
SETTINGS / LOCATIONS



1 Veterans Affairs hospital

PRIMARY OUTCOME

Change on PTSD checklist for *DSM-5* (PCL-5; range, 0-80; score of 31-33 indicates of probable PTSD). A change score of at least 10 points on the PCL-5 can be considered clinically meaningful.

RCT: Residential Therapy With Navigated Transcranial Magnetic Stimulation for Combat-Related PTSD**POPULATION****107 Men, 12 Women**

Military personnel with combat-related posttraumatic stress disorder (PTSD)

Mean age, 38 y**INTERVENTION****119** Participants randomized, all participants received intensive residential therapy**60 Active TMS**

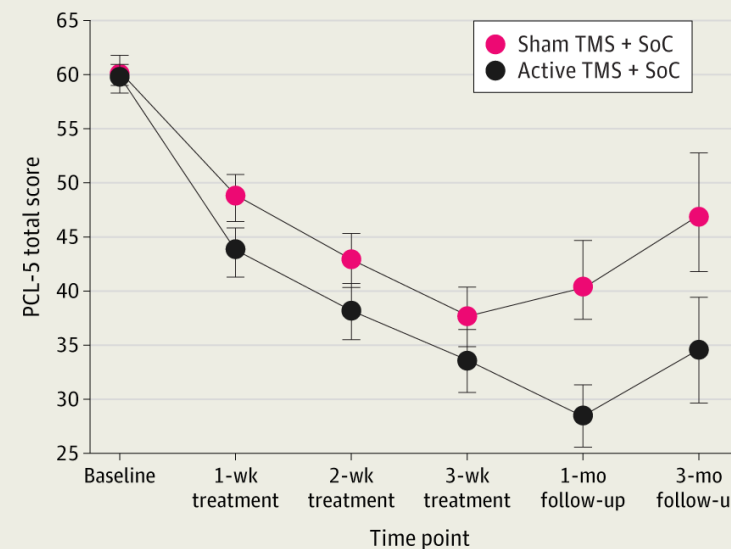
Active navigated transcranial magnetic stimulation (TMS) once daily for 20 sessions

