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Neurobiology and Treatment of Post-traumatic Stress Disorder

Presented by:

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DISCLOSURES

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Board of Directors:
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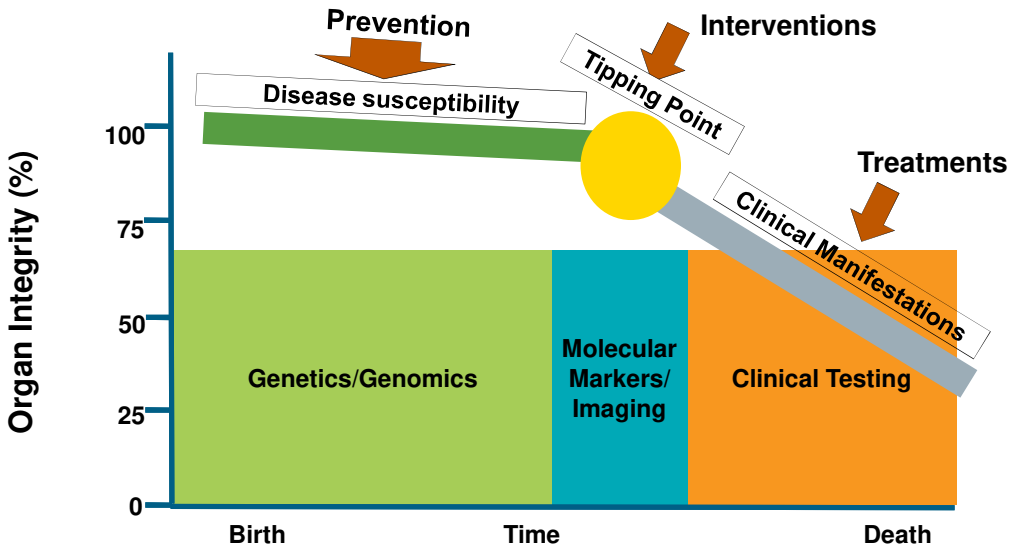
Patents:
Method and devices for transdermal delivery of lithium (US 6,375,990B1)
Method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (US 7,148,027B2)
Speakers Bureau:
None

21st Century Medicine



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For Survival we are Wired to have Universal Responses to Stress

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DSM-5 DIAGNOSTIC CRITERIA FOR PTSD IN ADULTS AND CHILDREN OLDER THAN 6 YEARS OF AGE	
Criterion	**Symptom or Description**
Criterion A: Stressor (both required)	1. Event involving actual or threatened death, serious injury, or sexual violence 2. Exposed to event: Directly; witnessed in person; indirectly by learning close loved one or family member exposed to trauma; repeated or extreme indirect exposure to disturbing details of trauma event, often through work
Criterion B: Intrusion symptoms (one required)	1. Recurrent, involuntary, and intrusive memories 2. Traumatic nightmares 3. Dissociative reactions (flashbacks) that may occur on a continuum from brief episodes to complete loss of consciousness 4. Intense or prolonged distress after exposure to traumatic reminders 5. Marked physiologic reactivity after exposure to trauma-related stimuli
Criterion C: Avoidance (one required)	1. Trauma-related thoughts or feelings 2. Trauma-related external reminders (places, conversations, activities, objects)
Criterion D: Cognitions and mood (two required)	1. Inability to recall key features of the traumatic event (from dissociative amnesia, not from head injury, alcohol, or drugs) 2. Persistent distorted, exaggerated negative beliefs or expectations about oneself, others, or the world ("I am bad," "The world is completely dangerous," "I've lost my soul forever," or "My nervous system is permanently ruined.") 3. Persistent distorted blame of self or others for the cause or consequences of traumatic event 4. Persistent negative trauma-related emotions such as fear, horror, anger, guilt, or shame 5. Loss of interest in (pre-traumatic) significant activities 6. Alienated from others 7. Constricted affect, inability to experience positive emotions

DSM-5 DIAGNOSTIC CRITERIA FOR PTSD IN ADULTS AND CHILDREN OLDER THAN 6 YEARS OF AGE	
Criterion	**Symptom or Description**
Criterion E: Arousal and reactivity (two required)	1. Irritable or aggressive behavior 2. Self-destructive or reckless behavior 3. Hypervigilance 4. Exaggerated startle response 5. Problems in concentration 6. Sleep disturbance
Criterion F: Duration	Persistence of Criteria B, C, D, and E symptoms >1 month
Criterion G: Functional significance	Significant symptom-related distress or functional impairment (e.g., social, occupational)
Criterion H: Exclusion	Disturbance not due to medication, substance use, or other illness
Specify if: With dissociative symptoms	The person experiences high levels of either of the following in reaction to trauma-related stimuli: 1. Depersonalization: The experience of being an outside observer of or detached from oneself (e.g., feeling as if "this is not happening to me" or one were in a dream) 2. Derealization: The experience of unreality, distance, or distortion (e.g., "things are not real")
Specify if: With delayed expression	Full diagnosis not met until ≥6 months post-trauma, though onset of some symptoms may occur immediately
Source: [1]	*Table 3*

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The PTSD Checklist for *DSM-5*

Scores ≥ 33 = Cutoff

PCL-5

Instructions: Below is a list of problems that people sometimes have in response to a very stressful experience. Please read each problem carefully and then circle one of the numbers to the right to indicate how much you have been bothered by that problem in the past month.

	In the past month, how much were you bothered by:	Not at all	A little bit	Moderately	Quite a bit	Extremely
Cluster B	1. Repeated, disturbing, and unwanted memories of the stressful experience?	0	1	2	3	4
	2. Repeated, disturbing dreams of the stressful experience?	0	1	2	3	4
	3. Suddenly feeling or acting as if the stressful experience were actually happening again (as if you were actually back there reliving it)?	0	1	2	3	4
	4. Feeling very upset when something reminded you of the stressful experience?	0	1	2	3	4
	5. Having strong physical reactions when something reminded you of the stressful experience (for example, heart pounding, trouble breathing, sweating)?	0	1	2	3	4
Cluster C	6. Avoiding memories, thoughts, or feelings related to the stressful experience?	0	1	2	3	4
	7. Avoiding external reminders of the stressful experience (for example, people, places, conversations, activities, objects, or situations)?	0	1	2	3	4

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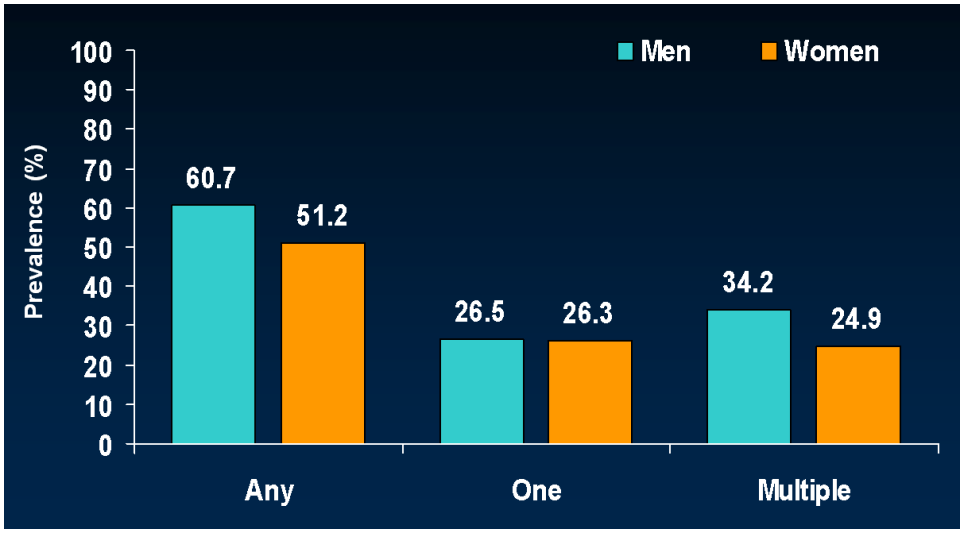
PCL-5

Instructions: Below is a list of problems that people sometimes have in response to a very stressful experience. Please read each problem carefully and then circle one of the numbers to the right to indicate how much you have been bothered by that problem in the past month.

	In the past month, how much were you bothered by:	Not at all	A little bit	Moderately	Quite a bit	Extremely
Cluster D	8. Trouble remembering important parts of the stressful experience?	0	1	2	3	4
	9. Having strong negative beliefs about yourself, other people, or the world (for example, having thoughts such as: I am bad, there is something seriously wrong with me, no one can be trusted, the world is completely dangerous)?	0	1	2	3	4
	10. Blaming yourself or someone else for the stressful experience or what happened after it?	0	1	2	3	4
	11. Having strong negative feelings such as fear, horror, anger, guilt, or shame?	0	1	2	3	4
	12. Loss of interest in activities that you used to enjoy?	0	1	2	3	4
	13. Feeling distant or cut off from other people?	0	1	2	3	4
	14. Trouble experiencing positive feelings (for example, being unable to feel happiness or have loving feelings for people close to you)?	0	1	2	3	4
Cluster E	15. Irritable behavior, angry outbursts, or acting aggressively?	0	1	2	3	4
	16. Taking too many risks or doing things that could cause you harm?	0	1	2	3	4
	17. Being "superalert" or watchful or on guard?	0	1	2	3	4
	18. Feeling jumpy or easily startled?	0	1	2	3	4
	19. Having difficulty concentrating?	0	1	2	3	4
	20. Trouble falling or staying asleep?	0	1	2	3	4

Lifetime Prevalence of Trauma



Kessler (2000) J Clin Psychiatry 61(Suppl 5) 4.

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PTSD AND TRAUMA EXPOSURE PREVALENCE IN HETEROSEXUALS AND PERSONS WITH MINORITY SEXUAL ORIENTATION

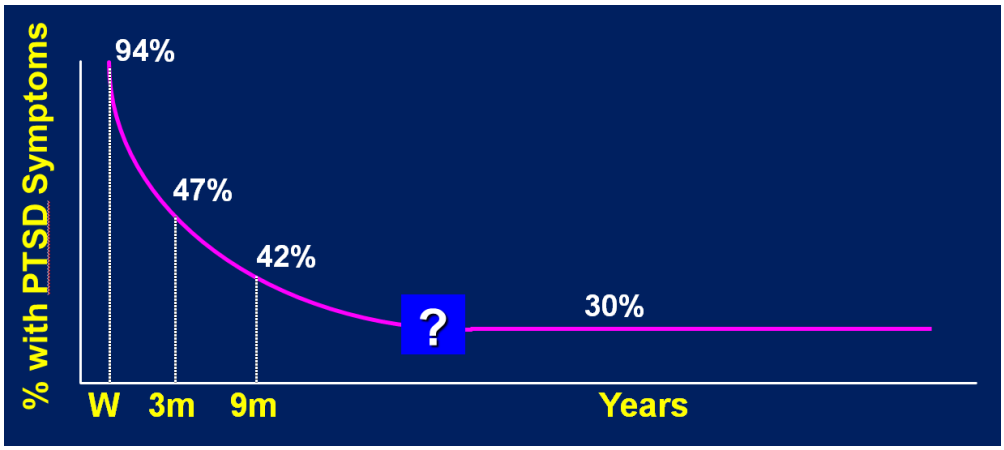
Sexual Identity	PTSD	Childhood Maltreatment	Interpersonal Violence Overall	Unwanted Sex	Attacked or Beaten	Domestic Violence Victim	Witnessed Another Injured or Killed
Men							
Heterosexual	5.03%	10.76%	24.95%	2.23%	11.73%	2.00%	32.45%
HSSP	10.13%	14.98%	33.98%	12.71%	16.64%	3.97%	34.74%
Gay	13.38%	18.26%	50.69%	17.95%	20.70%	11.52%	23.96%
Bisexual	9.00 %	12.15%	31.05%	12.04%	10.42%	0%	33.07%
Women							
Heterosexual	12.50%	13.07%	26.36%	13.41%	3.46%	9.44%	16.13%
HSSP	22.78%	19.55%	46.30%	29.57%	12.88%	23.81%	29.20%
Lesbian	18.04%	27.64%	60.21%	43.98%	10.37%	16.10%	29.39%
Bisexual	25.68%	30.52%	54.06%	47.26%	20.73%	20.17%	30.76%

HSSP = heterosexuals with same-sex partners.

Source: Reprinted with permission from Roberts AL, Austin SB, Corliss HL, Vandermorris AK, Koenen KC. Pervasive trauma exposure among US sexual orientation minority adults and risk of posttraumatic stress disorder. Am J Public Health. 2010;100(12):2433-2441. *Table 1*

Longitudinal Course of PTSD

Most People Who Develop PTSD Recover from it



Shalev & Yehuda, 1999

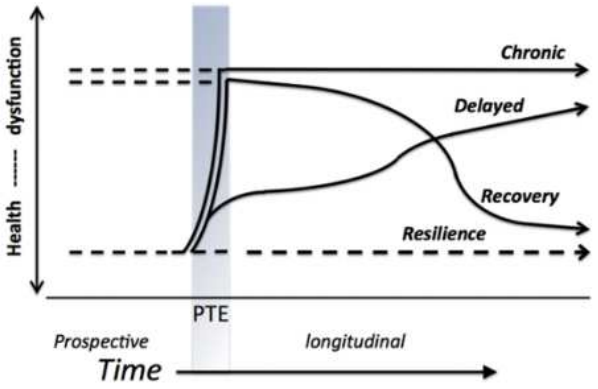


Fig. 1. Commonly observed prospective and longitudinal trajectories of response to potential trauma. Adapted from "Loss, trauma, and human resilience: Have we underestimated the human capacity to thrive after extremely aversive events?" by B. A. Bonanno, 2004, American Psychologist, 59(1), 20-28.

Pre-Existing Conditions: Risk/Vulnerability Factors for PTSD

- Demographics: Female
- Childhood and adolescent trauma exposure
- Family and personal history of anxiety or mood disorder
- Poorer social support before and after event
- Lower I.Q. and educational attainment
- Stressful life events in prior and following year
- Panic reaction at time of event; heart racing, shaking, sweating
- Dissociative reactions at time of event: slow motion, tunnel vision, like dream, movie, play

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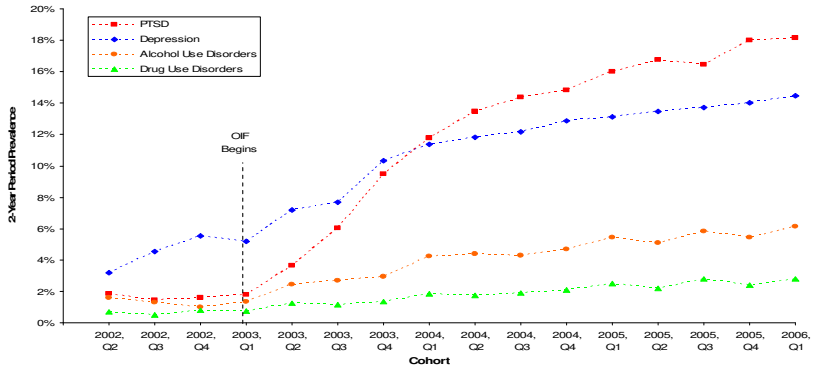
Mental Health Disorders among 289,328 US Veterans Returning from Iraq and Afghanistan Seen at VA Facilities

Karen H. Seal, M.D.,MPH; Daniel Bertenthal, MPH; Christian R. Miner, Ph.D.; Saunak Sen, Ph.D.; Charles R. Marmar, M.D.

Am J Public Health. 2009, 99:1651-8.

Figure 2b: Two-Year Period Prevalence of Specific Mental Health Diagnoses in Distinct Cohorts of OEF/OIF Veterans Entering VA in Successive Calendar Quarters and Followed for 2 years, April 1, 2002-March 31, 2006. (N= 289,328)



1The ICD-9 CM code for "PTSD" is 309.81
2 The ICD-9 CM codes for "Depressive Disorders" are 296.20-296.25 and 296.30-296.35, 300.4 and 311(excludes depression in remission and depression in conjunction with bipolar disorders).
3 The ICD-9 CM codes for "Alcohol Use Disorders" are 305.00-305.03 (alcohol abuse) and 303 (alcohol dependence)
4 The ICD-9 CM codes for "Drug Use Disorders" are 305.20-305.93 (drug abuse), 304 (drug dependence), excluding code for nicotine dependence, 305.1.

