PTSD and Comorbid Psychosis: Diagnostic and Treatment Challenges

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Psychotic Features in PTSD

- Chronic auditory and visual hallucinations and paranoid delusions may be relatively common in chronic PTSD—overlap with re-experiencing symptoms
- Psychotic features associated with more severe illness and major depression
- May be phenomenologically and biologically distinct subtype of PTSD
- Are antipsychotics indicated for these features? Case reports and pilot trials suggest that atypical antipsychotics may alleviate psychotic symptoms and some core PTSD symptoms but need more research

PTSD Comorbidity

- Depression and other mood disorders
- Dissociative disorders
- Other anxiety disorders, eg, obsessive-compulsive disorder, panic disorder
- Alcohol and other substance use disorders
- Psychotic features or psychotic disorders
- Personality disorders

Proposed Criteria for Secondary Psychotic Features in PTSD

1. Patients meet DSM-IV-TR criteria for PTSD
2. Positive psychotic symptoms including hallucinations and/or delusions are present
3. Psychotic features do not occur exclusively in the context of flashback episodes
4. No formal thought disorder is present
5. No brief psychotic disorder is present
6. PTSD precedes the onset of psychotic features
7. There is no history of psychotic symptoms before the traumatic event
8. Another psychiatric disorder does not better explain the symptoms, eg, schizophrenia, schizoaffective disorder, or bipolar disorder with psychotic features
9. For research purposes, a minimum score of moderate or higher on at least 1 of the positive items on the PANSS, eg, hallucinations or delusions

Prevalence Estimates for Psychotic Symptoms in PTSD

- Earlier studies suggested that the prevalence of PTSD-SP may be up to approximately 40% of Veterans with PTSD
- These were single site studies that had differing definitions of PTSD with psychotic symptoms
- There may be ethnic variations in the manifestation of psychotic symptoms
- Confound of specific, core PTSD symptoms, eg, “flashbacks” may include hallucinatory phenomena

Prevalence of Psychotic Symptoms in PTSD: Findings from the National Comorbidity Survey

- Sareen et al reported the high co-occurrence of positive psychotic symptoms and PTSD in the National Comorbidity Study
- PTSD was found to be associated with an increased likelihood of endorsing ≥ 1 psychotic symptoms after adjustment for sociodemographics and psychiatric and medical comorbidity (OR = 1.83; 95% CI: 1.43–2.45, P < .001)
- Co-occurrence of PTSD with psychotic symptoms was associated with greater levels of severity (higher total number of PTSD symptoms, greater levels of comorbidity, and high distress) compared with that for PTSD alone

PTSSS = Positive and Negative Syndrome Scale.

PANSS = Positive and Negative Syndrome Scale.
Prevalence of Psychotic Symptoms in PTSD: Findings from the National Comorbidity Survey (continued)

- Shevlin et al extended Sareen’s findings, suggesting that the data supported a distinct PTSD with psychotic features subtype.
- This group reported a latent class analysis of PTSD symptoms and psychotic symptoms, including hallucinations and delusions.
- 4 latent classes were identified:
  - 2 had high probabilities of endorsing hallucination and delusion indicators.
  - 1 class had high probabilities of endorsing both psychosis indicators and PTSD symptoms.
- This latter class met the characteristics expected to be evident in a psychotic PTSD subtype.

Counterpoint to Distinct Subtype

- Gaudiano and Zimmerman argued that their data did not support a psychotic subtyping of PTSD.
- These researchers assessed 1800 patients who completed diagnostic interviews.
- The lifetime prevalence of psychotic symptoms in this sample was 17% (OR = 3.48; 95% CI: 2.52–5.21). Excluding comorbid conditions associated with psychosis, the prevalence of PTSD with psychosis was 2.5% (OR = 0.6; 95% CI: 0.08–4.52).
- Rates of major depression did not change between PTSD with or without psychosis.
- Although the conclusions of this study appear to be conflicting, it does not address the fact that there is a strong overlap between symptoms of PTSD and those of depression, eg, irritability, difficulty concentrating, insomnia, diminished interest, or participation in significant activities. Moreover, some studies have demonstrated a positive correlation between the severity of depression and psychosis in patients with PTSD.

