Diagnosis and Treatment of Military-Related PTSD: Differential Diagnosis, Clinical Tools, and Effective Care

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Disclosure

• The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
  – The off-label use of fluoxetine, venlafaxine ER, D-cycloserine, and prazosin for the treatment of PTSD will be discussed. There will be mention of “atypical antipsychotics” and “mood stabilizers” without specific agents in these classes discussed.

• Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.

• This activity has been independently reviewed for balance.
Caring for the Veteran: Combined Medication and Psychotherapy Considerations

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Therapeutic Alliance

The first meeting with a Veteran
“No one cares how much you know
Until they know how much you care”
Holding
Thank the Veteran

• Thank the Veteran for their service

• Inquire about military service, branch of service, rank, roles, and so forth

• Let the Veteran know that you would like them to teach you about their experiences in the service, both positive and negative

• Indicate that as you learn from each Veteran, this will help you become a better provider for other Veterans

• Helping other Veterans is a critical message. The military culture involves altruism and team-building
Clinical Assessment

- **Trauma History**: Type, age, duration, prior trauma, assess index trauma
- **DSM-5 PTSD Symptoms**: Re-experiencing, avoidance/numbing, hyperarousal, mood, and cognitive
- **Other Psychiatric Disorders**: eg, Depression, anxiety disorder, substance use disorders
- **Safety**: Threat of harm to self/others, from others; substance use, medical comorbidities
- **Risks**: Medical nonadherence, violence
- **Personal Characteristics**: Individual resilience, coping skills, interpersonal relatedness, faith
- **Psychosocial Situation**: Home environment, social supports
- **Stressors**: Acute and ongoing

Therapy and Medication

Meta-Analyses
Psychotherapy vs Pharmacotherapy for PTSD: Systematic Review and Meta-Analyses to Determine First-Line Treatments

- Effect sizes for TFP vs active control conditions were greater than medications vs placebo and other psychotherapies vs active controls
- TFPs resulted in greater sustained benefit over time than medications
- Sertraline, venlafaxine, and nefazodone outperformed other medications
- Direct head-to-head trials of TFPs vs sertraline or venlafaxine are needed

TFP = trauma-focused psychotherapy.
Meta-Analysis of Medications Plus CBT in Anxiety Disorders

- Reviewed studies of anxiety disorders, including panic disorder, social phobia, GAD, and OCD; but not PTSD

- **Conclusion**: CBT plus medication more effective than CBT plus placebo at end of treatment in these anxiety disorders

- At 6-month follow-up, however, no difference between CBT plus medication vs placebo

CBT = cognitive-behavioral therapy; GAD = generalized anxiety disorder; OCD = obsessive-compulsive disorder.
# CBT Plus Medication in Anxiety Disorders: Effect Sizes

<table>
<thead>
<tr>
<th>Study name</th>
<th>Outcome</th>
<th>Hedges' $g$</th>
<th>Standard error</th>
<th>Variance</th>
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<th>Upper limit</th>
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<td>-0.36</td>
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## CBT Plus Medications in Anxiety Disorders: Odds Ratios

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<tr>
<th>Study name</th>
<th>Outcome</th>
<th>Statistics for each study</th>
<th>Odds ratio and 95% CI</th>
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<td>PDA - Sharp et al. (1996)</td>
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<td>PDA - Marks et al. (1993)</td>
<td>Free of major panic attacks</td>
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<td>CGI-I &lt;2 and CGI-S &gt;3</td>
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<td>CGI-I score of 1 or 2</td>
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<td>1.95</td>
<td>1.25</td>
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Antidepressants

Currently Considered Mainstay Medication Treatments for PTSD
Altered Serotonin Function in PTSD

- Increased serotonin in prefrontal cortex with stress
- Decreased stress-induced behavioral deficits with re-administration of serotonin in frontal cortex in preclinical models
- Reduced 5-HT₁A serotonin receptor binding in hippocampus and 5-HT₂A in parietal cortex
- Decreased binding to serotonin reuptake sites in platelet studies in PTSD
- Increased panic-PTSD symptoms with mCPP in PTSD
- Decreased prolactin response to serotonergic neuroendocrine challenge in PTSD

mCPP = meta-Chlorophenylpiperazine.
SERT or 5-HTT is encoded by the SLC6A4 gene. SERT is a type of monoamine transporter protein that transports serotonin from the synaptic cleft to the presynaptic neuron.