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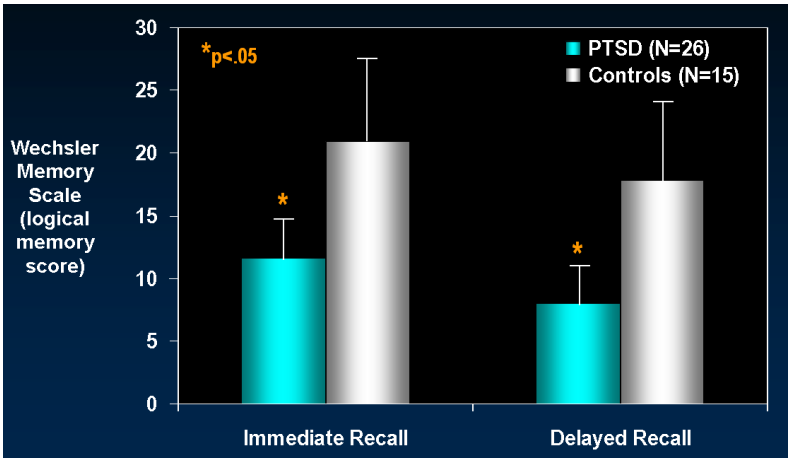
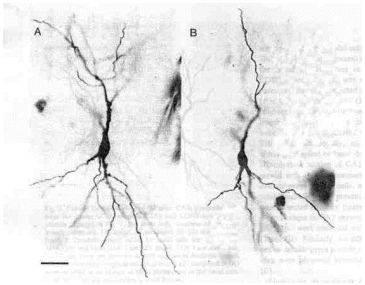
Deficits in Verbal Memory in Combat-Related PTSD



Bremner et al (1993) Am J Psychiatry 150:1015-1019.

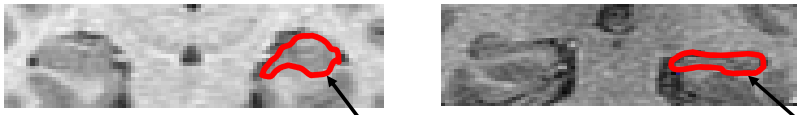
Stress Affects the Brain by Decreasing Neuroplasticity

Hippocampal Neurons



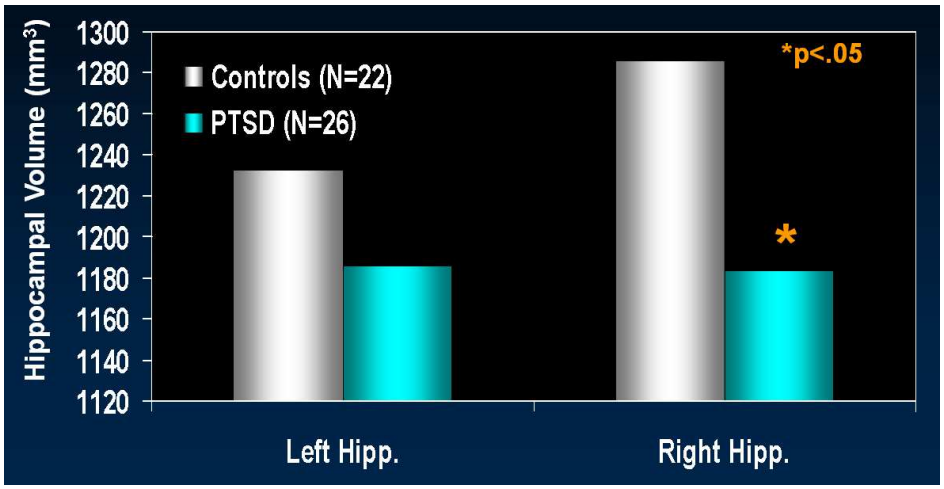
Non-Stressed Stressed

MRI Brain Scan

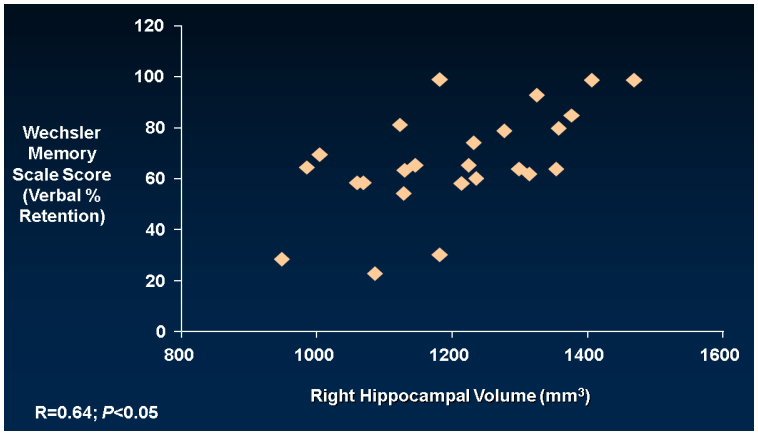


Normal PTSD

Decreased Right Hippocampal Volume in Combat-Related PTSD



Decreased Right Hippocampal Volume Correlates with Verbal Memory Deficits in Combat-Related PTSD



Bremner et al (1995) Am J Psychiatry 152:973.

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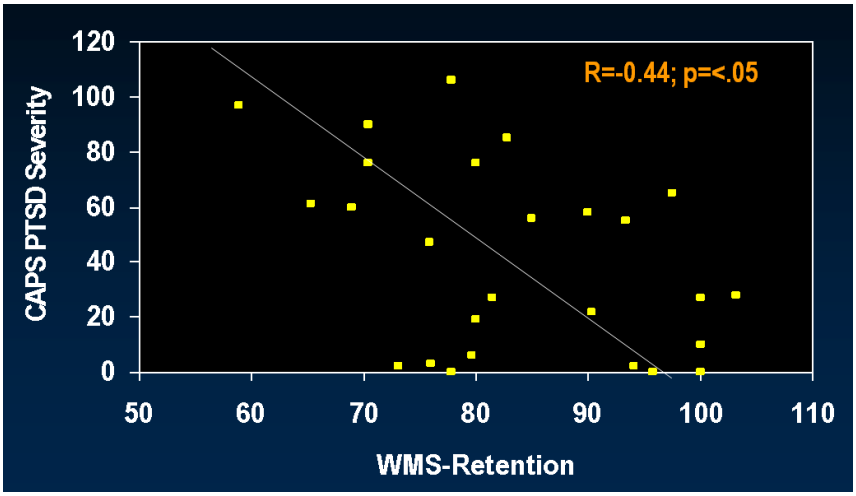
PTSD Symptom Severity Correlates with Impaired Memory in Abused Women



An [^{15}O]H_2 Pet Study of Rape-Related PTSD and Effect of Psychotherapy

Study Design

Female victims of sexual assault with PTSD (caps: 77±22) and Major Depression (HamD: 24±7)

Script-guided mental imagery to induce states of trauma re-experiencing, trauma-neutral mental imagery, shame/guilt, and threat (fear)

[^{15}O]H_2 Pet Studies performed before and after a 6 week trail with prolonged imaginal exposure(PE)

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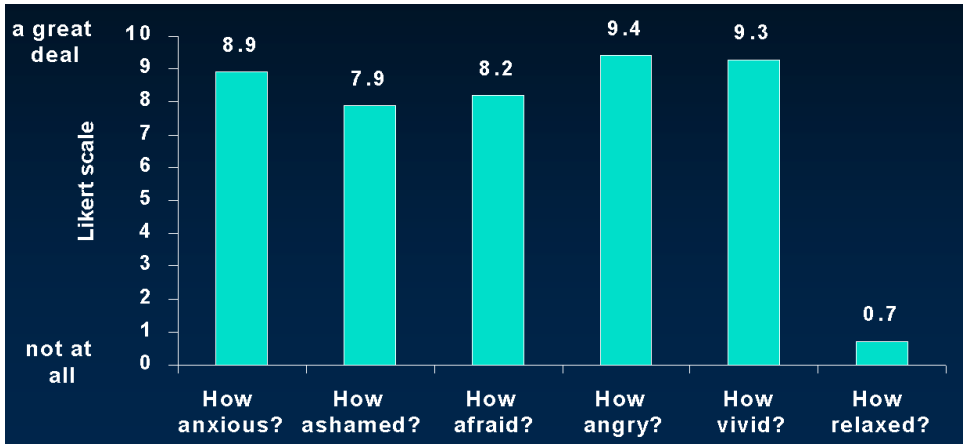
Example of PTSD Imagery Script

It's 11:30 at night and I just got back from McDonald's. I pull into the driveway and listen to the news update on the Peachtree fire. Suddenly as I get out of the car I'm grabbed around my neck from behind and pulled into the woods. My heart is absolutely racing with fear and I am scared to death. He keeps calling me "bitch" and "whore", telling me that I know I want it. I'm fighting to get away from him but he's beating me—beating my head into the tree and tearing at my clothes. Oh my God, I can't believe this is happening to me. Now he's got me layin' on the ground and his foot is on my chest—he's tellin' me that I better do what he wants me to do or I won't ever do anything again. I can smell the alcohol and cologne all over him as he forces me to perform oral sex and it sickens me. The sweat is pouring off my body and I'm trembling for my life. Now he's trying to get out of his pants and suddenly he stumbles and falls backwards. Quickly I roll over and now I'm running just as fast as I can to the house. As he's chasing behind me, he's yelling "get back here bitch" and I am out of my mind with fear.

Response to Guided Mental Imagery of the Rape Trauma

Pre-Treatment



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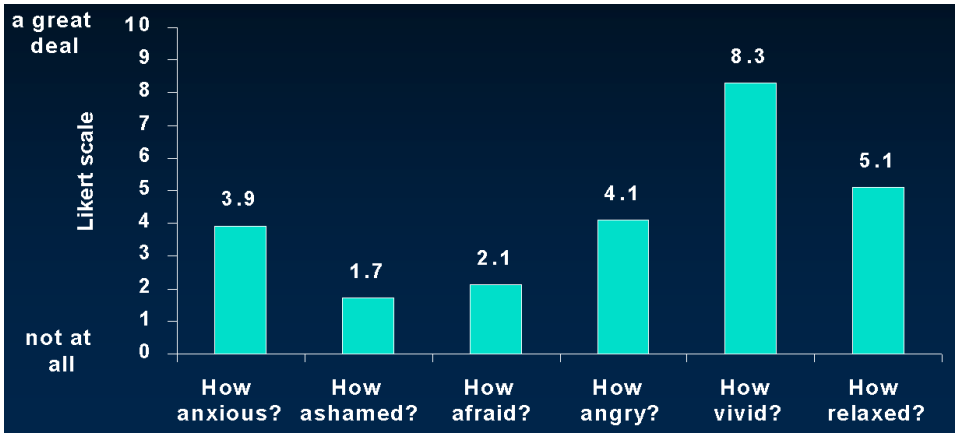
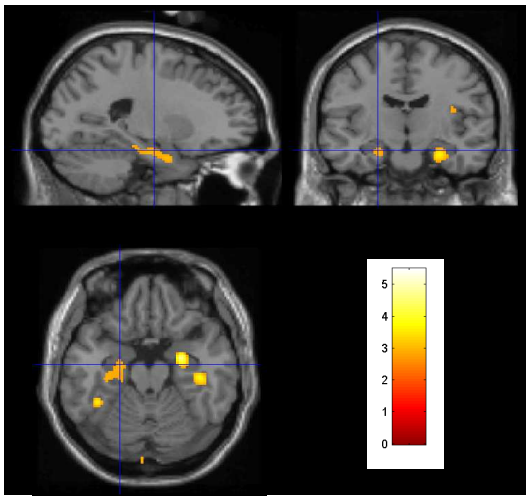
Response to Guided Mental Imagery of the Rape Trauma

Post-Treatment



PTSD: Post-Treatment

Decrease in limbic activity related to rape trauma re-experiencing



Control > re-experiencing

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NEUROSCIENCE

Resilience after trauma: The role of memory suppression

Alison Mary[1], Jacques Dayan[1,2], Giovanni Leone[1], Charlotte Postel[1], Florence Fraisse[1], Carine Malle[1], Thomas Vallée[1], Carine Klein-Peschanski[3], Fausto Viader[1], Vincent de la Sayette[1], Denis Peschanski[3], Francis Eustache[1], Pierre Gagnepain[1]*

In the aftermath of trauma, little is known about why the unwanted and unbidden recollection of traumatic memories persists in some individuals but not others. We implemented neutral and inoffensive intrusive memories in the laboratory in a group of 102 individuals exposed to the 2015 Paris terrorist attacks and 73 nonexposed individuals, who were not in Paris during the attacks. While reexperiencing these intrusive memories, nonexposed individuals and exposed individuals without posttraumatic stress disorder (PTSD) could adaptively suppress memory activity, but exposed individuals with PTSD could not. These findings suggest that the capacity to suppress memory is central to positive posttraumatic adaptation. A generalized disruption of the memory control system could explain the maladaptive and unsuccessful suppression attempts often seen in PTSD, and this disruption should be targeted by specific treatments.

Mary *et al.*, *Science* **367**, eaay8477 (2020) 14 February 2020

The expression and persistence of vivid, uncontrollable, and distressing intrusive memories is a central feature of posttraumatic stress disorder (PTSD) (*1*–*5*). After a traumatic event, attempts to suppress or avoid traumatic memories sometimes paradoxically increase the expression of intrusive memories (*6*–*8*). Successful treatments of intrusive memories involve overcoming such avoidance and suppression, as well as bringing back elements of the traumatic memory to promote its extinction or updating by the integration of a safe context (*2*, *5*, *9*, *10*). These treatments are in line with current neurobiological models that link PTSD to a learning impairment together with a deficit in processing contextual reminders in the fear circuit (*11*–*15*).

Theories of PTSD implicate experiential avoidance of traumatic memories via thought suppression as detrimental and central to the maintenance of intrusion symptoms (*2*, *16*–*19*). Experiential avoidance is mediated by the tonic maintenance of the to-be-avoided mental image in mind and by the engagement of a reactive inhibitory control process suppressing the momentary awareness of that unwanted thought (*20*, *21*). The former explains the paradoxical and maladaptive persistence of suppressed thoughts in memory and is exacerbated in PTSD (*22*, *23*). The latter, however, ultimately leads to forgetting of the suppressed event in healthy individuals (*24*–*31*).

Neurobiological Basis of PTSD

- Subset exhibits prolonged and abnormal, behavioral and physiological responses
- Manifested in the symptoms of PTSD
- Symptoms likely reflect:
  - Stress-induced changes in neurobiological systems and/or
  - Inadequate adaptation of neurobiological systems to stress

➔ Research focus on alterations in stress- regulating neurobiological systems

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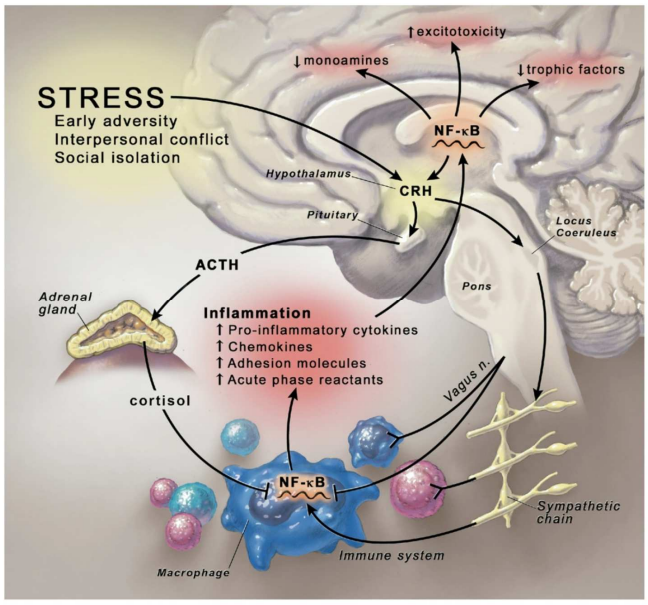
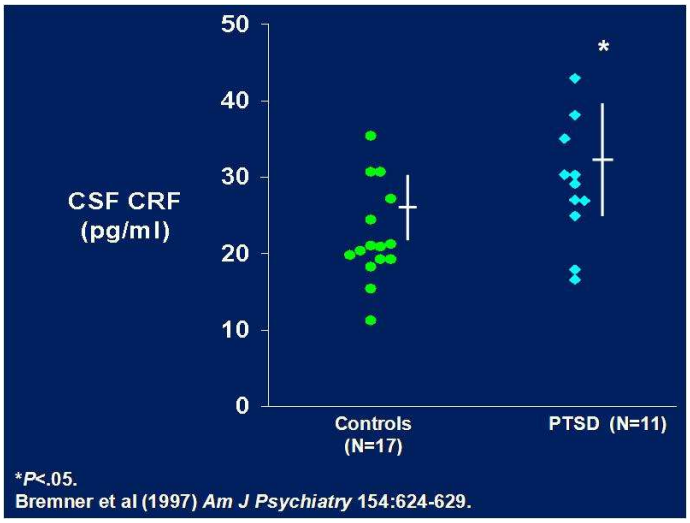


Miller et al (2009) Biol Psychiatry 65:732-741.

Elevated CSF Concentrations of Corticotropin Releasing Factor in Combat-Related PTSD



*P<.05.
Bremner et al (1997) *Am J Psychiatry* 154:624-629.