59 Sham TMS

Sham navigated TMS once daily for 20 sessions

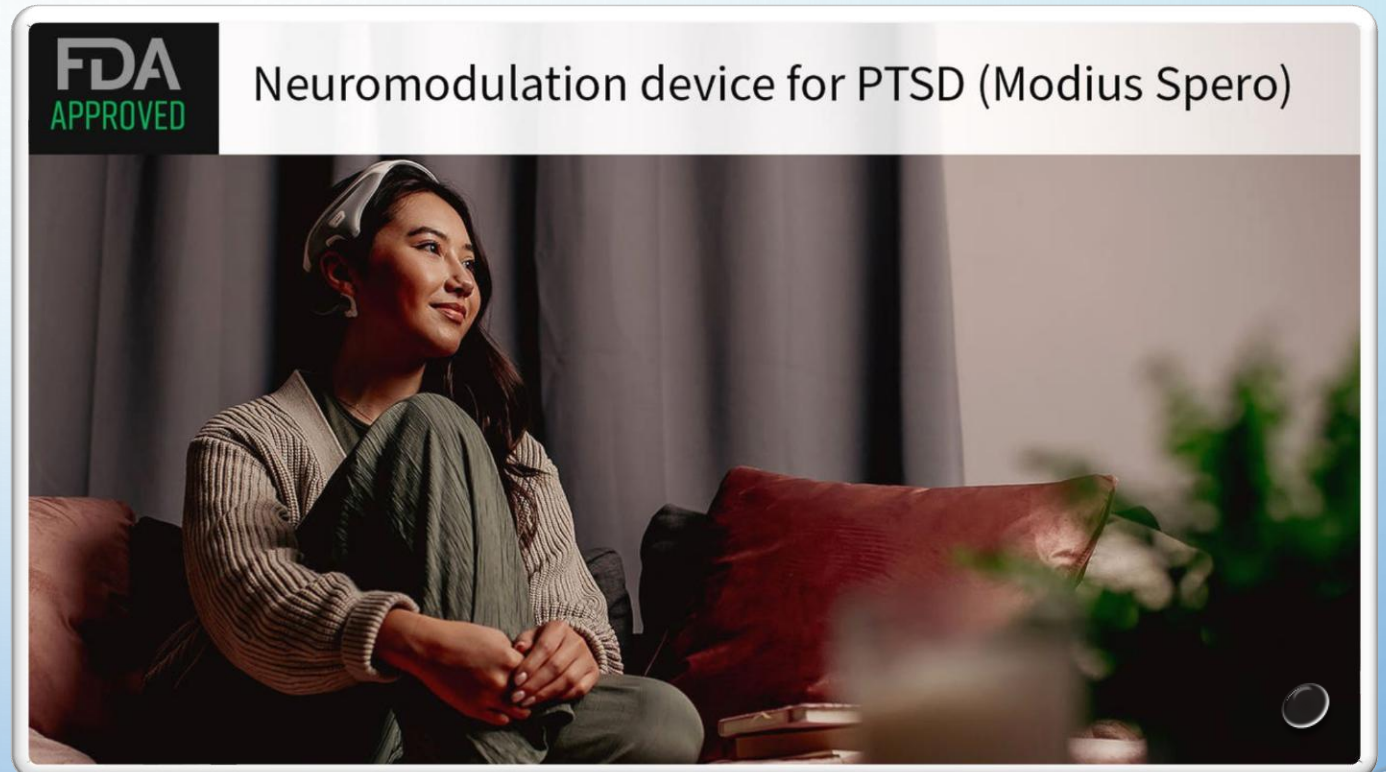
SETTINGS / LOCATIONS**1 Psychiatric
hospital in
Texas****PRIMARY OUTCOME**Change in PTSD symptom severity from baseline to 3 wk, measured by the PTSD checklist for DSM-5 (PCL-5; range, 0-80: mild, ≤ 22 ; moderate, ≥ 23 to ≤ 34 ; severe, ≥ 35 to ≤ 46 ; extreme, ≥ 47)**FINDINGS**

The active TMS group had a significantly greater improvement in PTSD symptom severity compared to the sham TMS group

**Between-group mean difference in change in PCL-5 score from baseline to 3 wk:**-5.94 points (95% CI, -11.77 to -0.10 points); $P = .02$

ELECTRICAL VESTIBULAR NERVE STIMULATION (MODIUS SPERO DEVICE) FOR TREATMENT OF PTSD

- Modius Spero is a wearable health tech device from Neurovalens targets the brain with low-level electrical stimulation to the vestibular nerve thought to influence key neurological processes such as the prefrontal cortex functions, aiding cognitive flexibility and emotional regulation.
- A neuromodulation device recently granted regulatory approval by the FDA to treat PTSD.
- Based on a clinical trial of over 300 participants with PTSD led by Peter Colvonen PhD, associate clinical professor at the University of California, San Diego.