Psychotic Symptoms and PTSD in a Population Survey

- Explored relationship between PTSD symptoms and psychotic symptoms.
- The Adult Psychiatric Morbidity Survey was utilized to examine the prevalence of lifetime trauma, symptoms of PTSD, and experiences of paranoia and auditory hallucinations (N = 7403).

Psychotic Symptoms and PTSD in a Population Survey (continued)

- There were significant bivariate associations between symptoms of PTSD and psychotic experiences. Multiple logistic regression analyses indicated that reliving and arousal symptoms were significant predictors for paranoia while reliving, but not arousal symptoms, also significantly predicted auditory hallucinations. Dose-response relationship was found: the greater the number of PTSD symptoms, the greater the odds were of experiencing both paranoia and hallucinations.
- Symptoms of PTSD are associated with increased odds of experiencing auditory hallucinations and paranoia. Overlaps appears to be present between the symptoms of PTSD and psychotic experiences.

Biological Studies of Psychotic Features in PTSD

- Altered DBH levels
- Elevated corticotrophin-releasing hormone
- Elevated platelet monoamine oxidase B activity
- Elevated platelet serotonin levels

Plasma DBH in Nonpsychotic vs Psychotic and Healthy Controls

- DBH = dopamine β-hydroxylase.
Psychotic Features and Severity of Symptoms in PTSD

CAPS = Clinical Administered PTSD Scale (based on DSM-III-R); IES = Impact of Events Scale; SCID-P = Structured Clinical Interview for DSM-IV with psychotic screen.

Hamner MB. Depress Anxiety. 1997;5:34-38.

PTSD Treatment

- Evidence-based psychotherapy, e.g., PE – psychosis per se may not be a contraindication to PE
- Medication treatment (antidepressants are current mainstay) – need studies specifically addressing comorbid psychotic symptoms
- Psychosis does not necessarily mean treatment with antipsychotics
- Combined psychotherapy and medication treatment likely effective, need controlled studies

The only FDA approved medications for PTSD are sertraline and paroxetine.

PE = prolonged exposure therapy.

Rationale for Studying the Use of Atypical Antipsychotics in PTSD

- Atypical antipsychotics reduce anxiety symptoms in schizophrenia and in bipolar disorder
- Comorbid psychosis may be relatively common in chronic PTSD patients
- Severely ill patients may have a relatively high positive, negative, and general psychopathology symptom burden
- Altered dopaminergic, serotonergic, and noradrenergic function is present in animal models of fear-conditioning, neurotransmitters affected by atypical agents
- Possible altered frontal cortical/anterior limbic function in PTSD, neural regions affected by atypical agents

Atypical antipsychotics are not FDA approved for the treatment of PTSD.

Rationale for Studying the Use of Atypical Antipsychotics in PTSD (continued)

Many PTSD patients are refractory or partially responsive to antidepressant monotherapy:
- Adjunctive atypical antipsychotics may be beneficial in other anxiety disorders or in mood disorders with or without comorbid psychotic features
- Case reports and initial studies suggest potential efficacy for risperidone, olanzapine, quetiapine, aripiprazole, and clozapine
- α-1 adrenergic receptor antagonist effects of atypicals may compare with prazosin, a selective α-1 antagonist with efficacy in reducing nightmares in PTSD
- Any efficacy must be balanced against potential risk of metabolic syndrome, pericarditis or myocarditis, and other adverse effects of antipsychotics

Olanzapine in PTSD

- Petty et al (2001): 8-week open-label trial (N = 48, 30 completers), positive response on CAPS
- Butterfield et al (2001): 10-week, double-blind, placebo-controlled trial (N = 15, randomized 2:1 to olanzapine or placebo). Both groups improved, no between-group differences
Olanzapine in PTSD (continued)

- Adjunctive controlled trial of olanzapine (8 weeks) in refractory PTSD patients (N = 19) previously treated with SSRI antidepressants (for 12 weeks prospectively).
- Significant reduction in PTSD (CAPS), depression, and sleep disorder ratings in PTSD patients receiving olanzapine vs placebo. Clinician-rated global response did not differ between groups.
- Authors conclude that there is a potential role for atypical agents in PTSD resistant to SSRI antidepressants and that sleep symptoms, in particular, may benefit.