Extensive clinical and preclinical data support the role of serotonin in PTSD as well as associated psychiatric disorders, including depression, alcohol and substance use disorders, and suicidal behavior.
The 5-HTTLPR Polymorphism and PTSD: A Meta-Analysis

- Association between SS genotype and PTSD in high trauma-exposed participants \((P<.001)\). To be a carrier of the SS genotype may represent a risk factor for PTSD in high trauma exposure. Further studies focusing on Gene × Environment interactions are needed to better understand the role of this polymorphism in PTSD.

Our group found the SS genotype association in a military population.

2 SSRIs—Sertraline and Paroxetine—are FDA Indicated for PTSD

SSRI = selective serotonin reuptake inhibitor; CAPS = Clinician-Administered PTSD Scale; CGI = Clinical Global Impressions; TOP-8 = Treatment Outcome PTSD Scale.

Norepinephrine and Cortisol Excretion in PTSD

N=616 Veterans.
PTSD Patients Compared with Trauma-Matched Healthy Controls

Activation map of patients contrasted with controls. Significant activations of PTSD patients compared to trauma exposed controls in response to trauma-related stimuli. (Numbers in brackets indicate Brodmann areas and coordinates of the peak voxel are in Talairach space).

MHPG Correlations with NPY

MHPG = 3-methyl-4-hydroxy-phenyl-glycol; NPY = neuropeptide Y.
NPY and Regional Brain Function

PFC = prefrontal cortex.
Venlafaxine (SNRI) in PTSD: 2 RCTs

- 6-month placebo-controlled RCT; N=329; mean daily dose = 221.5 mg/day
- Mean change CAPS
  - -51.7 drug and -43.9 placebo ($P=.006$)
- Drug greater than placebo in reducing re-experiencing and avoidance/numbing, but not hyperarousal
- Remission 50.9% drug and 37.5% placebo

- 12-week RCT venlafaxine, placebo, and sertraline; N=538
- Mean change CAPS
  - -41.8 venlafaxine, -39.4 sertraline, -33.9 placebo ($P<.05$ active vs placebo)
- Remission 30.2% venlafaxine ($P<.05$), 24.3% sertraline, 19.6% placebo

SNRI = serotonin-norepinephrine reuptake inhibitor; RCT = randomized controlled trial.
So, Both Serotonin and Norepinephrine Systems Altered in PTSD

Implications for pharmacotherapy:

- SSRIs: 2—sertraline and paroxetine—are now FDA indicated, story to follow
- SNRIs: Venlafaxine appears promising in 2 large RCTs
- Prazosin?: Positive data for nightmares, but now large RCT was negative
- Atypical antipsychotics?: Mixed data
- Others, such as mood stabilizers?: Mixed data

Venlafaxine in PTSD: A Sertraline- and Placebo-Controlled Study

• 12-week, double-blind, multicenter trial evaluated the efficacy of venlafaxine ER, sertraline, and placebo in adult outpatients (N=538) with PTSD
• Patients were randomly assigned to receive placebo or flexible doses of venlafaxine ER (37.5–300 mg/day) or sertraline (25–200 mg/day) for 12 weeks or less
• Week 12 remission rates were venlafaxine ER 30.2% ($P<.05$ vs placebo), sertraline 24.3%, and placebo 19.6%
• The venlafaxine ER group had significantly better Davidson Trauma Scale total and cluster scores than placebo
• Mean maximum daily doses were 225-mg venlafaxine ER and 151-mg sertraline. Both treatments were generally well tolerated
• Study results suggest that venlafaxine ER is effective and well tolerated in the short-term treatment of PTSD

ER = extended release.
Venlafaxine in PTSD: A Sertraline- and Placebo-Controlled Study (cont’d)


*P<.01 venlafaxine ER vs placebo; †P<.05 sertraline vs placebo; ‡P<.001 venlafaxine ER vs placebo; §P<.05 venlafaxine ER vs placebo.
Venlafaxine in PTSD: A Sertraline- and Placebo-Controlled Study (cont’d)