PTSD phase 2 and phase 3 trials Currently Recruiting

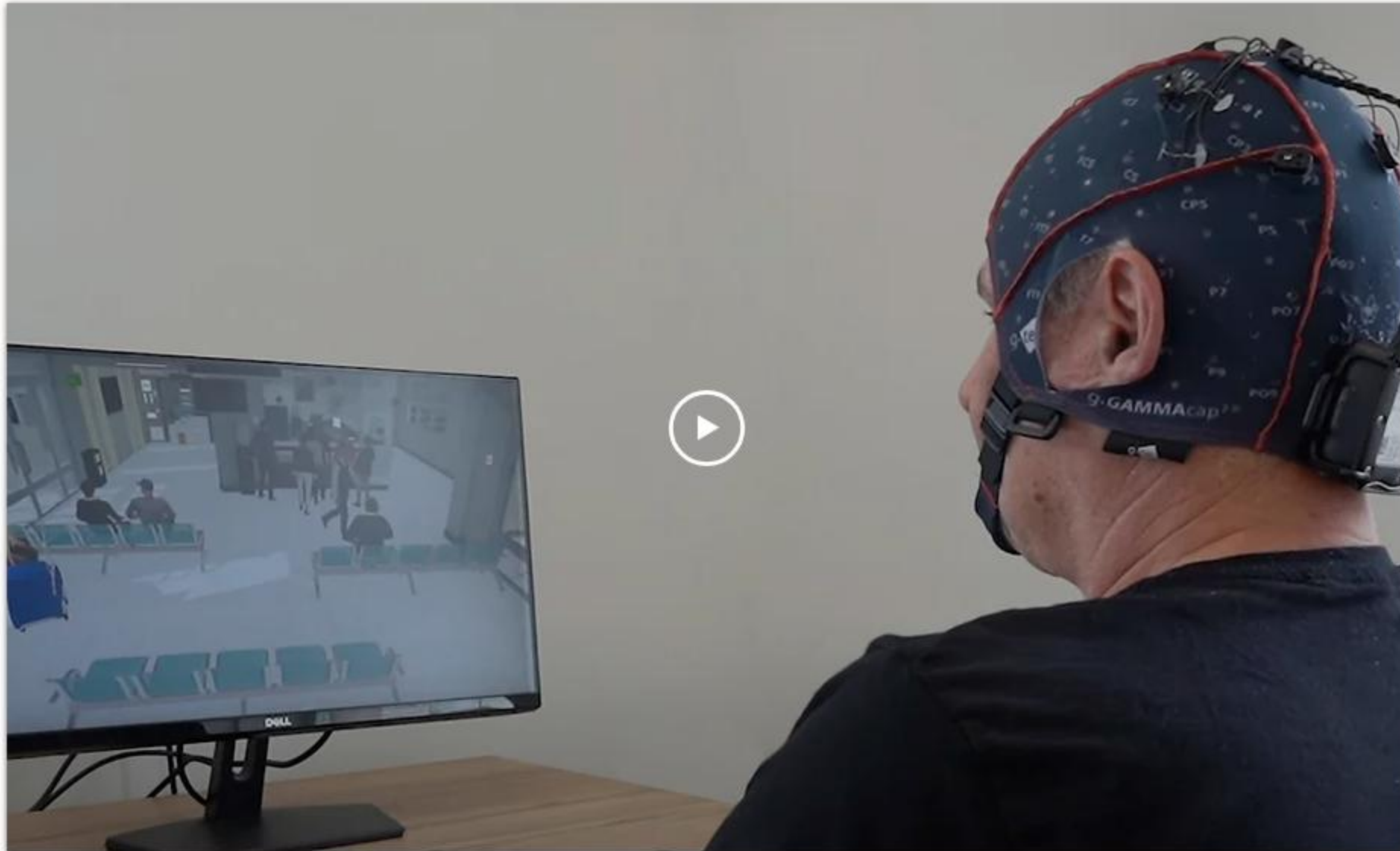
- Methylphenidate (Ritalin)
- Psilocybin
- MDMA (e.g., with massed prolonged exposure therapy; MDMA-assisted CBCT)
- Cannabidiol
- Ketamine
- PRISM neuromodulation
- Stellate Ganglion Block with Prolonged Exposure Therapy
- Glecaprevir/Pibrentasvir – a direct acting antiviral for Hep C repurposed
- Glucocorticoid Receptor antagonists (P150; CORT108297)
- Allopregnanolone
- BXCL501 (dexmedetomidine sublingual)
- Clonidine
- Pimavanserin for PTSD-related insomnia
- Daridorexant (DoD platform)
- Suvorexant for PTSD and alcohol use disorder
- Silexan (lavender oil capsules)
- Cyclobenzaprine (TNX-102 SL) acute stress disorder
- Reboxetine and methylphenidate