SSRI = selective serotonin reuptake inhibitor.

Risperidone in PTSD

- David et al (2004): Open trial, 12 weeks combat Veterans (N = 11 completed at least 6 weeks) decrease in PTSD and psychosis ratings.
- Bartzokis et al (2005): Double-blind, placebo-controlled, 16-week trial (N = 70), randomized, 48 completed, significant improvement in CAPS-total and CAPS-D subscale, also in HAM-A for risperidone vs placebo.

Risperidone in PTSD with Psychotic Features

- Adjunctive trial, patients randomized to risperidone (0.5 to 2.0 mg/day, n = 7) or placebo (n = 8) for 6 weeks.
- Reduction in intrusive memories on the Patient Checklist for PTSD and in irritability on the Overt Aggression Scale compared with placebo for risperidone-treated patients.


Risperidone or Placebo in PTSD with Comorbid Psychotic Features

- Pilot study of adjunctive treatment in chronic PTSD patients with psychotic symptoms (N = 37).
- To our knowledge, only medication RCT specifically addressing psychotic symptoms in PTSD.
- Average risperidone dose 2.5 mg qhs, range 1 to 3 mg qhs.
- Target symptoms were psychotic features as measured with PANSS.
- PANSS total scale scores improved over 5-week trial.

RCT = randomized controlled trial.

Risperidone in PTSD: Background Characteristics of PTSD Patients Randomized to Treatment with Risperidone or Placebo

<table>
<thead>
<tr>
<th></th>
<th>Risperidone (n = 19)</th>
<th>Placebo (n = 18)</th>
</tr>
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<tbody>
<tr>
<td>Age (mean ± SD yrs)</td>
<td>50.8 (4.9)</td>
<td>53.7 (7.6)</td>
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<tr>
<td>Education (mean ± SD yrs)</td>
<td>13.2 (2.0)</td>
<td>13.2 (1.8)</td>
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<tr>
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</tr>
<tr>
<td>White</td>
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<td>7</td>
</tr>
<tr>
<td>African American</td>
<td>9</td>
<td>11</td>
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<tr>
<td>Marital status</td>
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<tr>
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<td>9</td>
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<tr>
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<td>4</td>
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<tr>
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<td>5</td>
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<td>2</td>
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<tr>
<td>Comorbid Axis I diagnosis</td>
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<tr>
<td>Major depressive episode</td>
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<td>17</td>
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<tr>
<td>Other anxiety disorder</td>
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<td>Hx of substance abuse</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Receiving antidepressants</td>
<td>15</td>
<td>16</td>
</tr>
</tbody>
</table>


Mean Changes in PANSS Total Scores from Baseline Through Week 5 and at Endpoint

Mean changes in PANSS total scores from baseline through week 5 and at endpoint.
Mean Changes in CAPS Re-experiencing Scale Scores from Baseline Through Week 5 and at Endpoint


Re-experiencing Symptoms and Response to Antipsychotics in PTSD

- The Krystal study (RCT of risperidone in Veterans with PTSD) was negative based on the global CAPS response; however, the re-experiencing symptom cluster did show a trend towards separation from placebo
- We analyzed re-experiencing symptom cluster responses both in our RCT of risperidone and in the following 2 open trials of atypical antipsychotics in PTSD
- Do re-experiencing symptoms overlap with psychotic symptoms?