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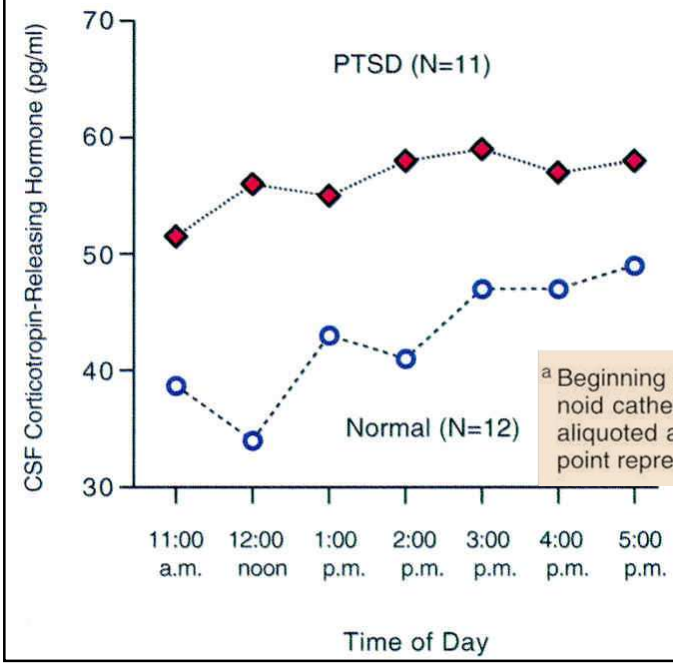

[a] Beginning after 15 hours of fasting and 3 hours after subarachnoid catheter placement, CSF was continuously withdrawn and aliquoted at 1-hour intervals from 11:00 a.m. to 5:00 p.m. Each point represents the mean.

Baker et al (1999) *Am J Psychiatry* 156:585-588

Early-Life Risk Factors of PTSD

- Early adverse experience predisposes for the development of PTSD in response to adulthood trauma
- In animal models and humans, early-life stress is associated with increased physiological and behavioral reactivity to stress
- Early-life stress permanently programs brain regions involved in the mediation of stress and anxiety.

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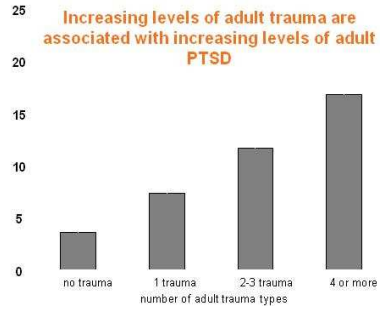
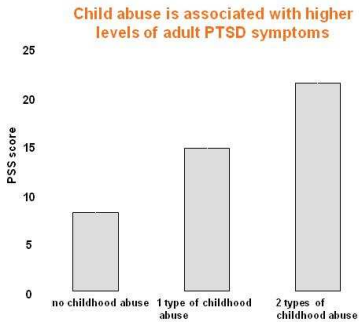
Sample Demographics

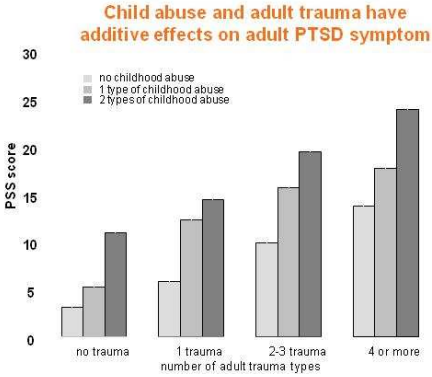
	N	Percentage
Gender		
Male	194	39%
Female	303	61%
Self-Identified Race/Ethnicity		
African American or Black	484	97%
Caucasian or White	4	.8%
Hispanic or Latino	2	.4%
Asian	1	.2%
Mixed	5	1%
Other	3	.6%
Education		
< 12th Grade	153	31%
High School Graduate or GED	217	44%
Some College or Technical School	78	15%
Technical School Graduate	21	4%
College Graduate	21	4%
Some Graduate School	9	2%
Employment Status		
Currently Unemployed	338	68%
Currently Employed	162	32%
Disability Status		
Not Currently Receiving Disability	394	79%
Currently Receiving Disability	103	21%
Household Monthly Income		
$0 – $249	158	32%
$250 – $499	51	10%
$500 - $999	136	28%
$1000 - $1999	106	21%
$2000 or more	158	9%

Bradley, Binder et al (2008) Arch Gen Psychiatry 65:190-200.

Adult Trauma and Child Abuse Predict PTSD







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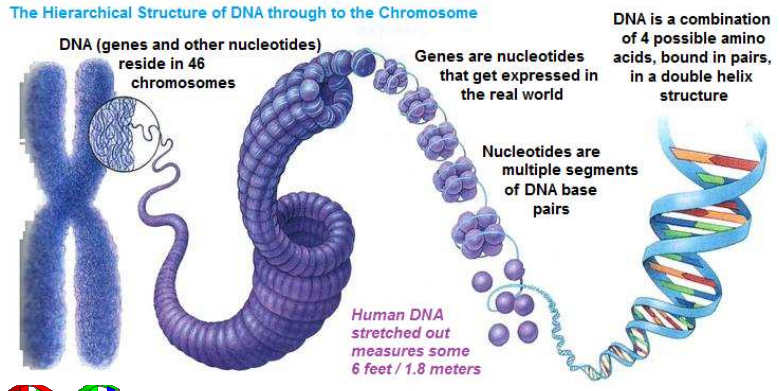
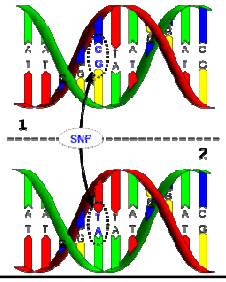
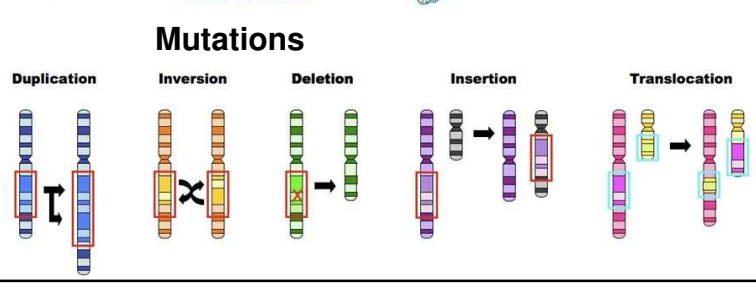
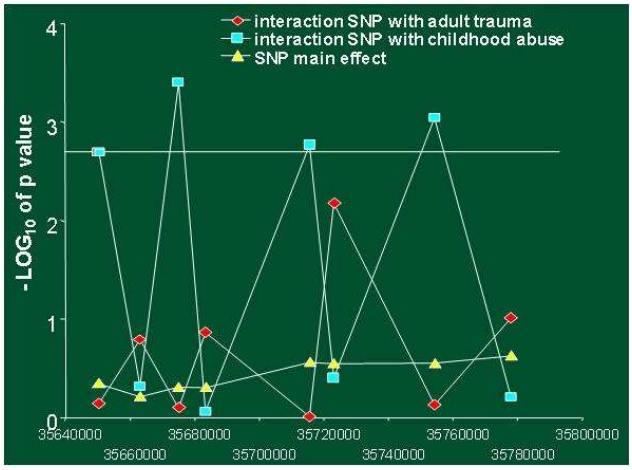
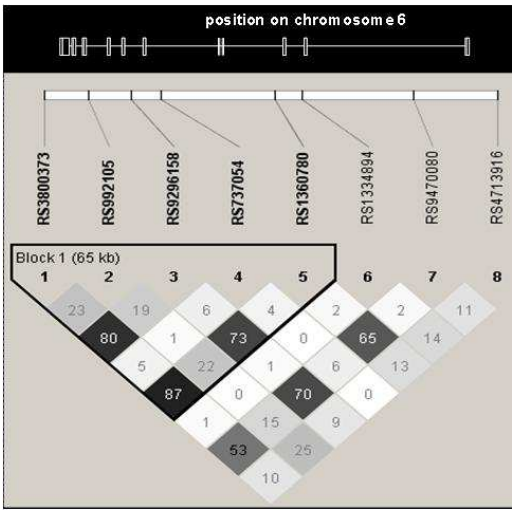






FKBP5 SNPs and Main Genetic Effect on PTSD Symptoms and Interaction Effects with Adult Trauma Levels and Child Abuse

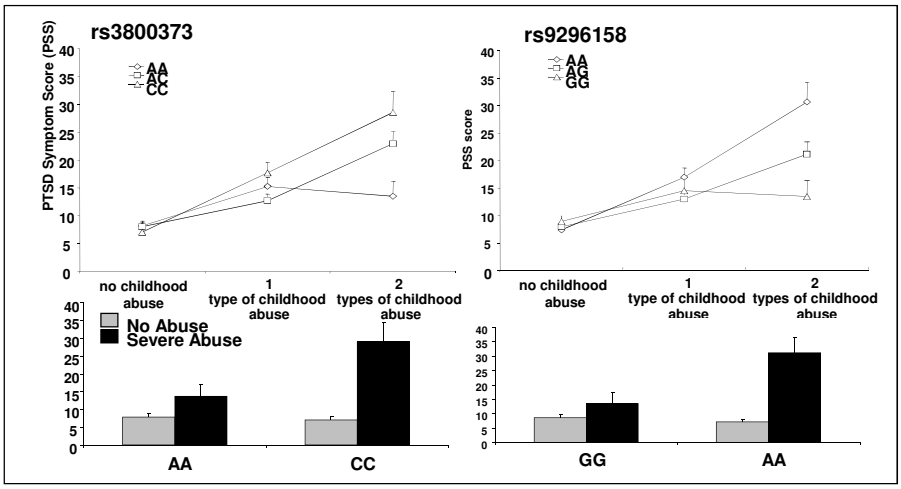




Binder et al (2008) *JAMA* 299:1291-1305

PTSD Severity, *FKBP5* SNP Genotypes and Child Abuse

For all 4 SNPs (rs1360780 and rs9470080 not shown)
an additive interaction effect with child abuse on PSS score is observed



Binder et al (2008) *JAMA* 299:1291-1305

Allele-specific DNA demethylation in FKBP5: a molecular mediator of gene x childhood trauma interactions

Torsten Klengel, Divya Mehta, Christoph Anacker, Jens C. Pruessner, Carmine M. Pariante, Thaddeus W.W. Pace, Kristina B. Mercer, Helen S. Mayberg, Bekh Bradley, Charles B. Nemeroff, Florian Holsboer, Christine M. Heim, Kerry J. Ressler, Theo Rein, and Elisabeth B. Binder

A polymorphism in the FK506 binding protein 5 (FKBP5) gene, an important regulator of the stress hormone system, increase the risk of developing stress-related psychiatric disorders in adulthood by allele-specific, childhood trauma-dependent DNA demethylation in functional glucocorticoid response elements (GREs) of FKBP5. This demethylation is linked to increased stress-dependent gene transcription followed by a long-term dysregulation of the stress hormone system and a global impact on the function of immune cells and brain areas associated with stress regulation.

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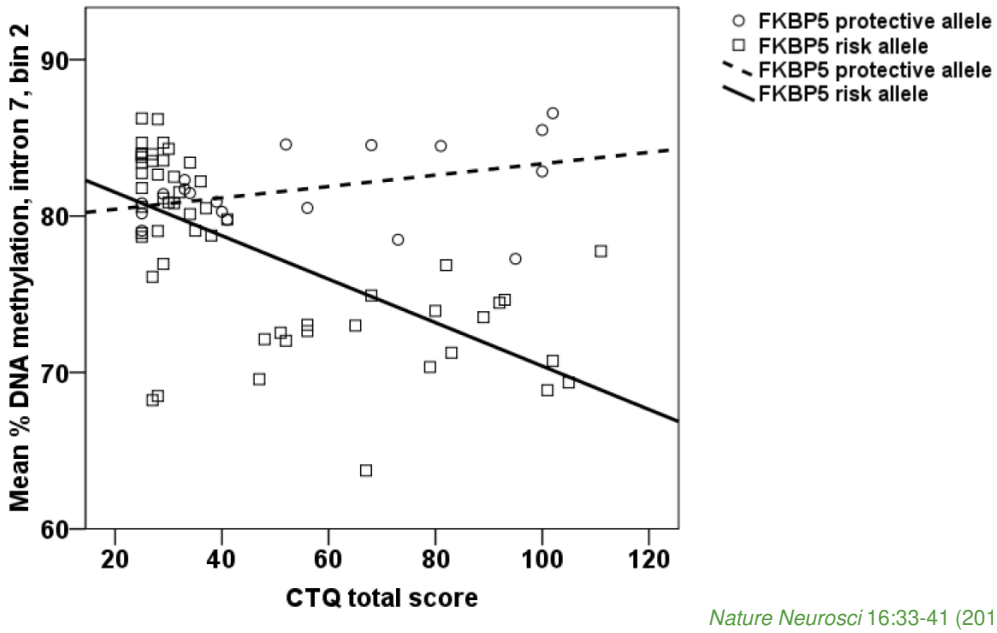

Nature Neurosci 16:33-41 (2013)

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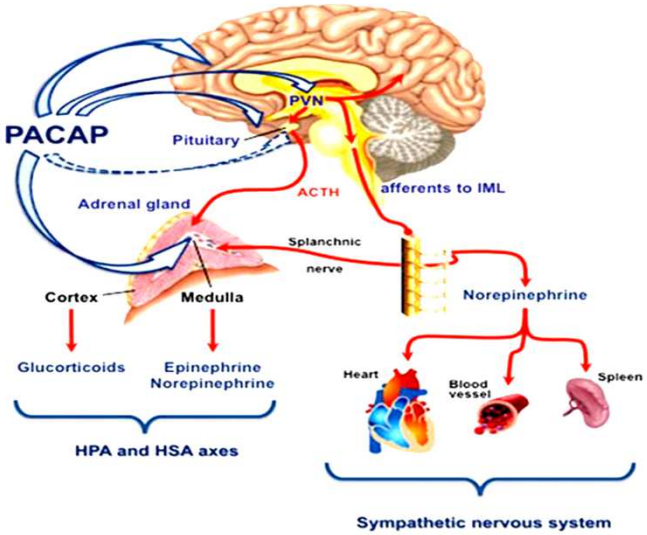
PACAP is a Central Stress Regulator



Stroth et al., 2011

ARTICLE

doi:10.1038/nature09856

Post-traumatic stress disorder is associated with PACAP and the PAC1 receptor

Kerry J. Ressler[1,2,4], Kristina B. Mercer[1], Bekh Bradley[2,3], Tanja Jovanovic[2], Amy Mahan[4], Kimberly Kerley[1], Seth D. Norrholm[2,3], Varun Kilaru[2], Alicia K. Smith[2], Amanda J. Myers[5], Manuel Ramirez[5], Anzhelika Engel[5], Sayamwong E. Hammack[6], Donna Toufexis[4,6], Karen M. Braas[7], Elisabeth B. Binder[2,8] & Victor May[7]

Pituitary adenylate cyclase-activating polypeptide (PACAP) is known to broadly regulate the cellular stress response. In contrast, it is unclear if the PACAP–PAC1 receptor pathway has a role in human psychological stress responses, such as post-traumatic stress disorder (PTSD). Here we find, in heavily traumatized subjects, a sex-specific association of PACAP blood levels with fear physiology, PTSD diagnosis and symptoms in females. We examined 44 single nucleotide polymorphisms (SNPs) spanning the PACAP (encoded by *ADCYAP1*) and PAC1 (encoded by *ADCYAP1R1*) genes, demonstrating a sex-specific association with PTSD. A single SNP in a putative oestrogen response element within *ADCYAP1R1*, rs2267735, predicts PTSD diagnosis and symptoms in females only. This SNP also associates with fear discrimination and with *ADCYAP1R1* messenger RNA expression in human brain. Methylation of *ADCYAP1R1* in peripheral blood is also associated with PTSD. Complementing these human data, *ADCYAP1R1* mRNA is induced with fear conditioning or oestrogen replacement in rodent models. These data suggest that perturbations in the PACAP–PAC1 pathway are involved in abnormal stress responses underlying PTSD. These sex-specific effects may occur via oestrogen regulation of *ADCYAP1R1*. PACAP levels and *ADCYAP1R1* SNPs may serve as useful biomarkers to further our mechanistic understanding of PTSD.