PRISM NEUROFEEDBACK FOR PTSD

[HTTPS://WWW.GRAYMATTERS-HEALTH.COM](https://www.graymatters-health.com)

- PRISM is a novel neurofeedback training that enables subjects to learn to control a surrogate activity associated with amygdala activation using a specific electroencephalography (**EEG**) brain activity biomarker.
- Biomarker derived from prior machine learning modeling that linked real-time activity in surface EEG electrodes to real-time functional magnetic resonance imaging (**fMRI**) activity in the amygdala.
- PRISM uses this amygdala-derived biomarker termed the amygdala EEG-FMRI-pattern (**AMYG-EFP**) from subjects in real time to control an audio-visual display of a virtual busy waiting room with noisy, agitated avatars.
- Avatars calm down as subjects decrease their AMYG-EFP computed based on their continuous EEG recording. Over repeat training sessions, subjects learn to downregulate the AMYG-EFP, and this training results in reduced PTSD symptoms.
- Double-blind, sham-controlled trial of active PRISM training vs. Sham PRISM training added to TAU for veteran and civilian subjects with PTSD. 15 training sessions (twice/week) + 2 booster sessions.
- Erica Duncan, MD – Lead PI; DoD funded multisite study

PRISM IN ACTION



A Multi-site Randomized Controlled Trial of Psilocybin for Treatment-Resistant Depression (TRD) in Veterans: PIVOT study (Psilocybin Intervention for Veterans Overcoming TRD) lead investigator: Lori Davis, MD



U.S. Department of Veterans Affairs
Veterans Health Administration
Office of Research & Development

Q1. *Project Description:

Describe Key Research Aims:

Aim 1: Evaluate antidepressant effects of 25mg compared to 1mg psilocybin under blinded conditions from baseline to week-4 post-dose utilizing Montgomery-Asberg Depression Rating Scale (MADRS) by centralized independent rater.

Aim 2: Evaluate the risks of psilocybin in participants who took $\geq$ one dose of study drug (Swiss Psychedelic Side Effects Inventory; reported AE).

Exploratory Aims: Estimate the change from baseline to week 4 on Clinician-Administered PTSD Scale-5-Revised (CAPS-5-R) by group in those with PTSD. Examine the effects of one vs two 25mg psilocybin sessions by comparing change in MADRS from baseline to week 8 between groups. Explore rates of response (Δ MADRS $\geq 50\%$ reduction) and remission (MADRS score ≤ 10) at week 4, week 8 and month 6, within group and between groups. Explore potential effects of treatment on patient-reported outcomes over time, including expectancy, depression, PTSD, suicidality, psychological flexibility, and functional outcomes. Explore impact of altered experiences and functional unblinding on outcomes.