*P<.05 venlafaxine ER vs placebo; †P<.01 venlafaxine vs sertraline; ‡P<.001 venlafaxine ER vs placebo; §P<.05 venlafaxine ER vs sertraline. Davidson J, et al. J Clin Psychopharmacol. 2006;26(3):259-267.
Therapy Plus Medications in PTSD

Prospective Studies
Paroxetine Augmentation for PTSD Refractory to Prolonged Exposure Therapy

- Adult outpatients meeting DSM-IV criteria for PTSD

- **Phase I**: 8 sessions of individual PE over 4- to 6-week period

- **Phase II**: Participants with significant remaining symptoms randomized to paroxetine or placebo + additional 5 sessions of PE (N=23)

- Phase I completers had significant benefit (N=44, \( P<.0001 \)). No difference between paroxetine or placebo and minimal additional benefit in Phase II

PE = prolonged exposure.
Combined Prolonged Exposure Therapy and Paroxetine for PTSD Related to the World Trade Center Attack: RCT

- 10-week double-blind treatment trial
- N=37 participants meeting DSM-IV criteria for PTSD after World Trade Center attacks
- PE combined with paroxetine or placebo for the 10 weeks
- Additional 12 weeks of double-blind treatment with paroxetine or placebo alone
- PE delivered in 10 weekly 90-minute sessions
- Paroxetine or placebo given after 30-minute visits weekly for 6 weeks, 2 weeks for 4 weeks, then every 4 weeks
- Study medication dose titrated to maximum of 50 mg/day
Primary Outcome:
CAPS Scores during Acute (10 weeks) Phase

- Significant improvement in CAPS scores for both PE + paroxetine and PE + placebo ($P<.001$)

- Between group comparison: PE + paroxetine had greater improvement than PE + placebo ($P<.01$)

- Response rate and quality of life also greater for PE + paroxetine

- For 12-week extension phase: No difference between paroxetine or placebo

CAPS Scores during Acute (10 weeks) Phase

Remission Rates during Acute (10 weeks) Phase

Prolonged Exposure Therapy
Augmentation of Sertraline in PTSD

• Outpatients with chronic PTSD by *DSM-IV* criteria completed 10 weeks of open-label treatment with sertraline

• Then randomized to 5 weeks of sertraline alone (n=31) or sertraline plus 10 sessions of PE (n=34)

• Significant improvement in PTSD symptoms in open-label treatment phase

• PE resulted in further reduction in PTSD symptoms in participants who had only a partial response to open-label sertraline

Prolonged Exposure Therapy
Augmentation of Sertraline in PTSD (cont’d)

Table 2. Outcome Variables (M, SD, n) for Participants Entering Phase II

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<th>Measure</th>
<th>Treatment</th>
<th>Week 0</th>
<th>Week 10</th>
<th>Week 15</th>
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<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
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<tr>
<td>SIP</td>
<td>Sertraline (n = 31)</td>
<td>36.0</td>
<td>8.64</td>
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<td>Sertraline/PE (n = 34)</td>
<td>35.9</td>
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<tr>
<td></td>
<td>Combined (n = 65)</td>
<td>35.9</td>
<td>8.98</td>
<td>15.3</td>
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<td>BDI</td>
<td>Sertraline (n = 30)</td>
<td>22.1</td>
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<td>9.5</td>
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<td>Sertraline/PE (n = 34)</td>
<td>21.0</td>
<td>8.55</td>
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<td>Combined (n = 64)</td>
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<td>STAI-S</td>
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<td>54.2</td>
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<td>Combined (n = 64)</td>
<td>54.7</td>
<td>12.45</td>
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</table>

Figure 2. The Structured Interview for PTSD (SIP) scores for excellent responders (Ex/R) and partial responders (PR) at each assessment point in response to sertraline alone (sertraline) or sertraline augmented with prolonged exposure (sertraline/PE). The SIP scores obtained at Week 10 were used to determine responder status. Ex/Rs were defined as participants with Week 10 SIP scores <14 and PRs were defined as participants with Week 10 SIP scores ≥14. Participants were randomly assigned to sertraline or sertraline/PE at Week 10.