Nature 470:492-497 (2011)

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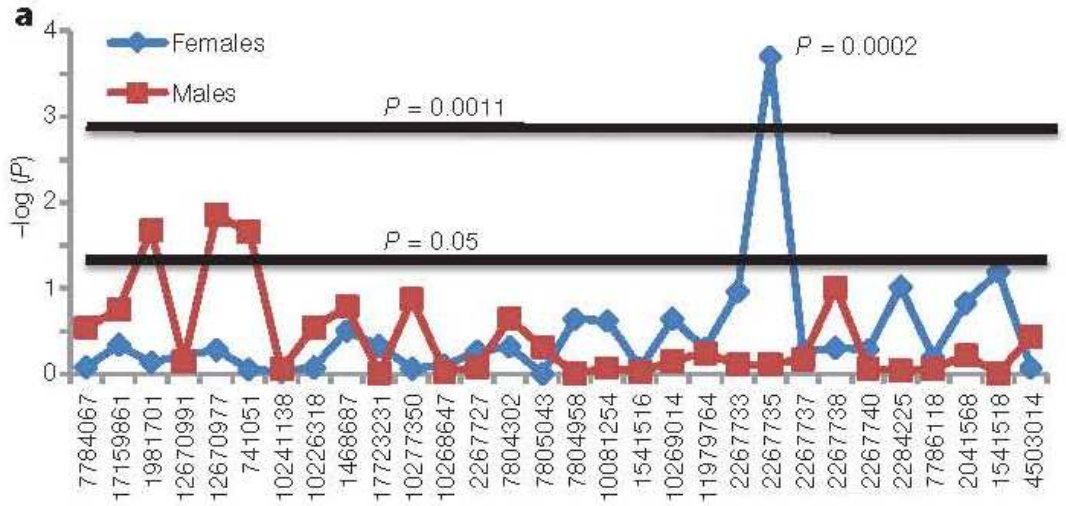
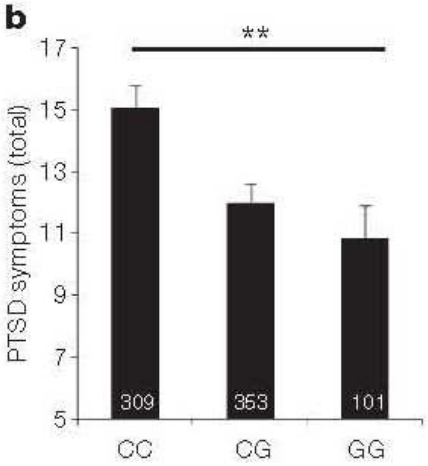


Nature 470:492-497 (2011)

a

rs2267735–PTSD	*N* (1,237)	*Wald* χ^2	OR (CI)	*P*-value
Male original	295	0.036	1.03 (0.71–1.49)	0.85
Male replication	179	0.57	0.83 (0.52–1.33)	0.45
Male combined	474	0.123	0.95 (0.71–1.27)	0.73
Female original	503	13.7	1.72 (1.29–2.28)	**0.00021**
Female replication	260	4.8	1.54 (1.04–2.29)	**0.029**
Female combined	763	18.4	1.66 (1.32–2.09)	**0.000018**

b



Nature 470:492-497 (2011)

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PTSD Blood Transcriptome Mega-Analysis: Shared Inflammatory Pathways across Biological Sex and Modes of Trauma

Michael S Breen[*,1,2], Daniel S Tylee[3], Adam X Maihofer[4], Thomas C Neylan[5,6], Divya Mehta[7], Elisabeth B Binder[8,9], Sharon D Chandler[4], Jonathan L Hess[3], William S Kremen[4,10], Victoria B Risbrough[4,10], Christopher H Woelk[11,12], Dewleen G Baker[4,10], Caroline M Nievergelt[4,10], Ming T Tsuang[4,10], Joseph D Buxbaum[1,2] and Stephen J Glatt[3]

Neuropsychopharmacology (2018) 43, 469–481

Transcriptome-wide screens of peripheral blood during the onset and development of posttraumatic stress disorder (PTSD) indicate widespread immune dysregulation. However, little is known as to whether biological sex and the type of traumatic event influence shared or distinct biological pathways in PTSD. We performed a combined analysis of five independent PTSD blood transcriptome studies covering seven types of trauma in 229 PTSD and 311 comparison individuals to synthesize the extant data. Analyses by trauma type revealed a clear pattern of PTSD gene expression signatures distinguishing interpersonal (IP)-related traumas from combat-related traumas. Co-expression network analyses integrated all data and identified distinct gene expression perturbations across sex and modes of trauma in PTSD, including one wound-healing module downregulated in men exposed to combat traumas, one IL-12-mediated signaling module upregulated in men exposed to IP-related traumas, and two modules associated with lipid metabolism and mitogen-activated protein kinase activity upregulated in women exposed to IP-related traumas. Remarkably, a high degree of sharing of transcriptional dysregulation across sex and modes of trauma in PTSD was also observed converging on common signaling cascades, including cytokine, innate immune, and type I interferon pathways. Collectively, these findings provide a broad view of immune dysregulation in PTSD and demonstrate inflammatory pathways of molecular convergence and specificity, which may inform mechanisms and diagnostic biomarkers for the disorder.

Neuropsychopharmacology (2018) 43, 469–481

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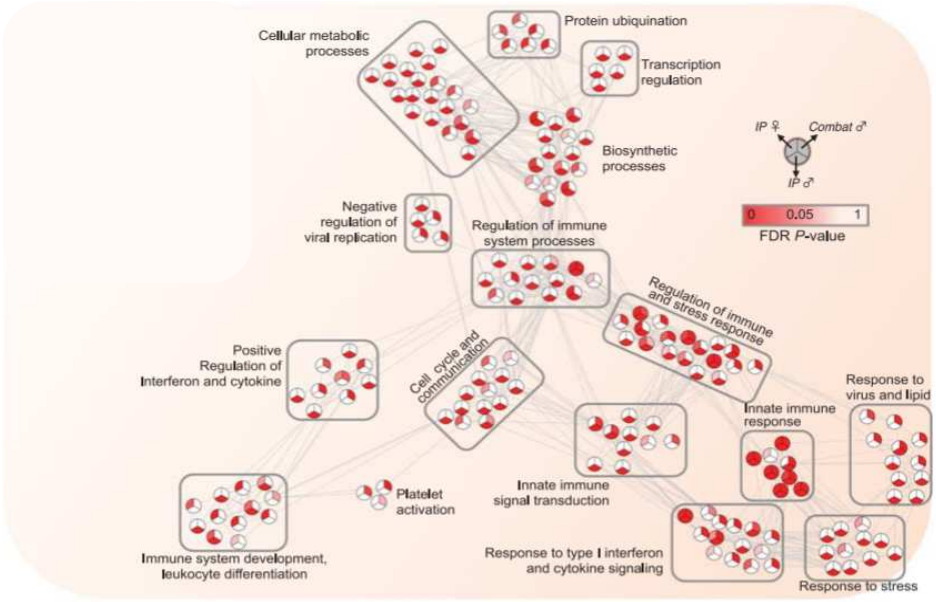
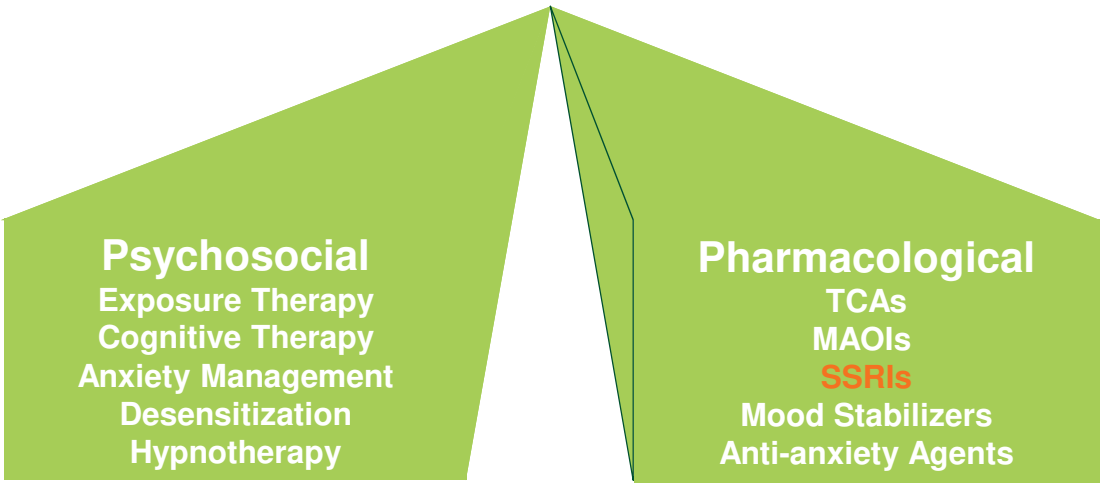


Neuropsychopharmacology (2018) 43, 469–481

PTSD Treatment Options



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General Goals of Treatment

- Reduce core symptoms
- Improve function and quality of life
- Strengthen resilience
- Relieve comorbid disorders
- Prevent relapse
- Rehabilitation

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EARLY INTERVENTION FOR PTSD (4 TO 30 DAYS POST-TRAUMA)	
Evidence of Benefit	**Intervention Modality**
Greatest benefit with the highest level of evidence	Brief cognitive-behavioral therapy (4 to 5 sessions)
Some positive benefit	Social support Psychoeducation and normalization
May be effective with multiple group sessions	Groups that provide trauma-related education, coping skills training, social support
Unknown benefit	Spiritual support Psychological first aid >4 days post-event
No evidence for or against the use of these drug therapies to prevent the development of ASD or PTSD	Prazosin Atypical antipsychotics Propranolol Imipramine Other antidepressants Anticonvulsants
Recommend against using	Typical antipsychotics
Strongly recommend against, may be harmful	Individual or group psychological debriefing Formal psychotherapy in asymptomatic individuals Benzodiazepines
Source: [68]	*Table 2*

Prolonged Imaginal Exposure: Theory

- Information/Emotional Processing
- Fear Normal Response to Trauma
- Fear, Anxiety, Social Conventions Lead to Avoidance
- Avoidance Reinforced
- Avoidance Prohibits Emotional Processing
- Emotional Processing Requires:
  1) Activation, 2) Corrective information

Foa & Rothbaum (1998) Treating the Trauma of Rape: A Cognitive-Behavioral Therapy for PTSD. Guilford: NY.

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Prolonged Imaginal Exposure: Techniques

- Imaginal Exposure
- In Vivo Exposure
- Includes
  - Education
  - Breathing Relaxation
  - Cognitive Therapy
- Virtual Reality Exposure

Foa & Rothbaum (1998) Treating the Trauma of Rape: A Cognitive-Behavioral Therapy for PTSD. Guilford: NY.

Evidence for Exposure

- 12 studies
- all positive
- 8 get AHCPR “A” rating
- Across Trauma Populations

Rothbaum et al (2000) J Traumatic Stress 13:558-563.

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JAMA Psychiatry | Original Investigation

Effect of Group vs Individual Cognitive Processing Therapy in Active-Duty Military Seeking Treatment for Posttraumatic Stress Disorder

A Randomized Clinical Trial

Patricia A. Resick, PhD; Jennifer Schuster Wachen, PhD; Katherine A. Dondanville, PsyD; Kristi E. Pruiksma, PhD; Jeffrey S. Yarvis, PhD; Alan L. Peterson, PhD; Jim Mintz, PhD; and the STRONG STAR Consortium

JAMA Psychiatry. 2017;74(1):28-36. doi:10.1001/jamapsychiatry.2016.2729
Published online November 23, 2016.

IMPORTANCE Cognitive processing therapy (CPT), an evidence-based treatment for posttraumatic stress disorder (PTSD), has not been tested as an individual treatment among active-duty military. Group CPT may be an efficient way to deliver treatment.

DESIGN, SETTING, AND PARTICIPANTS In this randomized clinical trial, 268 active-duty servicemembers consented to assessment at an army medical center from March 8, 2012, to September 23, 2014, and were randomized to group or individual CPT. Inclusion criteria were PTSD after military deployment and stable medication therapy. Exclusion criteria consisted of suicidal or homicidal intent or psychosis. Data collection was completed on June 15, 2015. Analysis was based on intention to treat.

INTERVENTIONS Participants received CPT (the version excluding written accounts) in 90-minute group sessions of 8 to 10 participants (15 cohorts total; 133 participants) or 60-minute individual sessions (135 participants) twice weekly for 6 weeks. The 12 group and individual sessions were conducted concurrently.

JAMA Psychiatry. 2017;74(1):28-36. doi:10.1001/jamapsychiatry.2016.2729
Published online November 23, 2016.

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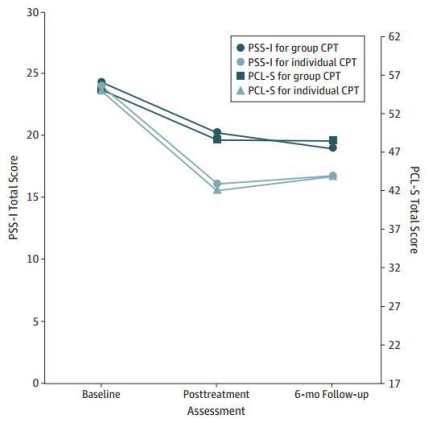
RESULTS Among the 268 participants (244 men [91.0%]; 24 women [9.0%]; mean [SD] age, 33.2 [7.4] years), improvement in PTSD severity at posttreatment was greater when CPT was administered individually compared with the group format (mean [SE] difference on the PSS-I, −3.7 [1.4]; Cohen *d* = 0.6; *P* = .006).

CONCLUSIONS AND RELEVANCE Individual treatment resulted in greater improvement in PTSD severity than group treatment. Depression and suicidal ideation improved equally with both formats. However, even among those receiving individual CPT, approximately 50% still had PTSD and clinically significant symptoms. In the military population, improving existing treatments such as CPT or developing new treatments is needed.

JAMA Psychiatry. 2017;74(1):28-36. doi:10.1001/jamapsychiatry.2016.2729
Published online November 23, 2016.

Figure 2. Change in Posttraumatic Stress Disorder (PTSD) Measures Across the Study Period



The Posttraumatic Symptom Scale–Interview Version (PSS-I) evaluates frequency and severity of *DSM-IV* PTSD symptoms (range, 0-51, with higher scores indicating worse symptoms). The stressor-specific Posttraumatic Stress Disorder Checklist (PCL-S) measures self-reported PTSD symptoms (range, 17-85, with higher scores indicating greater PTSD severity. CPT indicates cognitive processing therapy.

JAMA Psychiatry. 2017;74(1):28-36. doi:10.1001/jamapsychiatry.2016.2729
Published online November 23, 2016.

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JAMA | Original Investigation

Effect of Prolonged Exposure Therapy Delivered Over 2 Weeks vs 8 Weeks vs Present-Centered Therapy on PTSD Symptom Severity in Military Personnel
A Randomized Clinical Trial

Edna B. Foa, PhD; Carmen P. McLean, PhD; Yinyin Zang, PhD; David Rosenfield, PhD; Elna Yadin, PhD; Jeffrey S. Yarvis, PhD; Jim Mintz, PhD; Stacey Young-McCaughan, RN, PhD; Elisa V. Borah, PhD; Katherine A. Dondanville, PsyD; Brooke A. Fina, MSW; Brittany N. Hall-Clark, PhD; Tracey Lichner, PhD; Brett T. Litz, PhD; John Roache, PhD; Edward C. Wright, PhD; Alan L. Peterson, PhD; for the STRONG STAR Consortium

JAMA. 2018;319(4):354-364.

IMPORTANCE Effective and efficient treatment is needed for posttraumatic stress disorder (PTSD) in active duty military personnel.

OBJECTIVE To examine the effects of massed prolonged exposure therapy (massed therapy), spaced prolonged exposure therapy (spaced therapy), present-centered therapy (PCT), and a minimal-contact control (MCC) on PTSD severity.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial conducted at Fort Hood, Texas, from January 2011 through July 2016 and enrolling 370 military personnel with PTSD who had returned from Iraq, Afghanistan, or both. Final follow-up was July 11, 2016.

INTERVENTIONS Prolonged exposure therapy, cognitive behavioral therapy involving exposure to trauma memories/reminders, administered as massed therapy (n = 110; 10 sessions over 2 weeks) or spaced therapy (n = 109; 10 sessions over 8 weeks); PCT, a non–trauma-focused therapy involving identifying/discussing daily stressors (n = 107; 10 sessions over 8 weeks); or MCC, telephone calls from therapists (n = 40; once weekly for 4 weeks).

JAMA. 2018;319(4):354-364.

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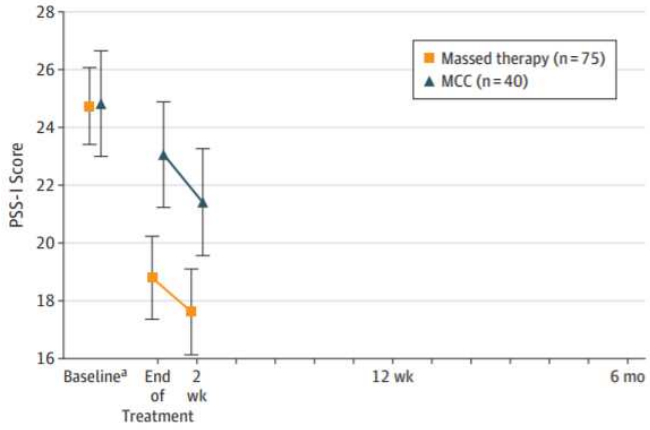
RESULTS Among 370 randomized participants, data were analyzed for 366 (mean age, 32.7 [SD, 7.3] years; 44 women [12.0%]; mean baseline PSS-I score, 25.49 [6.36]), and 216 (59.0%) completed the study. At 2 weeks posttreatment, mean PSS-I score was 17.62 (mean decrease from baseline, 7.13) for massed therapy and 21.41 (mean decrease, 3.43) for MCC (difference in decrease, 3.70 [95% CI,0.72 to 6.68]; $P = .02$). At 2 weeks posttreatment, mean PSS-I score was 18.03 for spaced therapy (decrease, 7.29; difference in means vs massed therapy, 0.79 [1-sided 95% CI, $-\infty$ to 2.29; $P = .049$ for noninferiority]) and at 12 weeks posttreatment was 18.88 for massed therapy (decrease, 6.32) and 18.34 for spaced therapy (decrease, 6.97; difference, 0.55 [1-sided 95% CI, $-\infty$ to 2.05; $P = .03$ for noninferiority]). At posttreatment, PSS-I scores for PCT were 18.65 (decrease, 7.31; difference in decrease vs spaced therapy, 0.10 [95% CI, −2.48 to 2.27]; $P = .93$).