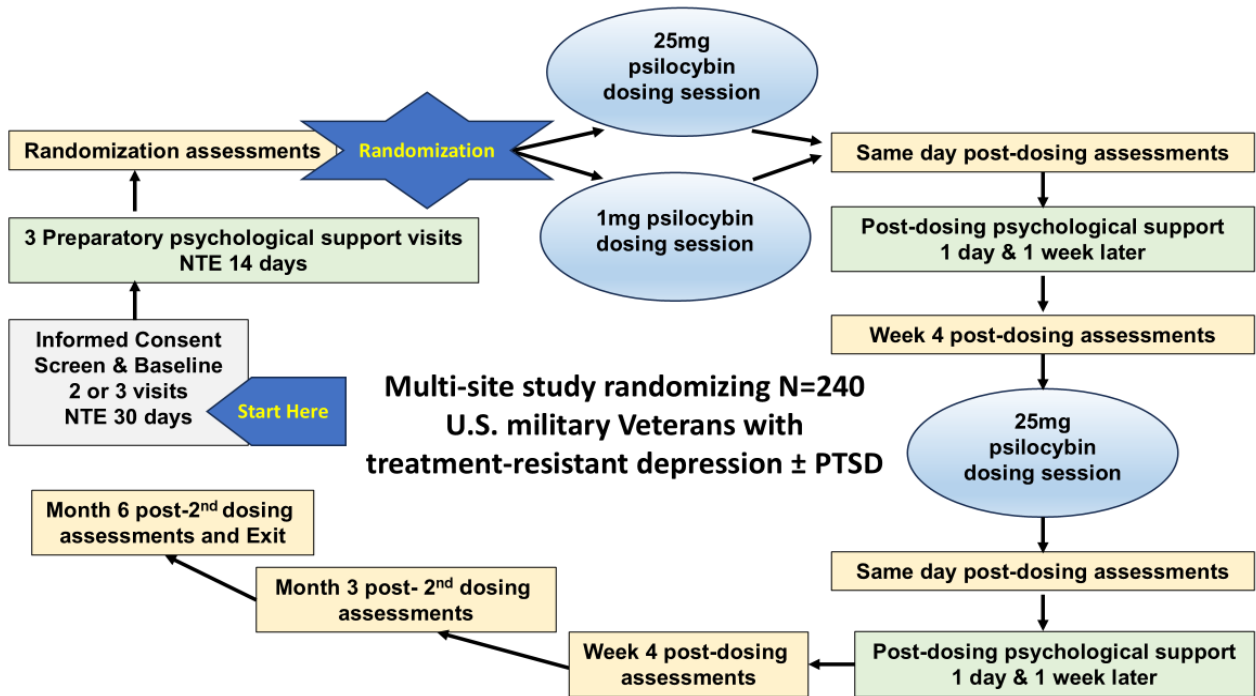
Q2. * Project Benefits and Innovations

Scientific Innovations:

- 1st multisite randomized controlled trial of psilocybin in Veterans
- Evaluates repeated dosing of psilocybin
- Allows concomitant SSRI/SNRI antidepressants to be continued
- Evaluates short-term (week 4 and 8) and long-term (6 months) antidepressant effects of psilocybin to understand durability
- Includes comorbid PTSD to evaluate psilocybin effects on PTSD
- Utilizes state-of-art assessment of risks and side effects

Benefits to Veterans:

- Provides access to treatment with a psychedelic compound in a supervised medical setting
- Will provide the evidence (or not) of therapeutic benefits
- Will provide a better understanding of associated risks
- May provide improvement in symptoms of depression and PTSD
- May provide durable therapeutic effects and improved quality of life



VA Sites:
Birmingham, Tuscaloosa,
Philadelphia, Portland, Seattle

Recruitment to start in summer 2026
40-month recruitment period

OPEN LABEL PSILOCYBIN FOR PTSD

22 participants enrolled (63.6% female; age, 39.0 (7.91) years)

Pre-post comparisons indicated a clinically meaningful change from Baseline in mean CAPS-5 total score at Week 4 (-29.9 (14.06)) and Week 12 (-29.5 (15.43)), which was associated with the intensity of psychedelic experience on Day 1.

PCL-5 scores showed symptom reduction was rapid and sustained. SDS total score and EQ-5D-5L index score showed similar improvements.

117 treatment-emergent adverse events (TEAEs)
70 (59.8%) were reported on administration day, of which
91.4% resolved by the end of the next day.
TEAEs commonly included headache (50%),
nausea (36%), crying (27%), fatigue (27.3%).

There were no serious TEAEs or TEAEs leading to study withdrawal.