SIP = Structured Interview for PTSD; BDI = Beck Depression Inventory; STAI-S = state-anxiety portion of the State-Trait Anxiety Inventory.
Pilot Study of a Telehealth-Delivered Medication-Augmented Exposure Therapy Protocol for PTSD

- 11 adults working in occupations at risk with PTSD enrolled and 7 completed 12 to 15 sessions

- Individuals were randomized to receive the cognitive enhancer D-cycloserine or placebo, and participants provided saliva samples for genetic analysis

- Treatment completers demonstrated decreases in PTSD and depressive symptomatology (measured by CAPS [\(P<.001, d = 2.79\)] and BDI-II [\(P=.004, d = 0.92\)])

- Participants reported high therapeutic alliance, treatment satisfaction, and telehealth satisfaction. There were no significant technical, medication, or safety issues, and no clinical emergencies

BDI = Beck Depression Inventory.
Summary

• Psychotherapy is an essential treatment of PTSD, evidence-based psychotherapies that are trauma-focused have larger treatment effect sizes than antidepressant medications

• Antidepressants can reduce PTSD symptoms, enhance quality of life and level of functioning, and treat comorbid depression and other anxiety disorders. To date, sertraline and venlafaxine have the largest effect sizes of medications studied in PTSD

• 2 antidepressants are FDA-indicated for PTSD: Sertraline and Paroxetine

• Combination of psychotherapy with antidepressants may be more effective overall than either alone—more studies are needed to confirm this clinical impression, in particular studying combined evidence-based psychotherapies and sertraline or venlafaxine

Military-Related PTSD: Differential Diagnosis and Clinical Tools for Effective Care

Peter Tuerk, PhD
Professor, Curry School of Education
University of Virginia
Director, Sheila Johnson Center for Human Services
Charlottesville, Virginia
Assessment of PTSD: Common Pitfalls

Assessing the trauma and not the symptoms

Trauma does not equal PTSD

PTSD symptoms = PTSD

Or

Failure of natural recovery from trauma = PTSD
A Prospective Examination of PTSD

Having Only PTSD is a Tricky Proposition

- **PTSD co-occurring rates with other mental health disorders**
  - Anxiety or mood disorder 92%
  - Current MDD 69%
  - Lifetime alcohol abuse or dependence 31%
  - Current dysthymia, panic disorder, GAD, OCD, or lifetime SUDs each 23%
  - Current social phobia or specific phobia each 15%

- **Among Veterans**
  - Depressive disorder 70%
  - Other anxiety disorder 35%
  - Alcohol use disorder 22%
  - Any other psychiatric disorder 87%

SUD = substance use disorder.
Assessment of PTSD: Common Pitfalls

Arousal

• Physiological reactivity when exposed to trauma cues
• Problems falling/staying asleep
• Increased irritability/angry outbursts
• Problems concentrating
• Overly alert—always scanning environment
• Elevated startle response
Assessment of PTSD: Common Pitfalls

**Arousal** (red also common in bereaved)
- Physiological reactivity when exposed to trauma cues
- Problems falling/staying asleep
- Increased irritability/angry outbursts
- Problems concentrating
- Overly alert—always scanning environment
- Elevated startle response
Assessment of PTSD: Common Pitfalls

Avoidance

• Avoidance of thoughts, feelings, or conversations related to trauma (or deceased)
• Avoidance of people, places, or things that are reminders of the trauma (or deceased)
• Inability to recall important aspects of event
• Reduction of interest/participation in previously enjoyable/important activities
• Feelings of detachment/isolation
• Fear of, or inability to feel strong positive or negative emotions—numbing
Assessment of PTSD: Common Pitfalls

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Assessment of PTSD: Common Pitfalls

**Negative Alterations in Cognitions or Mood**
- Overly negative thoughts and assumptions about oneself or the world
- Exaggerated blame of self or others
- Negative affect
- Decreased interest in activities
- Feeling isolated
- Difficulty experiencing positive affect
Assessment of PTSD: Common Pitfalls

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Assessment of PTSD: Common Pitfalls

**Re-Experiencing**

- Recurring intrusive thoughts or images of the event
- Recurring dreams or nightmares about the event
- Experience of *severe anxiety* when exposed to reminders of event, such as similar locations, noises, or smell
- Acting or feeling as if the event were recurring (flashbacks)

Re-experiencing symptoms are the only unique symptoms to PTSD and set it qualitatively apart from other disorders.
Assessment of PTSD: Common Pitfalls

Assessment of Compulsive Rumination vs Intrusions
Intrusions pop up or are cued, but they quickly are identified as unsafe and uncomfortable; a place one shouldn’t go to (like taped off crime sites) and they are actively avoided.