CONCLUSIONS AND RELEVANCE Among active duty military personnel with PTSD, massed therapy (10 sessions over 2 weeks) reduced PTSD symptom severity more than MCC at 2-week follow-up and was noninferior to spaced therapy (10 sessions over 8 weeks), and there was no significant difference between spaced therapy and PCT. The reductions in PTSD symptom severity with all treatments were relatively modest, suggesting that further research is needed to determine the clinical importance of these findings.

JAMA. 2018;319(4):354-364.

A Hypothesis 1: Massed therapy superior to MCC



No. of participants					
Massed therapy	75	63	59		
MCC	40	40	39		

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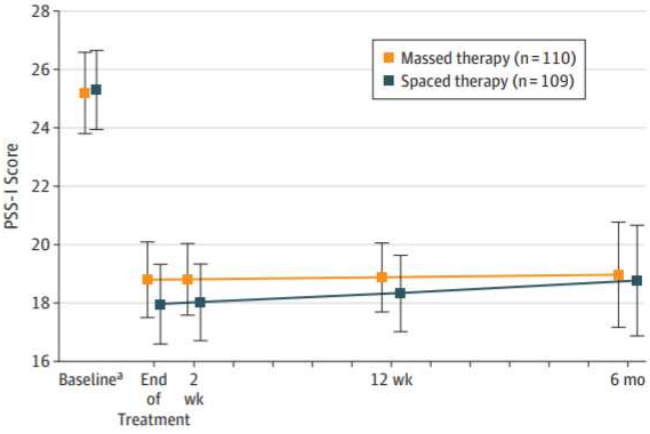
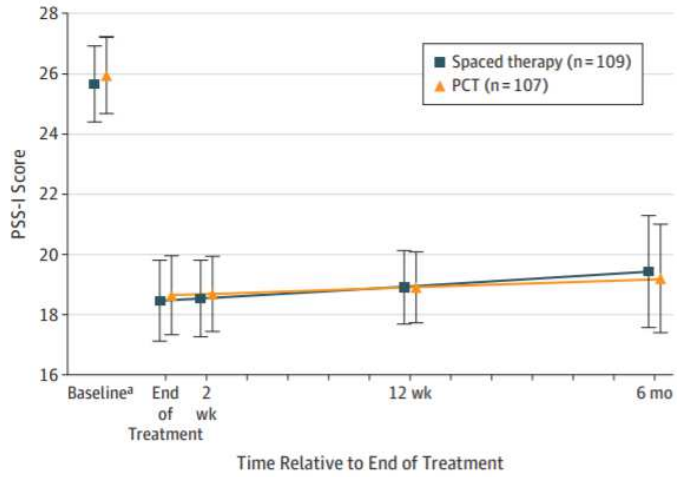
B Hypothesis 2: Massed therapy noninferior to spaced therapy



No. of participants					
Massed therapy	110	93	85	65	56
Spaced therapy	109	79	76	63	49

C Hypothesis 3: Spaced therapy superior to PCT



No. of participants					
Spaced therapy	109	79	76	63	49
PCT	107	86	77	69	53

JAMA. 2018;319(4):354-364.

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Controlled Trial of Psychotherapy for Congolese Survivors of Sexual Violence

Judith K. Bass, Ph.D., M.P.H., Jeannie Annan, Ph.D., Sarah McIvor Murray, M.S.P.H., Debra Kaysen, Ph.D., Shelly Griffiths, M.S.W., Talita Cetinoglu, M.A., Karin Wachter, M.Ed., Laura K. Murray, Ph.D., and Paul A. Bolton, M.B., B.S.

N ENGL J MED 368;23 NEJM.ORG JUNE 6, 2013

METHODS

In this trial in the Democratic Republic of Congo, we randomly assigned 16 villages to provide cognitive processing therapy (1 individual session and 11 group sessions) or individual support to female sexual-violence survivors with high levels of PTSD symptoms and combined depression and anxiety symptoms. One village was excluded owing to concern about the competency of the psychosocial assistant, resulting in 7 villages that provided therapy (157 women) and 8 villages that provided individual support (248 women). Assessments of combined depression and anxiety symptoms (average score on the Hopkins Symptom Checklist [range, 0 to 3, with higher scores indicating worse symptoms]), PTSD symptoms (average score on the Harvard Trauma Questionnaire [range, 0 to 3, with higher scores indicating worse symptoms]), and functional impairment (average score across 20 tasks [range, 0 to 4, with higher scores indicating greater impairment]) were performed at baseline, at the end of treatment, and 6 months after treatment ended.

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RESULTS

A total of 65% of participants in the therapy group and 52% of participants in the individual-support group completed all three assessments. Mean scores for combined depression and anxiety improved in the individual-support group (2.2 at baseline, 1.7 at the end of treatment, and 1.5 at 6 months after treatment), but improvements were significantly greater in the therapy group (2.0 at baseline, 0.8 at the end of treatment, and 0.7 at 6 months after treatment) ($P<0.001$ for all comparisons). Similar patterns were observed for PTSD and functional impairment. At 6 months after treatment, 9% of participants in the therapy group and 42% of participants in the individual-support group met criteria for probable depression or anxiety ($P<0.001$), with similar results for PTSD.

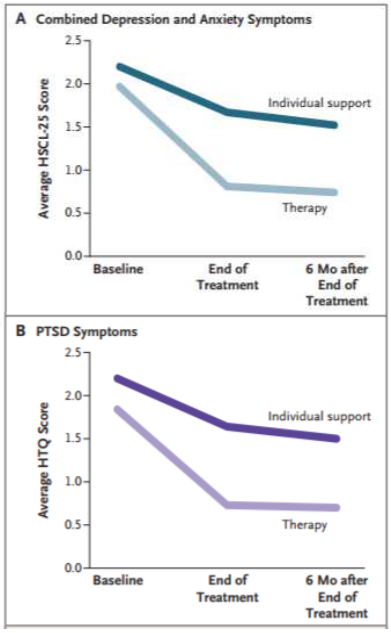

Figure 2. Symptom Scores at Trial Assessment Points.
Panel A shows the average Hopkins Symptom Checklist (HSCL-25) score for combined depression and anxiety, and Panel B shows the average Harvard Trauma Questionnaire (HTQ) score. Scores on both scales range from 0 to 3, with higher scores indicating worse symptoms. Scores of 1.75 or higher are consistent with clinically significant depression or anxiety and with PTSD, respectively. In both panels, P<0.001 for the comparisons at all three time points.

N ENGL J MED 368;23 NEJM.ORG JUNE 6, 2013

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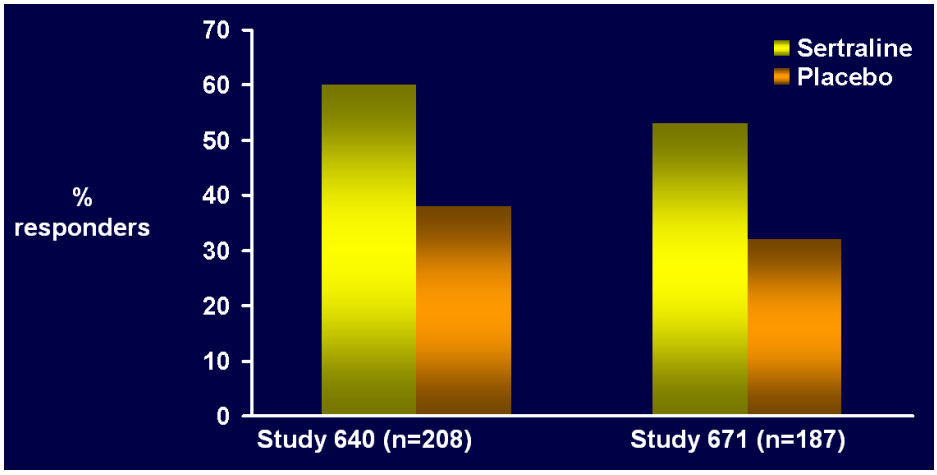
Sertraline in PTSD: Responder Analysis*

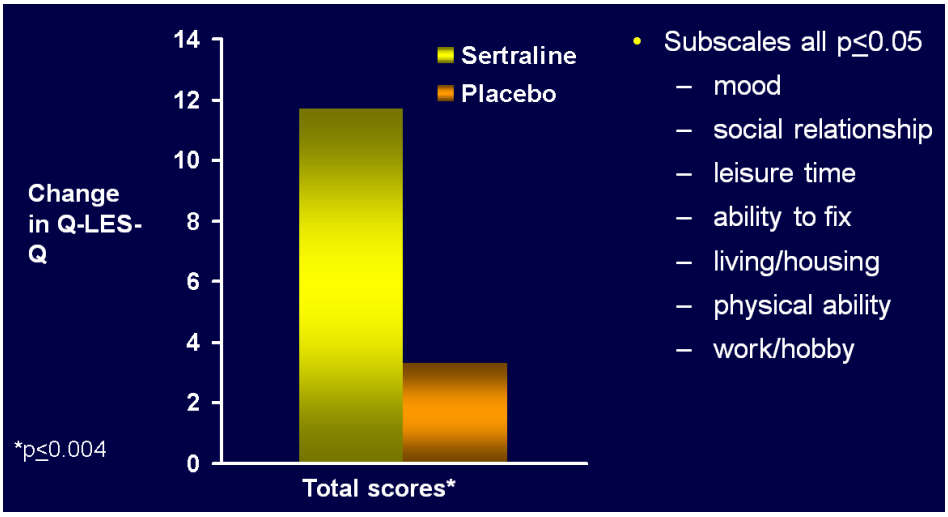


***Criteria: CAPS-2 ≥30% and CGI = 1 or 2 at endpoint**

p<0.05 sertraline vs. placebo

(Brady 2000; Davidson 2001)

Sertraline in PTSD: Quality of Life



- Subscales all p≤0.05
  - mood
  - social relationship
  - leisure time
  - ability to fix
  - living/housing
  - physical ability
  - work/hobby

(Brady 2000)

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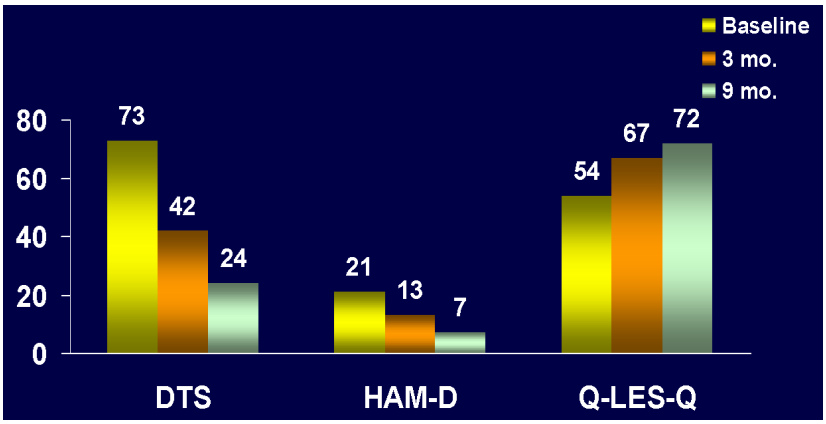
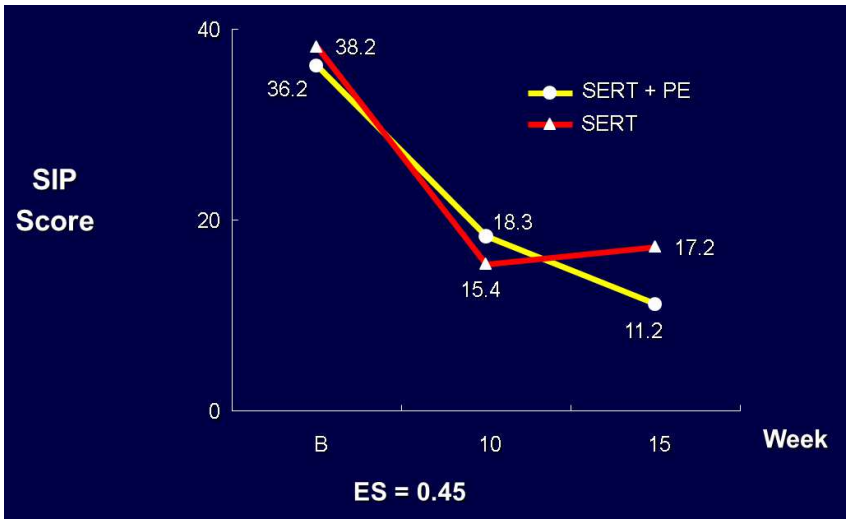
Sertraline in PTSD
Long-term Effects of Pharmacotherapy



DTS – Davidson Trauma Scale
Q-LES-Q – Quality of Life Enjoyment and Satisfaction Questionnaire

(Londborg 2001)

Augmentation of Sertraline with PE



(Foa, Rothbaum, Davidson 2002)

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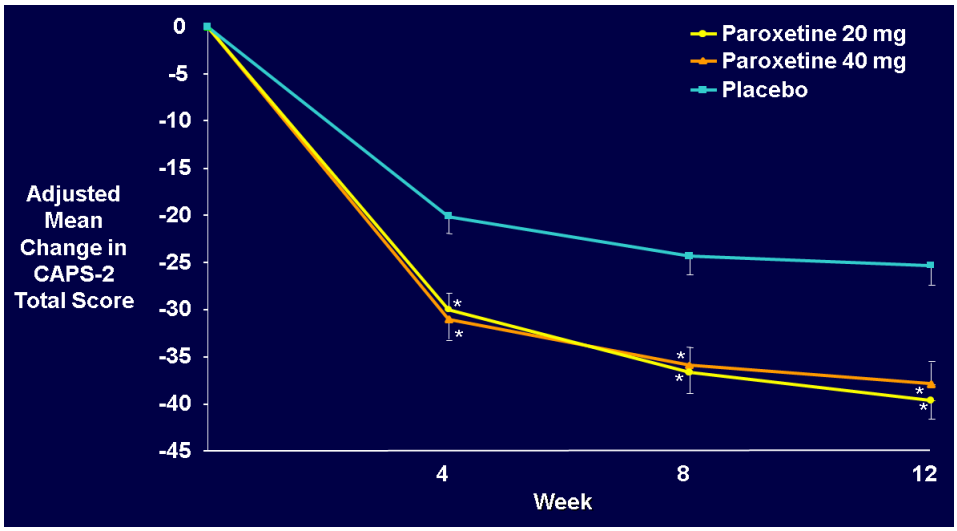
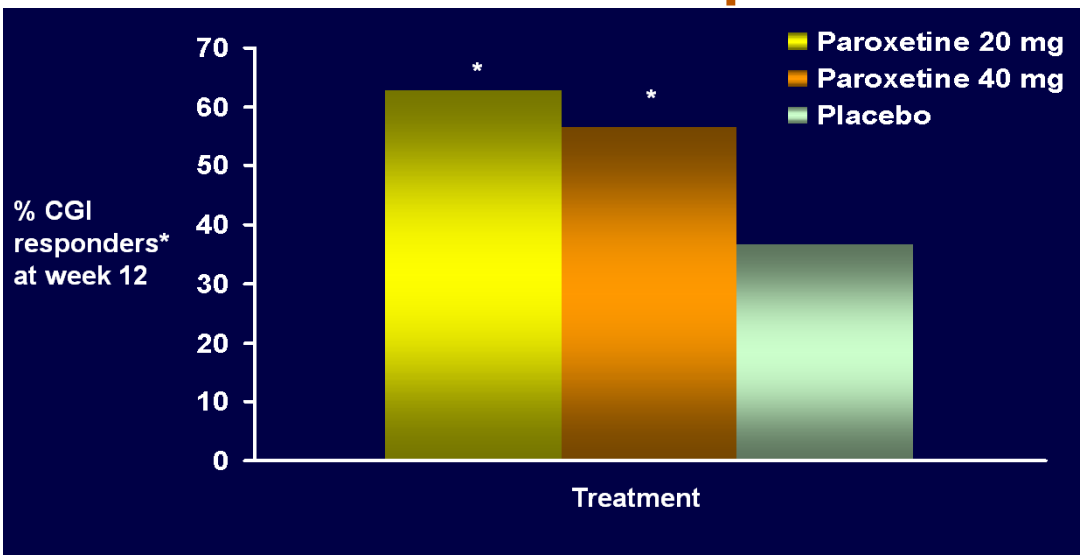
Paroxetine in PTSD: Fixed-Dose Study