McGowan NM, Rucker JJ, Yehuda R, et al. Investigating the safety and tolerability of single-dose psilocybin for post-traumatic stress disorder: A nonrandomized open-label clinical trial. *J Psychopharmacol.* 2026;40(1):139-148. doi:10.1177/02698811251362390

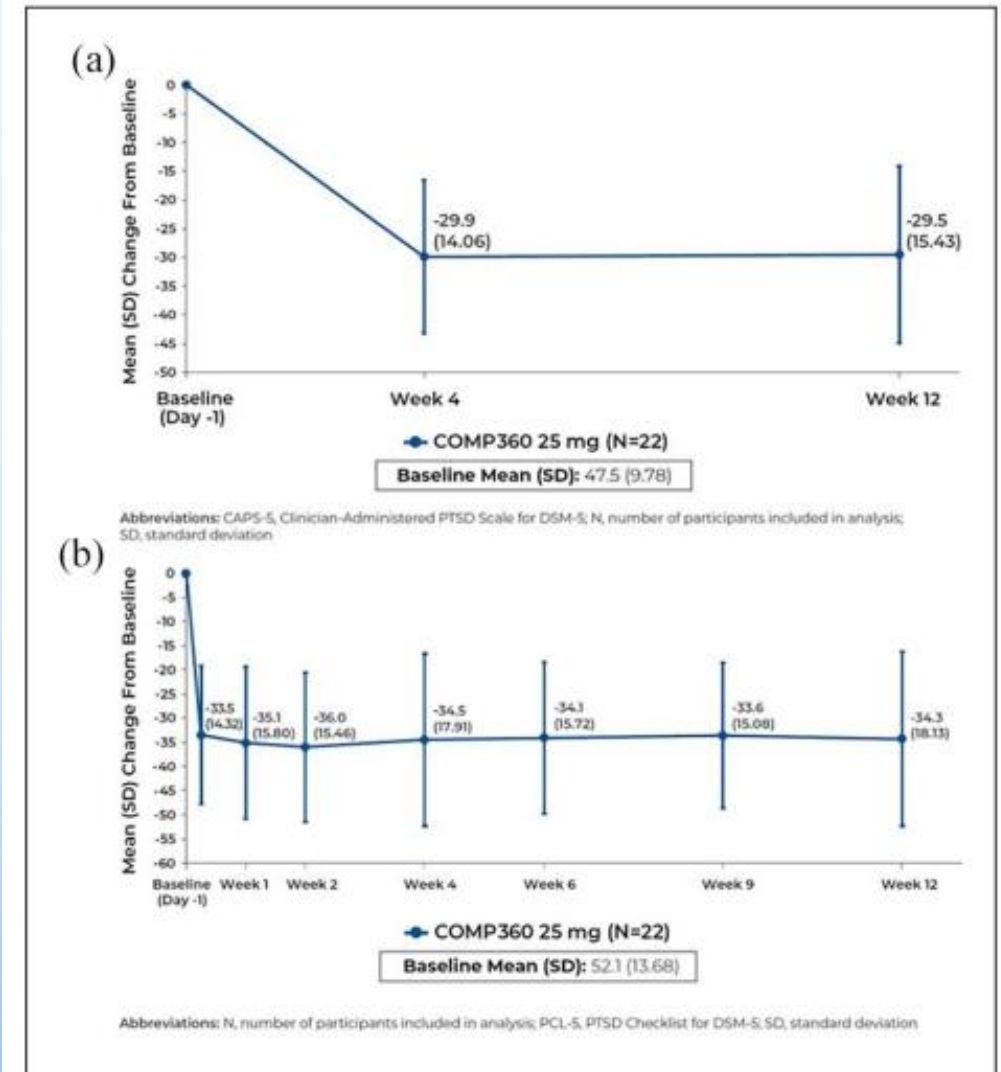


Figure 1. (a) Summary of Change from Baseline in CAPS-5 total score. (b) Summary of Change from Baseline in PCL-5 total score. CAPS-5: Clinician-Administered PTSD Scale for DSM-5; N: number of participants included in analysis; PCL-5: PTSD Checklist for DSM-5; SD: standard deviation.



*THANK YOU FOR YOUR
ATTENTION AND ATTENDANCE*