Focus PTSD treatment on re-experiencing intrusions not on ruminations.

Rumination can also be cued and “intrusive,” but rather than identifying danger and running, patients engage in the process (like ax grinding, not police tape). PTSD is most often accompanied by ruminations, but it is not a sufficient criterion for intrusions or diagnosis.
Focus PTSD differential diagnosis and treatment on re-experiencing intrusions not on ruminations.
Expression of Symptoms Specific to Military-Related PTSD?
Hypervigilance and compulsive checking are different behaviors

Both are negatively reinforced reactions to anxiety

Both can sabotage progress in treatment and often require therapeutic creativity

Big difference for us clinicians is that the ecology of an in vivo exposure can do the work for us to reduce hypervigilance; whereas compulsive checking past a certain point needs response prevention

CHECKING DOWNSTAIRS

SLEEPING

COUNTER

PORCH FRONT DOOR

Noise

แรกหน้า: วาดแผนที่ของบ้าน สามารถเห็นชื่อห้องต่าง ๆ และเส้นทางการเดินที่ถูกเรียกว่า "Noise".

ชื่อแผนที่: Checking Downstairs

ส่วนห้องนอน: แสดงตำแหน่งห้องนอนในบ้าน

ส่วนครัว: แสดงตำแหน่งของห้องซักผ้าและที่สัมผัสกับอุปกรณ์ที่ต้องการเช่น "Noise"

ส่วนประตูหน้า: แสดงตำแหน่งของประตูหน้าบ้าน ที่เรียกว่า "PORCH FRONT DOOR".

ส่วนเเผ่นที่โดยรวม: แสดงเส้นทางการเดินที่ผ่านเส้น "Noise" ไปยังห้องนอน

ที่หมายถึง: แผนที่ที่ชัดเจนสำหรับการจัดการกับ "Noise" ที่เกิดขึ้นในบ้าน
Prolonged Exposure Therapy
Prolonged Exposure Therapy
Daily Tracking of Imaginal Exposure Recordings at Home

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<th>SUDS Peak</th>
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*Meet with Doctor*
Daily Tracking of *In Vivo* Exposure

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Summary of Prolonged Exposure Therapy Outcomes
Summary of Prolonged Exposure Therapy Outcomes

Citations for Previous Slides

Prolonged Exposure Therapy

Independent Replication from the Field
Treating Veterans with PTSD
Charleston VA PTSD Team (PCT)
Randomized Controlled Trials

Chart Review Effectiveness Trials
Pre-post PE PCL and BDI-II outcomes with 95% confidence intervals for the ITT sample, treatment completers, and non-completers.

Mean number of session for completers = 10

OEF = Operation Enduring Freedom; OIF = Operation Iraqi Freedom; OND = Operation New Dawn; PCL = PTSD Checklist.

Peer-Reviewed Evidence-Base for the Effectiveness of Prolonged Exposure: PTSD Clinical Team, Charleston VA

- **Veterans of Different Eras**
  Yoder et al. (2012)

- **Older Veterans**
  Yoder et al. (2013)

- **Veterans Living in Rural Areas accessing care via Telehealth:**
  Initial Relevant Case Studies
  Tuerk et al. (2009)
  Tuerk et al. (2010)

- **Pilot Open Trial**
  Tuerk et al. (2010)

- **Objective Measurement of Treatment Effectiveness**
  Tuerk et al. (2013)

- **Female Veterans**
  Mouilso et al. (2016)

Prolonged Exposure successfully disseminates to real-world treatment contexts. Pre-Post PE Outcomes for Depression and PTSD at the Philadelphia VA Medical Center. Thorp et al. 2012.
Advanced Techniques for Therapists Treating PTSD
Expert clinicians know that:

Visible distress or Inability to talk about trauma is a sign that the patient is a great candidate for EBT for PTSD, **not a sign** that they need to “prepare” for it or that they “are not ready for it.”