(Marshall 2001)

Paroxetine in PTSD: Response Rates



(Marshall 2001)

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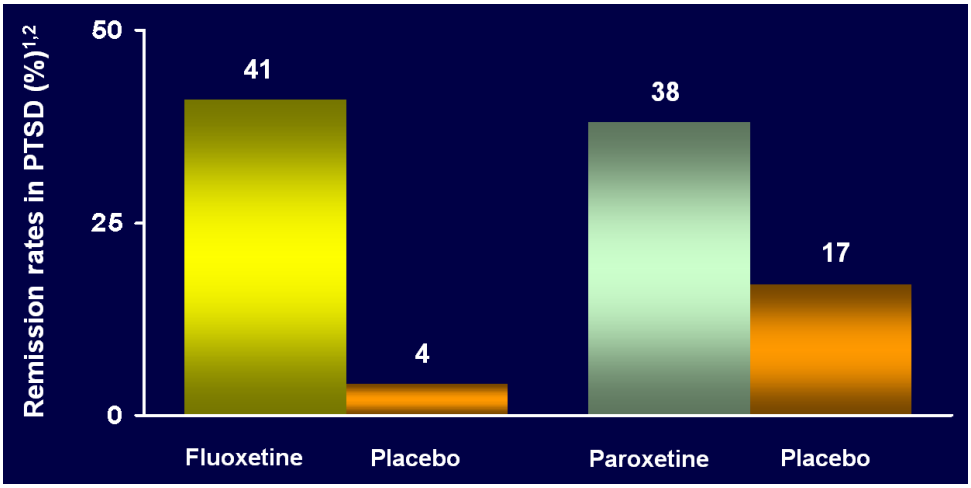
Remission Rates in PTSD



[1]CHEF (CGI-1 (score of 1), TOP-8 (score≤3), DTS (score≤17), SDS (≤6))
[2]CAPS-2 <20

(Connor 1999; Ballenger 2001)

Paroxetine in PTSD
Effect of Treatment on Functional Impairment: Sheehan Disability Scale (SDS)

(Tucker 2001)

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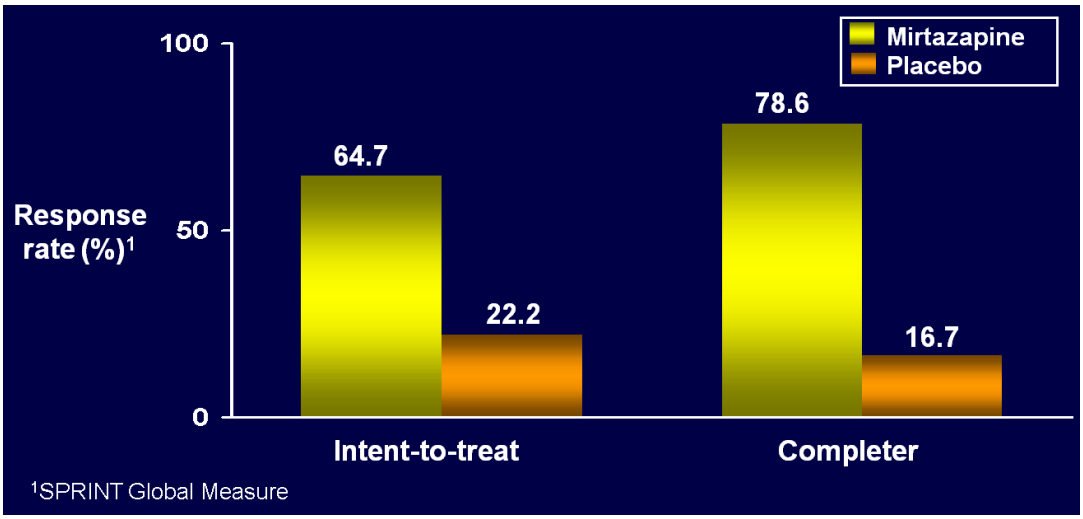
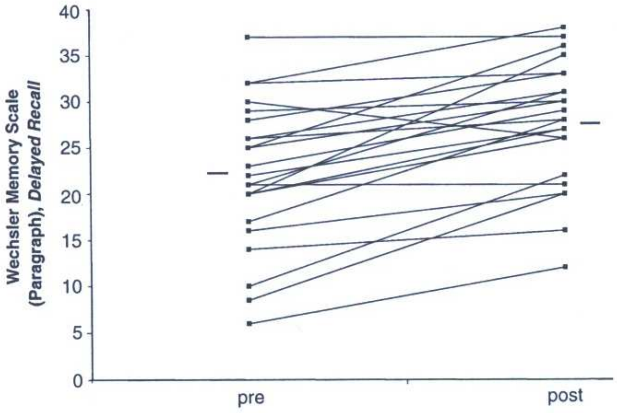
Mirtazapine in PTSD



(Davidson 2002)

Effects of Paroxetine on Hippocampal-Based Verbal Declarative Memory in PTSD



Mean improvement of 35%

Effects of 9-12 months of treatment with 10-40 mg paroxetine.

Vermetten et al (2003) Biol Psychiatry 54:693-702.

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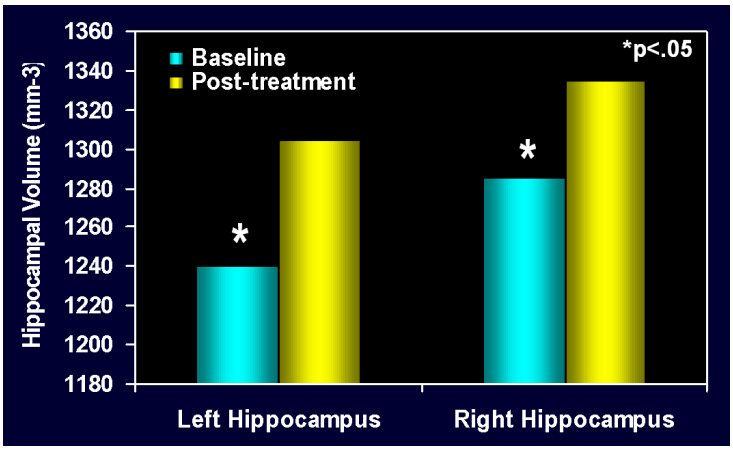
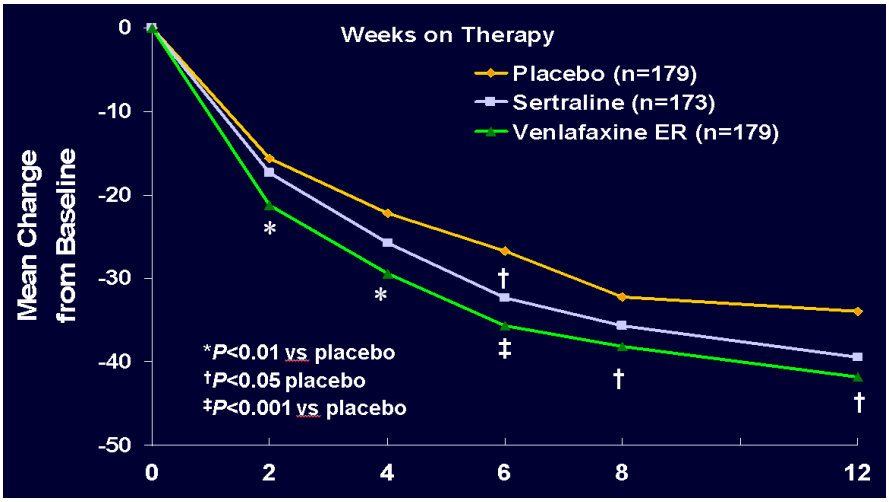
Increased Hippocampal Volume with Paroxetine in PTSD



Effects of 9-12 months of treatment with 10-40 mg paroxetine.

Vermetten et al (2003) Biol Psychiatry 54:693-702.

CAPS-SX$_{17}$ Change from Baseline (LOCF)



Rothbaum (2004). IV International Congress on Psychic Trauma and Traumatic Stress of the Argentine Society for Psychotrauma. Buenos Aires, Argentina.

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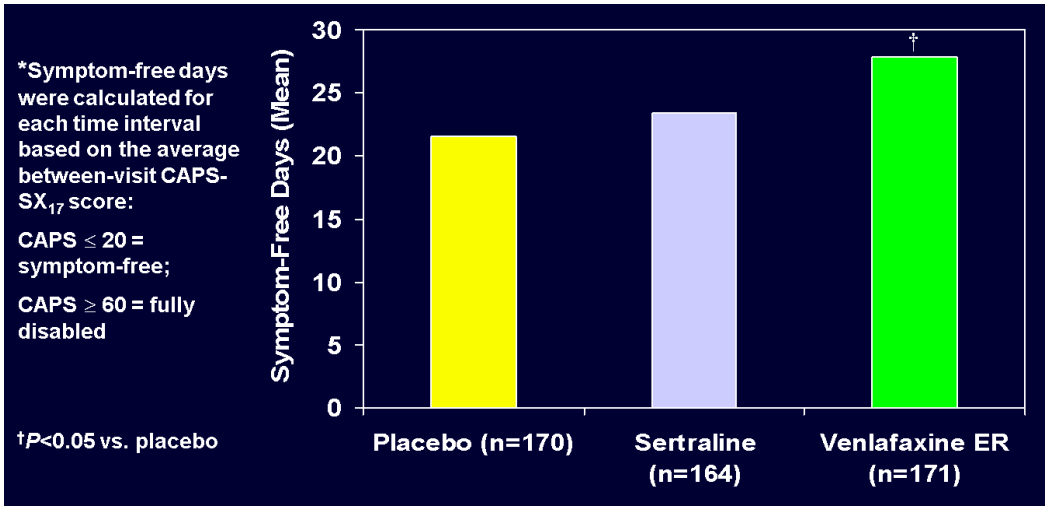
Symptom-Free Days* (Final On-Therapy)



Rothbaum (2004). IV International Congress on Psychic Trauma and Traumatic Stress of the Argentine Society for Psychotrauma. Buenos Aires, Argentina.

Study or subgroup	Experimental Mean	s.d.	Total	Control Mean	s.d.	Total	Weight	SMD IV, random, 95% CI
Brady (2000)[38]	−33	28.1	94	−23.2	28.7	93	5.8%	−0.34 (−0.63, −0.05)
Brady (2005)[61]	32.56	15.69	49	32.7	28.75	45	4.1%	−0.01 (−0.41, 0.40)
Connor (1999)[40]	10.1	9.8	25	20.5	12.6	22	2.4%	−0.91 (−1.52, −0.31)
Davidson[A]	−39.4	27.12	173	−34.17	28.42	179	7.3%	−0.19 (−0.40, 0.02)
Davidson (2001)[42]	−33	23.76	100	−26.2	23.9	108	6.1%	−0.28 (−0.56, −0.01)
Eli Lilly[B]	−10.42	7.5	323	−10.59	10.21	88	6.8%	0.02 (−0.21, 0.26)
Friedman (2007)[21]	−13.1	27.5	86	−15.4	28.07	83	5.6%	0.08 (−0.22, 0.38)
Hertzberg (2000)[47]	47	8	6	42	11	6	0.8%	0.48 (−0.68, 1.64)
Marshall (2001)[50]	−38.75	27.2	375	−25.3	25.8	188	8.0%	−0.50 (−0.68, −0.32)
Marshall (2004)[64]	55.6	33.4	25	62.8	40.8	27	2.8%	−0.19 (−0.73, 0.36)
Martenyi (2002)[51]	−34.6	28.1	226	26.8	26.1	75	6.3%	−0.28 (−0.54, −0.02)
Martenyi (2007)[23]	−42.85	25.5	323	−36.6	25.7	88	6.8%	−0.24 (−0.48, −0.01)
Panahi (2011)[26]	−22.7	7.3	35	−17.5	7.5	35	3.3%	−0.69 (−1.18, −0.21)
Pfizer 588[C]	−27.4	27.12	94	−27.9	28.42	94	5.9%	0.02 (−0.27, 0.30)
Pfizer 589[D]	−13.1	27.12	84	−15.4	28.42	82	5.6%	0.08 (−0.22, 0.39)
Shaleve (2011)[27]	−31.12	29.63	23	−27.8	20.13	23	2.5%	−0.13 (−0.71, 0.45)
SKB627[E]	−36.5	26.1	109	−30.8	25.37	103	6.2%	−0.22 (−0.49, 0.05)
Tucker (2001)[53]	−35.5	24.58	151	−24.7	24.98	156	7.0%	−0.43 (−0.66, −0.21)
Tucker (2003)[68]	−41.82	29.09	23	−38.7	29.07	10	1.7%	−0.10 (−0.85, 0.64)
Van der Kolk (2007)[70]	−33.23	22.11	30	−30.95	22.6	29	3.0%	−0.10 (−0.61, 0.41)
Zohar (2002)[54]	−18.7	6.7	23	−13.5	6.6	19	2.2%	−0.77 (−1.40, −0.14)
Total (95% CI)			2377			1553	100.0%	−0.23 (−0.33, −0.12)

Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 42.90$, d.f. = 20 ($P = 0.002$); $I^2 = 53\%$
Test for overall effect: $Z = 4.23$ ($P < 0.0001$)

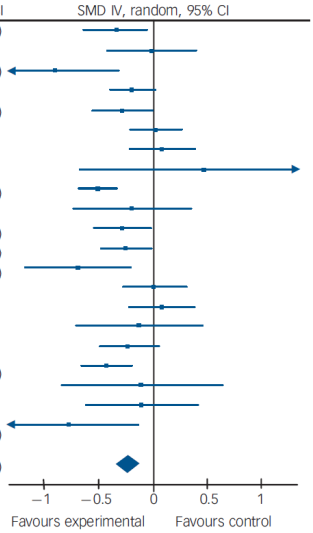


Figure 1: Meta-analysis of SSRIs vs. placebo for the treatment of PTSD. Reprinted from Hoskins et al. [45] with permission from The Royal College of Psychiatrists.

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Treatment of Posttraumatic Stress Disorder With Venlafaxine Extended Release

A 6-Month Randomized Controlled Trial

Jonathan Davidson, MD; David Baldwin, DM, FRCPsych; Dan J. Stein, MD; Enrique Kuper, BCETS, FAAETS; Isma Benattia, MD; Saeed Ahmed, MD; Ron Pedersen, MS; Jeff Musgnung, MT

Arch Gen Psychiatry. 2006;63:1158-1165

Results: Mean changes from baseline in Clinician-Administered Posttraumatic Stress Disorder Scale total scores at end point were –51.7 for venlafaxine ER and –43.9 for placebo ($P=.006$). Improvement was significantly greater for the venlafaxine ER group than for the placebo group in cluster scores for reexperiencing ($P=.008$) and avoidance/numbing ($P=.006$), but not for hyperarousal. Remission rates were 50.9% for venlafaxine ER and 37.5% for placebo ($P=.01$). The venlafaxine ER group also showed significantly greater improvement at end point than the placebo group ($P<.05$) on all other reported outcome measures. The mean maximum daily dose of venlafaxine ER was 221.5 mg/d. Withdrawal rates were similar between groups with no significant difference in dropouts attributable to adverse events.

Conclusion: In this study, venlafaxine ER was effective and well tolerated in short-term and continuation treatment of patients with posttraumatic stress disorder.

Arch Gen Psychiatry. 2006;63:1158-1165

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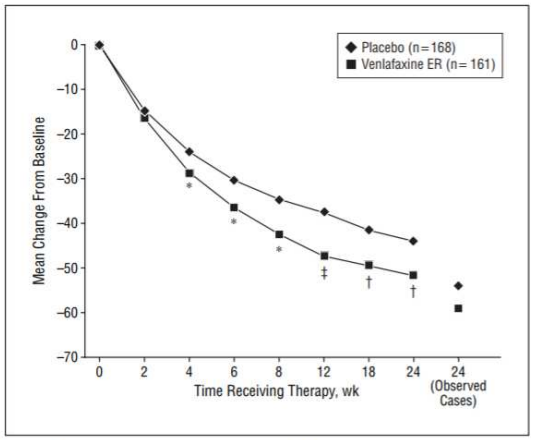

Figure 2. Change in score on the Clinician-Administered Posttraumatic Stress Disorder Scale, the abbreviated 1-Week Symptom Status Version, from the baseline score. All values represent last observation carried forward unless otherwise stated. ER indicates extended release. *P* values are based on pairwise comparisons from an analysis of covariance model with treatment as the main effect and baseline as the covariate. Asterisk indicates $P<.05$; dagger, $P<.01$; and double dagger, $P<.001$.

Arch Gen Psychiatry. 2006;63:1158-1165

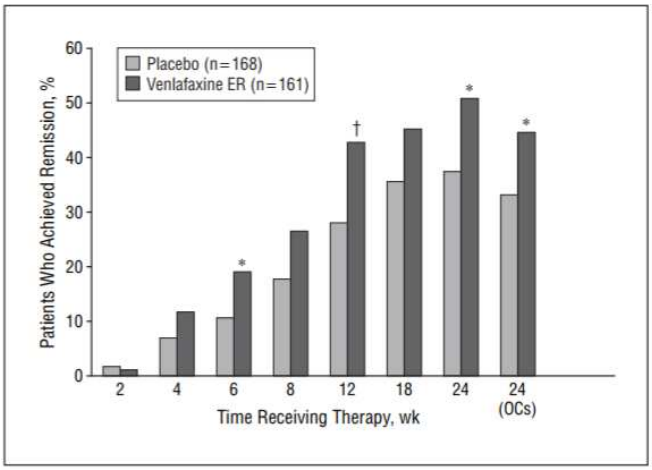

Figure 3. Patients who achieved remission (last observation carried forward). Remission is defined as a total score of 20 or lower on the Clinician-Administered Posttraumatic Stress Disorder Scale, the abbreviated 1-Week Symptom Status Version. ER indicates extended release; OCs, observed cases. Asterisk indicates $P<.05$; dagger, $P<.01$.

Arch Gen Psychiatry. 2006;63:1158-1165

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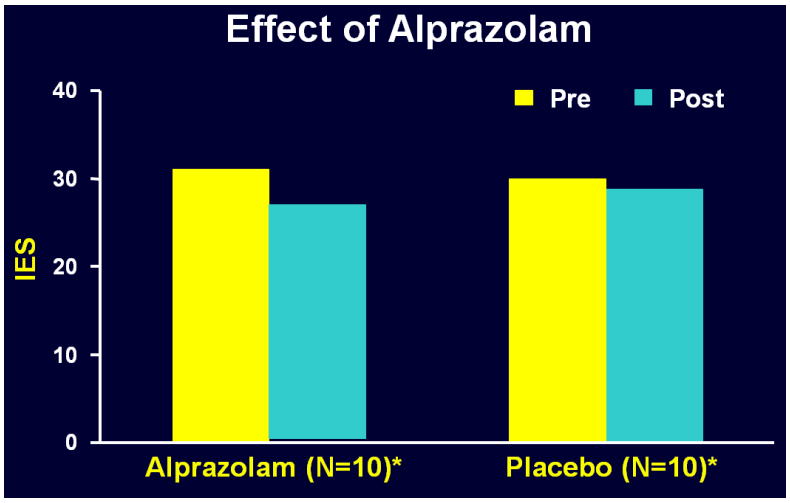
Treatment of PTSD with Benzodiazepines



**NS; Brown et al (1990)*

Original Investigation

Efficacy of Intravenous Ketamine for Treatment of Chronic Posttraumatic Stress Disorder
A Randomized Clinical Trial

Adriana Feder, MD; Michael K. Parides, PhD; James W. Murrough, MD; Andrew M. Perez, MD; Julia E. Morgan, BA; Shireen Saxena, MScPH; Katherine Kirkwood, MS; Marije aan het Rot, PhD; Kyle A. B. Lapidus, MD, PhD; Le-Ben Wan, MD, PhD; Dan Iosifescu, MD; Dennis S. Charney, MD

JAMA Psychiatry. 2014;71(6):681-688. doi:10.1001/jamapsychiatry.2014.62
Published online April 16, 2014.

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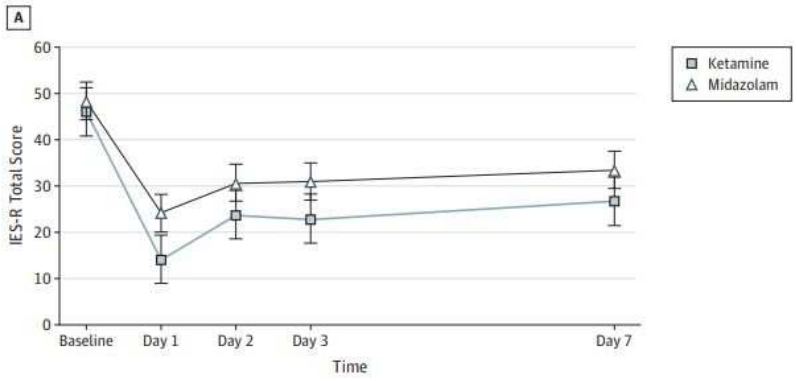
DESIGN, SETTING, AND PARTICIPANTS Proof-of-concept, randomized, double-blind, crossover trial comparing ketamine with an active placebo control, midazolam, conducted at a single site (Icahn School of Medicine at Mount Sinai, New York, New York). Forty-one patients with chronic PTSD related to a range of trauma exposures were recruited via advertisements.

INTERVENTIONS Intravenous infusion of ketamine hydrochloride (0.5 mg/kg) and midazolam (0.045 mg/kg).

RESULTS Ketamine infusion was associated with significant and rapid reduction in PTSD symptom severity, compared with midazolam, when assessed 24 hours after infusion (mean difference in Impact of Event Scale–Revised score, 12.7 [95% CI, 2.5-22.8]; $P = .02$). Greater reduction of PTSD symptoms following treatment with ketamine was evident in both crossover and first-period analyses, and remained significant after adjusting for baseline and 24-hour depressive symptom severity. Ketamine was also associated with reduction in comorbid depressive symptoms and with improvement in overall clinical presentation. Ketamine was generally well tolerated without clinically significant persistent dissociative symptoms.

Figure 2. Changes in Posttraumatic Stress Disorder and Depressive Symptom Levels During the First Period



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A Randomized Controlled Trial of Repeated Ketamine Administration for Chronic Posttraumatic Stress Disorder

Adriana Feder, M.D., Sara Costi, M.D., Sarah B. Rutter, M.A., Abigail B. Collins, B.S., Usha Govindarajulu, Ph.D., Manish K. Jha, M.D., Sarah R. Horn, M.A., Marin Kautz, M.A., Morgan Corniquel, M.A., Katherine A. Collins, Ph.D., M.S.W., Laura Bevilacqua, M.D., Ph.D., Andrew M. Glasgow, M.D., Jess Brallier, M.D., Robert H. Pietrzak, Ph.D., M.P.H., James W. Murrough, M.D., Ph.D., Dennis S. Charney, M.D.

Am J Psychiatry 178:2, February 2021

nature medicine
ARTICLES
https://doi.org/10.1038/s41591-021-01336-3
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MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study

Post-traumatic stress disorder (PTSD) presents a major public health problem for which currently available treatments are modestly effective. We report the findings of a randomized, double-blind, placebo-controlled, multi-site phase 3 clinical trial (NCT03537014) to test the efficacy and safety of 3,4-methylenedioxymethamphetamine (MDMA)-assisted therapy for the treatment of patients with severe PTSD, including those with common comorbidities such as dissociation, depression, a history of alcohol and substance use disorders, and childhood trauma. After psychiatric medication washout, participants ($n = 90$) were randomized 1:1 to receive manualized therapy with MDMA or with placebo, combined with three preparatory and nine integrative therapy sessions. PTSD symptoms, measured with the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5, the primary endpoint), and functional impairment, measured with the Sheehan Disability Scale (SDS, the secondary endpoint) were assessed at baseline and at 2 months after the last experimental session. Adverse events and suicidality were tracked throughout the study. MDMA was found to induce significant and robust attenuation in CAPS-5 score compared with placebo ($P < 0.0001$, $d = 0.91$) and to significantly decrease the SDS total score ($P = 0.0116$, $d = 0.43$). The mean change in CAPS-5 scores in participants completing treatment was −24.4 (s.d. 11.6) in the MDMA group and −13.9 (s.d. 11.5) in the placebo group. MDMA did not induce adverse events of abuse potential, suicidality or QT prolongation. These data indicate that, compared with manualized therapy with inactive placebo, MDMA-assisted therapy is highly efficacious in individuals with severe PTSD, and treatment is safe and well-tolerated, even in those with comorbidities. We conclude that MDMA-assisted therapy represents a potential breakthrough treatment that merits expedited clinical evaluation.

Mitchell et al, Nature Medicine

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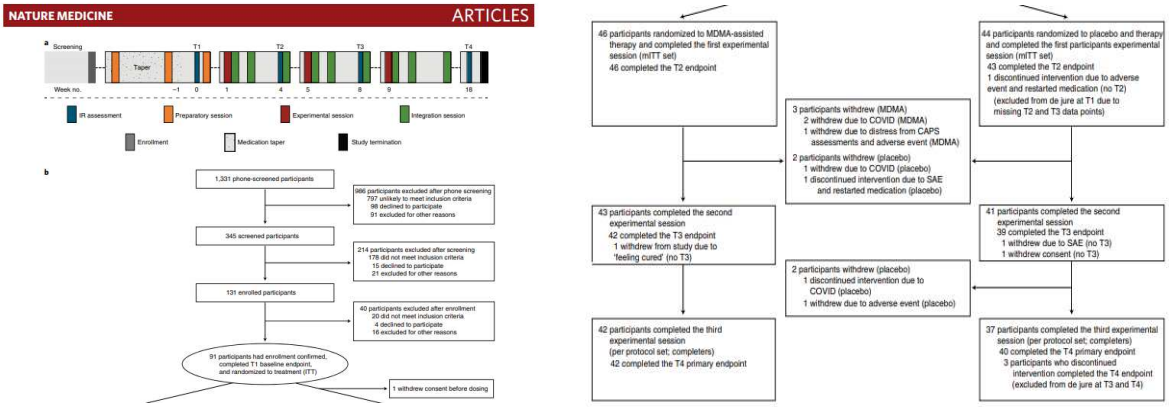
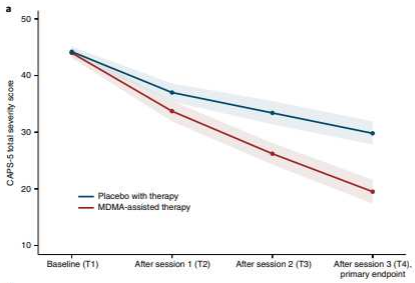
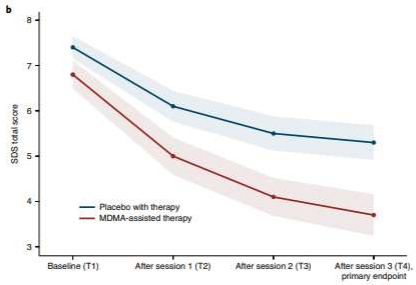


Fig. 1 | Procedure timeline and study flow diagram. a, Procedure timeline. Following the screening procedures and medication taper, participants attended a total of three preparatory sessions, three experimental sessions, nine integration sessions and four endpoint assessments (T1–4) over 18 weeks, concluding with a final study-termination visit. IR, independent rater; T, timepoint of endpoint assessment; T1, baseline; T2, after the first experimental session; T3, after the second experimental session; T4, 18 weeks after baseline. **b**, CONSORT diagram indicating participant numbers and disposition through the course of the trial.





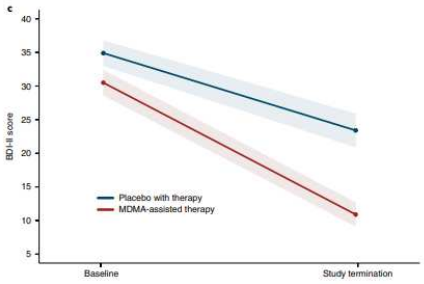


Fig. 2 | Measures of MDMA efficacy in the MDMA-assisted therapy group and the placebo group. a. Change in CAPS-5 total severity score from T1 to T4 ($P < 0.0001$, $d = 0.91$, $n = 89$ (MDMA $n = 46$)), as a measure of the primary outcome. Primary analysis was completed using least square means from an MMRM model. **b**. Change in SDS total score from T1 to T4 ($P = 0.0116$, $d = 0.43$, $n = 89$ (MDMA $n = 46$)), as a measure of the secondary outcome. Primary analysis was completed using least square means from an MMRM model. **c**. Change in BDI-II score from T1 to study termination ($t = -3.11$, $P = 0.0026$, $n = 81$ (MDMA $n = 42$)), as a measure of the exploratory outcome. Data are presented as mean and s.e.m.

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A sham controlled study of repetitive transcranial magnetic stimulation for posttraumatic stress disorder

Bradley V. Watts,[a,b,c] Barbara Landon,[d] Alicia Groft,[b] Yinong Young-Xu[b,c]

[a]*Veterans Engineering Resource Center, White River Junction, Vermont*
[b]*Department of Psychiatry, Dartmouth Medical School, Hanover, New Hampshire*
[c]*Veterans Administration National Center for Patient Safety, White River Junction, Vermont*
[d]*Saint Georges University, Grenada, British West Indies*

Background
Posttraumatic stress disorder (PTSD) is a commonly occurring and often debilitating psychiatric condition. There currently is not definitive information regarding the efficacy of repetitive transcranial magnetic stimulation (rTMS) for PTSD.

Objective
This study seeks to examine the efficacy of rTMS for PTSD.

Methods
Twenty subjects with PTSD were randomly assigned to receive either 10 rTMS sessions delivered at 1 Hz to the right dorsolateral prefrontal cortex (DLPRC) or 10 sham rTMS sessions to the same area. A blinded rater assessed PTSD, depressive, anxiety, and neurocognitive symptoms before treatment, after the treatment series, and during a 2-month follow-up period.

Results
Trancranial magnetic stimulation delivered at 1 Hz to the right DLPRC resulted in statistically and clinically significant improvements in core PTSD symptoms and depressive symptoms compared with sham treatments. The effectiveness showed some degradation during the 2 months after treatments were stopped.

Brain Stimulation (2012) 5, 38–43

DEPRESSION AND ANXIETY 1:1–8 (2015)

EFFICACY AND LONG-TERM CLINICAL OUTCOME OF COMORBID POSTTRAUMATIC STRESS DISORDER AND MAJOR DEPRESSIVE DISORDER AFTER ELECTROCONVULSIVE THERAPY

Naser Ahmadi, M.D. Ph.D.,[1,2]* Lori Moss, M.D.,[1] Edwin Simon, M.D.,[1] Charles B. Nemeroff, M.D. Ph.D.,[3] and Nutan Atre-Vaidya, M.D.[1]

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Background: *Many patients fulfill criteria for both posttraumatic stress disorder (PTSD) and major depressive disorder (MDD). Electroconvulsive therapy (ECT) is generally acknowledged to be the most-effective treatment for refractory MDD. This study investigated the efficacy of ECT on long-term clinical outcome of comorbid PTSD and MDD.* **Methods:** *This retrospective nested matched case-control study is inclusive of 22,164 subjects [3,485 with comorbid MDD and PTSD (92 with ECT and 3,393 without ECT) and 18,679 without MDD and PTSD].* **Results:** *Using the clinical global impression scale (CGI) to assess efficacy, more-robust improvement of PTSD and MDD symptoms was observed with ECT (90%), compared to antidepressant-treatment alone(50%) ($P = 0.001$). During the median of 8 years of follow-up, the death-rate was 8% in subjects without PTSD and MDD, 9.7% in PTSD and MDD treated with ECT and 18% in PTSD and MDD without ECT ($P < 0.05$).*

The relative risk of suicidality, all-cause, and cardiovascular mortality was reduced 64, 65, and 46% in MDD and PTSD patients treated with ECT, compared to those without ECT (P < 0.05). Conclusion: ECT is associated with a significant reduction of symptoms of PTSD and MDD, as well as reduction in risk of suicidality, cardiovascular, and all-cause mortality in MDD and PTSD, an effect more robust than antidepressant-therapy alone.

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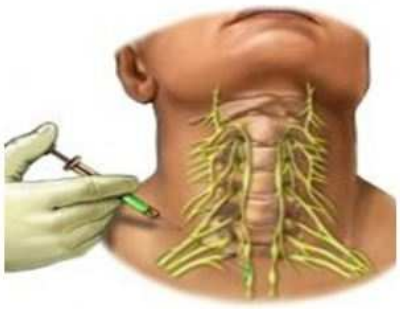
Ketamine & Stellate Ganglion Blocks for PTSD



Stellate Ganglion blocks act on the sympathetic nervous system and are effective in 70% of PTSD patients.

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JAMA Psychiatry | Original Investigation

Effect of Stellate Ganglion Block Treatment on Posttraumatic Stress Disorder Symptoms
A Randomized Clinical Trial

Kristine L. Rae Olmsted, MSPH; Michael Bartoszek, MD; Sean Mulvaney, MD; Brian McLean, MD; Ali Turabi, MD; Ryan Young, MD; Eugene Kim, MD; Russ Vandermaas-Peeler, MS; Jessica Kelley Morgan, PhD; Octav Constantinescu, MD; Shawn Kane, MD; Cuong Nguyen, MD; Shawn Hirsch, MPH; Breda Munoz, PhD; Dennis Wallace, PhD; Julie Croxford, BSN, MPH; James H. Lynch, MD; Ronald White, MD; Bradford B. Walters, MD, PhD

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2019.3474
Published online November 6, 2019.

IMPORTANCE This is the first multisite, randomized clinical trial of stellate ganglion block (SGB) outcomes on posttraumatic stress disorder (PTSD) symptoms.