EBT = exposure-based therapy.
PTSD Brief Reactivity (PBR) Task

Neutral Trauma
Heart Rate Reactivity in Script Driven Imagery

Similar findings related to baseline trauma reactivity being related to positive exposure therapy outcomes:

Preparation for Trauma-Focused Therapy: Bolstering Stability? Enhancing Motivation?

There is no evidence that “preparing” patients for EBT is effective and quite a bit of evidence suggesting that getting to symptom reduction faster is better

1. When working with Veterans, initial engagement can be a larger problem than dropout

2. Remember, preparation for EBT is included in EBT protocols

3. Patients should have stable safe housing, and not be actively suicidal

![Graph showing current clinic flow](image)
Therapist Factors in Presenting Treatment Rationale for Trauma-Focused EBT

• Develop shared metaphors, refer back to them often

• Doing exposure is much different than symptoms of re-experiencing, ie, purposely catching a ball and looking at it is different than getting blind-sided in the head with one
Expert Clinicians Address Avoidance and Think about it as a Symptom of PTSD Not Personality
Accordingly, they keep expectations high!

Protection Motivation Theory (PMT), a model informed by the principles of reinforcement, but specifically geared to study how fear influences internal reinforcers for health-related behaviors via measurable constructs.
Expert Clinicians Address Avoidance and Think about it as a Symptom of PTSD Not Personality Accordingly, they keep expectations high!

Protection Motivation Theory (PMT), a model informed by the principles of reinforcement, but specifically geared to study how fear influences internal reinforcers for health-related behaviors via measurable constructs. **Confidence, Competence, Expectation**
Expert Clinicians Find Objective Ways to Support Homework Compliance

Smart phone cameras can be used during homework assignments:

- Document exposure
- Elicit meta-awareness
- Improve therapist coaching
- Help titration of exposure
- Build team work
- Celebrate success

Low tech methods can also help increase accountability for highly avoidant patients.
Expert Clinicians are Specific in Their Homework Assignments to Set Patients Up for Success
Expert Clinicians: Reinforcing Tracking as Much or More than the Target Behavior Change

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Expert Clinicians Prioritize Addressing Avoidance at the Cost of Routine Clinical Habits

- Call your patients the first few weeks of treatment between sessions, to check in and ask about homework
- If they “forget” their homework tracking sheets, have them recreate it in the office
- The first time important homework is not done, make a big deal about it, you can take the blame for not conveying to them how extremely important is
- For repeat occurrences, frame the issue in terms of the relationship and expectations
- If they did not do homework at all a second or third week, cancel the session agenda and they can use the time to do their homework
- Some dropout is good dropout
- The bottom line is it is potentially iatrogenic to allow patients to continue PE if they are not getting a dose of PE, as it might influence them to believe that their PTSD is not treatable
Expert Therapists Track Data at Every Session to Guide Treatment and Provide Patient with Positive Reinforcement

1. Self report measures
2. SUDS
3. A running tab of exposures completed or goals met
4. Or even psychophysiological data
“It showed me that my reactions are not just mental, that I am actually having a physical response that can go away.”

“It showed me that I’m not crazy, that my body was reacting and that I could get better.”

“Being able to see it working, helped me to trust the process and what my doc was saying.”

“Can I take this home to show my wife?”

Expert Therapists Conduct Every Session as if Students and Colleagues Were Watching
A Look at Therapist Effects

The Charleston VA PTSD Clinical Team
Results

Slope in outcomes for PE therapy with 95% CI (N = 328 patients)

Therapist slopes in outcomes for PE therapy with 95% CI 8 out of 26 therapists with at least 30 cases (N = 32-102)
Expert Therapists Attend to Their Own Treatment Fidelity

Pre- and post-treatment outcomes for PE completers by protocol fidelity designations with 95% confidence intervals. Clinical effectiveness data, Charleston PCT.

Unpublished, Tuerk, Yoder & Acienmo
Pre- and post-treatment outcomes for PE completers by mutually exclusive therapist groups and protocol fidelity designations with 95% confidence intervals. Clinic effectiveness data, Charleston PCT.
Expert Clinicians Know the Odds

Odds of good outcome

Coin flip?

Percent

Patients