OBJECTIVE To determine whether paired SGB treatments at 0 and 2 weeks would result in improvement in mean Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5) total symptom severity scores from baseline to 8 weeks.

DESIGN, SETTING, AND PARTICIPANTS This multisite, blinded, sham-procedure, randomized clinical trial used a 2:1 SGB:sham ratio and was conducted from May 2016 through March 2018 in 3 US Army Interdisciplinary Pain Management Centers. Only anesthesiologists performing the procedures and the procedure nurses were aware of the intervention (but not the participants or assessors); their interactions with the participants were scripted and limited to the 2 interventions. Active-duty service members on stable psychotropic medication dosages who had a PTSD Checklist–Civilian Version (PCL-C) score of 32 or more at screening were included. Key exclusion criteria included a prior SGB treatment, selected psychiatric disorders or substance use disorders, moderate or severe traumatic brain injury, or suicidal ideation in the prior 2 months.

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INTERVENTIONS Paired right-sided SGB or sham procedures at weeks 0 and 2.

MAIN OUTCOMES AND MEASURES Improvement of 10 or more points on mean CAPS-5 total symptom severity scores from baseline to 8 weeks, adjusted for site and baseline total symptom severity scores (planned a priori).

RESULTS Of 190 screened individuals, 113 (59.5%; 100 male and 13 female participants; mean [SD] age, 37.3 [6.7] years) were eligible and randomized (74 to SGB and 39 to sham treatment), and 108 (95.6% of 113) completed the study. Baseline characteristics were similar in the SGB and sham treatment groups, with mean (SD) CAPS-5 scores of 37.6 (11.2) and 39.8 (14.4), respectively (on a scale of 0-80); 91 (80.0%) met CAPS-5 PTSD criteria. In an intent-to-treat analysis, adjusted mean total symptom severity score change was −12.6 points (95% CI, −15.5 to −9.7 points) for the group receiving SGB treatments, compared with −6.1 points (95% CI, −9.8 to −2.3 points) for those receiving sham treatment (P = .01).

CONCLUSIONS AND RELEVANCE In this trial of active-duty service members with PTSD symptoms (at a clinical threshold and subthreshold), 2 SGB treatments 2 weeks apart were effective in reducing CAPS-5 total symptom severity scores over 8 weeks. The mild-moderate baseline level of PTSD symptom severity and short follow-up time limit the generalizability of these findings, but the study suggests that SGB merits further trials as a PTSD treatment adjunct.

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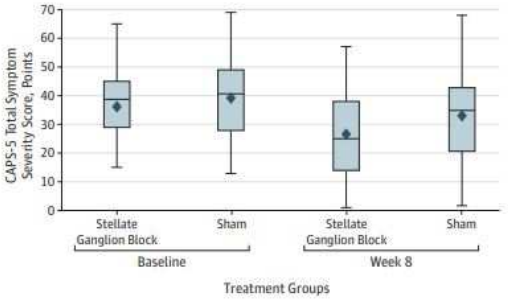
Figure 2. Unadjusted Clinician-Administered Posttraumatic Stress Disorder Scale for *DSM-5* (CAPS-5) Total Symptom Severity Score at Baseline and Week 8 by Treatment Group



Within each box plot, the top of the box represents the 75th percentile, the diamond represents the mean, the horizontal line within the box represents the median, and the bottom of the box represents the 25th percentile. The upper and lower ends of the whiskers correspond to the highest value and the lowest value, respectively.

Sleep Problems in PTSD

- Hypnotics (Temazepam)
- Antidepressants (Trazodone, Mirtazapine)
- Gabapentin (Neurontin)
- Clonidine
- Prazosin
- Guanfacine
- Imagery Rehearsal Therapy
- CPAP

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Trial of Prazosin for Post-Traumatic Stress Disorder in Military Veterans

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ABSTRACT

BACKGROUND

In randomized trials, prazosin, an α_1-adrenoreceptor antagonist, has been effective in alleviating nightmares associated with post-traumatic stress disorder (PTSD) in military veterans.

METHODS

We recruited veterans from 13 Department of Veterans Affairs medical centers who had chronic PTSD and reported frequent nightmares. Participants were randomly assigned to receive prazosin or placebo for 26 weeks; the drug or placebo was administered in escalating divided doses over the course of 5 weeks to a daily maximum of 20 mg in men and 12 mg in women. After week 10, participants continued to receive prazosin or placebo in a double-blind fashion for an additional 16 weeks. The three primary outcome measures were the change in score from baseline to 10 weeks on the Clinician-Administered PTSD Scale (CAPS) item B2 ("recurrent distressing dreams"; scores range from 0 to 8, with higher scores indicating more frequent and more distressing dreams); the change in score from baseline to 10 weeks on the Pittsburgh Sleep Quality Index (PSQI; scores range from 0 to 21, with higher scores indicating worse sleep quality); and the Clinical Global Impression of Change (CGIC) score at 10 weeks (scores range from 1 to 7, with lower scores indicating greater improvement and a score of 4 indicating no change).

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RESULTS

A total of 304 participants underwent randomization; 152 were assigned to prazosin, and 152 to placebo. At 10 weeks, there were no significant differences between the prazosin group and the placebo group in the mean change from baseline in the CAPS item B2 score (between-group difference, 0.2; 95% confidence interval [CI], −0.3 to 0.8; P=0.38), in the mean change in PSQI score (between-group difference, 0.1; 95% CI, −0.9 to 1.1; P=0.80), or in the CGIC score (between-group difference, 0; 95% CI, −0.3 to 0.3; P=0.96). There were no significant differences in these measures at 26 weeks (a secondary outcome) or in other secondary outcomes. At 10 weeks, the mean difference between the prazosin group and the placebo group in the change from baseline in supine systolic blood pressure was a decrease of 6.7 mm Hg. The adverse event of new or worsening suicidal ideation occurred in 8% of the participants assigned to prazosin versus 15% of those assigned to placebo.

CONCLUSIONS

In this trial involving military veterans who had chronic PTSD, prazosin did not alleviate distressing dreams or improve sleep quality. (Funded by the Department of Veterans Affairs Cooperative Studies Program; PACT ClinicalTrials.gov number, NCT00532493.)

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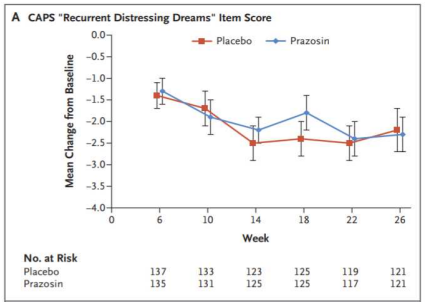

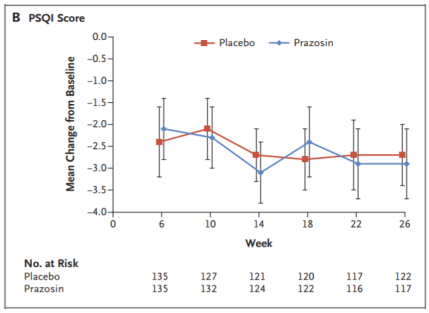

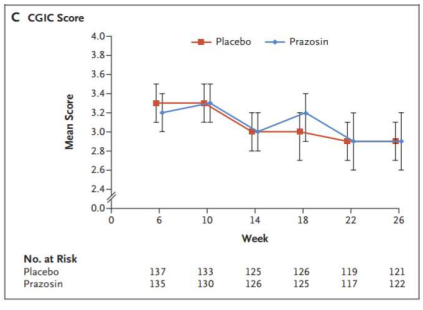

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TABLE 1. Assessment and management of treatment-resistant PTSD

Factor	Comment
Allow natural recovery: resilience is important, varies between individuals, and can lead to recovery without specific intervention	One meta-analysis showed 44% recovery without specific treatment a mean of 40 months after diagnosis (42 studies, N = 81,6423)[2]
Provide support with evidence-based intervention	A meta-regression analysis of psychotherapies for combat PTSD found individual TF-CBT > group alone; and exposure or CPT > stress management or (possibly) EMDR[12]
Provide sufficient treatment duration	While RCTs are generally 6-12 weeks long, continued improvement over 6 months may be seen with medication; over the long term, changes with medication may lead to changes in benefit from TF-CBT and vice versa
Address comorbidity	Substance use disorders: treat PTSD concomitantly, especially sleep-related hyperarousal with prazosin and onset insomnia with trazodone or mirtazapine; mood disorders: may justify initiation of antidepressant or mood stabilizer before TF-CBT; medical conditions: may require ongoing collaboration with primary care providers, particularly when injuries resulted from the index trauma that also led to PTSD
Address sleep disturbance: lack of improvement in sleep predicts poor PTSD treatment outcome; nightmares and associated dysfunctional REM sleep can impair processing of other aspects of PTSD and affect outcome	Consider work-up for primary sleep disorder: OSA, restless legs, RBD; monitor and address sleep complaints at initiation: prazosin for nightmares and sleep-related hyperarousal; trazodone, mirtazapine, or other non-benzodiazepine hypnotics for onset insomnia; CBT for insomnia, particularly for those with fear of sleep
Identify most salient symptom cluster(s) based on DSM-5 criteria	Make treatment decision based on cause of trauma: TF-CBT or medication, exposure, CPT, peer support group, antidepressant; some patients may prefer to adapt their lifestyles to the persisting effects of their trauma, including avoidance; some patients can translate the effects of their traumatic experience into actions to change public policy, protect others, etc
Identify subtypes	Dissociation: unclear differential treatment implications; psychosis: atypical antipsychotic augmentation and antidepressant; complex PTSD: multimodal, staged treatment usually starting with practical and for some (eg, refugees), cultural adaptations
Consider trauma severity	The effect of increasing trauma severity on more severe symptoms and worsened functional outcome persisted over a 14-y period in one study of combat PTSD
Consider trauma type	Fewer RCTs comprise combat veterans, but compared with civilian trauma, military sexual trauma does not reduce likelihood of treatment response; PTSD associated with childhood abuse has been least specifically studied in medication trials; patients with multiple traumas may require longer treatment with more nuanced interventions
Address specific psychological factors	Survivor guilt; disillusionment in combat veterans; mental "defeat" in relation to domestic violence

RCT, randomized clinical trial; TF-CBT, trauma-focused CBT; CPT, cognitive-processing therapy; EMDR, eye movement desensitization and reprocessing; OSA, obstructive sleep apnea; REM, rapid eye movement; RBD, REM sleep behavior disorder.

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TABLE 1. Assessment and management of treatment-resistant PTSD

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TABLE 2. RCTs in PTSD patients refractory to standard treatments[10]

Pharmacologic category	RCT+[a] (N)	RCT–[b] (N)
Antidepressants	Amitriptyline (40 V); cluster C Mirtazapine (100 V[c])	Paroxetine-CR (33 C) Tianeptine (35 V)[d]
Antipsychotics	Risperidone (65 V) Olanzapine (19 V) Quetiapine (80 M)[19]	Risperidone (20 C, 267 V[11]) Aripiprazole (14 V)[e]
Anticonvulsants	Pregabalin (37 V) Topiramate (67 V)	Divalproex (28 V)[f] Topiramate (40 V)
Antiadrenergic agents	Prazosin (10 V, 40 V[g])	Guanfacine
NMDA receptor modulators	Ketamine (41 M)[h]	
Other	MDMA (20 M)[i]	MDMA (12 M)[j] Inositol (13 M)

RCT, randomized clinical trial; C, civilian trauma; V, veterans with combat trauma; M, mixed civilian and combat trauma; MDMA, 3,4-methylenedioxy-methamphetamine.

[a]Placebo-controlled, randomized trials showing improvement in PTSD symptoms in patients unresponsive to paroxetine or sertraline; [b]Placebo-controlled, randomized trials showing *lack of improvement* in PTSD symptoms in patients unresponsive to paroxetine or sertraline; [c]WWII and Korean combat veterans; [d]5HT reuptake *enhancer* with glutamate/*N*-methyl-D-aspartate (NMDA) modulating and brain-derived neurotrophic factor enhancing effects in amygdala in animals; as effective as fluoxetine. Another large (N = 100) civilian trauma RCT showed equal benefit compared with fluoxetine; [e]Numerically but not statistically significantly > placebo; [f]See also Davis et al[20]; [g]Without daytime dosing, significantly > placebo on sleep measures but not overall symptoms, while with daytime dosing both sleep and overall symptoms improve[21]; [h]Midazolam controlled; [i]MDMA > placebo, but more than 90% of patients and clinicians guessed treatment assignment correctly; [j]Full-dose MDMA no better than ultralow-dose MDMA used as active placebo for better blinding.

Note: This table overlooks many important elements of the trials catalogued: age, gender, dose, duration, setting, year, outcome measure used, monotherapy vs augmentation therapy, prior medication and/or psychotherapy trials, and concomitant psychosocial treatment.[10]

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TABLE 3. Open-label investigations in patients described as refractory to other treatments[10]

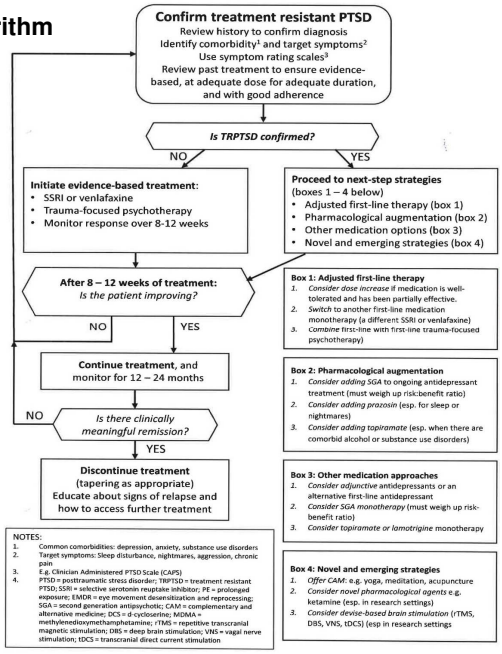
Pharmacologic category	OLI+[a] (N)	OLI–[b] (N)
Antidepressants	Duloxetine (21)	Bupropion (17)
	Mirtazapine (17)	Fluvoxamine (24)
	Nefazodone (64)	
Antipsychotics	Quetiapine (87)	Aripiprazole (32)
	Risperidone (17)	
Anticonvulsants	Carbamazepine (18)	Divalproex (10)
	Divalproex (37)	
	Levetiracetam (23)	
	Pregabalin (9)	
	Tiagabine (7)	
Antiadrenergic agents	Clonidine (9)	
	Prazosin (9)	
Other	Buspirone (14)	Tetrahydrocannabinol (10)
	Creatine monohydrate (10)	
	Naltrexone (10)	
	Rivastigmine (3)	
	Fermented soy oil FSWW08 monotherapy (10)	
	Tramadol (4)	
	Triiodothyronine (5)	

[a]Open-label investigations (OLIs) showing improvement in PTSD symptoms in patients unresponsive to paroxetine or sertraline.

[b]Open-label investigations showing lack of improvement in PTSD symptoms in patients unresponsive to paroxetine or sertraline.

Psychiatric Times, Volume 34, Issue 11, November 2017

Management of Treatment resistant PTSD algorithm



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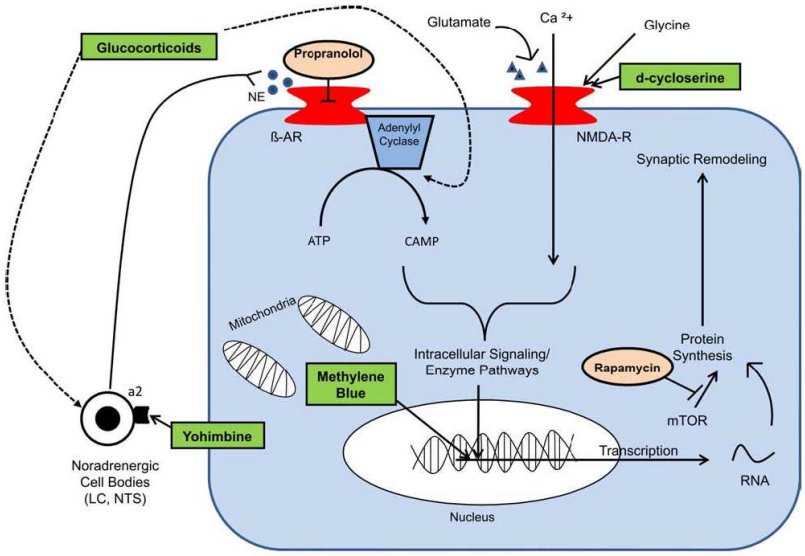

Fig. (1). Sites of action of medications used to enhance psychotherapy currently in clinical trials

Medications in green rectangles act to enhance extinction learning; medications in peach-colored ovals disrupt reconsolidation.

Conclusions

- Benzodiazepines don’t work for PTSD
- Use caution with early interventions
- SSRIs and SNRIs are effective
- Atypical antipsychotics may help nonresponders or psychotic PTSD patients
- CBT and its variants works very well for PTSD
- Consider rTMS and ECT