Open Trial of Adjunctive Quetiapine in PTSD

- 6-week open trial in 20 chronic PTSD patients with inadequate response to prior medications
- 18 were continued on antidepressants and/or other medications and 2 received quetiapine monotherapy
- Average dose of quetiapine 100 mg qhs, range 25 to 300 mg qd
- Primary outcome measure: CAPS-baseline average of 90 reflected severe illness


Change in PTSD (CAPS) Global and Symptom Ratings with Adjunctive Quetiapine Treatment


Summary

- Positive symptoms of psychosis are relatively prevalent in PTSD
- Antidepressants can reduce PTSD symptoms, enhance quality of life and level of functioning; however, alternative medication treatments may be indicated if psychosis is present
- Evidence-based psychotherapy is an essential treatment of PTSD; psychosis is not necessarily a contraindication to its use (Dr. Tuerk)
- Although antidepressants are a mainstay of medication treatment, combination with anticonvulsants, antipsychotics, or other agents are often needed in light of the heterogeneity of symptom clusters and comorbidity

Summary (continued)

- Complete remission of symptoms may not occur in chronic PTSD with secondary psychotic symptoms; maintenance treatment is generally required.
- The combination of psychotherapy and pharmacotherapy may enhance response in refractory, chronic PTSD.
- More randomized, controlled clinical trials are needed, including drug monotherapy studies, combined psychotherapy and drug therapy studies, and drug combination trials, as well as investigations of early interventions.
- Dr. Tuerk is next! Questions, comments, and discussion afterwards. Thank you!

What Do We Know about Trauma and PTSD among Adults with SMI?

- Individuals with SMI experience higher rates of trauma (58%–98%) and PTSD (19%–43%) relative to the general population.
- Trauma exposure includes high rates of sexual and physical victimization.
- Victimization among patients with SMI is strongly correlated with psychiatric difficulties and substance abuse.
- There are also data to suggest a relationship between trauma exposure/PTSD and exacerbations in the primary symptoms of SMI.

What Do We Know about Trauma and PTSD among Adults with SMI? (continued)

- Although studies often combine groups of individuals with different forms of SMI, trends with regard to trauma and PTSD tend to be more pronounced for individuals with a psychotic disorder.
- Despite all of the above, there are few studies on the assessment or treatment of PTSD in this population.

Why are There So Little Data on Assessment and Treatment of PTSD with Psychotic Disorders?

- Emphasis on internal vs external validity in clinical trials.
- Diagnostic trumping rules often leave comorbid conditions in this group unattended to.
- Clinicians’ fears that intensive PTSD interventions will exacerbate their patients other symptoms.

Between a Rock and a Hard Place

- Emphasis on internal vs external validity in clinical trials.
- Diagnostic trumping rules often leave comorbid conditions in this group unattended to.
- Clinicians’ fears that intensive PTSD interventions will exacerbate their patients other symptoms.

SmI = serious mental illness.


Between a Rock and a Hard Place (continued)

Key findings:
- Consensus among providers that trauma and PTSD are prevalent in their patients; and that trauma has a broad adverse effect on their patients' symptoms and quality of life.
- Despite believing that PTSD interventions could be effective for their patients, providers were reluctant to address these issues due to:
  - Concerns about their own ability to deliver effective PTSD interventions.
  - Concerns that their patients might "decompensate" and a general fear of "opening Pandora's box."


Assessment of PTSD in Individuals with SMI

There is evidence of:
- Reliable test-retest of physical and sexual assault exposure and PTSD.
- Validity of reports of physical and sexual assault against a structured interview.
- Reliable inter-rater agreement of PTSD diagnoses.
- Adequate convergent validity between interview and self-report measures of PTSD (ie, between the CAPS and PCL).
- There are no PTSD measures specifically tailored for individuals with a psychotic disorder.
- It is unclear if such measures would improve the diagnostic accuracy of PTSD.


Between a Rock and a Hard Place (continued)

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.

**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 the 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.

**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 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 rumination, but it is not a sufficient criterion for intrusions or diagnosis.
Assessment of PTSD in Individuals with SMI

- Most patients can accurately report on their traumatic event histories and associated symptoms
- However, some challenges include:
  - Temporal sequence of symptoms
  - Disentangling symptoms related to a diagnosis of PTSD vs other disorders
  - Having patients accurately report on the severity of their PTSD symptoms independent of overall illness burden

These sound like the challenges related to PTSD assessment in all settings.

Evidence-Based Treatment of PTSD in Individuals with SMI

- EBTs for PTSD are trauma-focused and recovery-focused (i.e., not coping-focused)
- Why would we assume such EBTs would be effective for individuals with PTSD and psychosis?
- Why would we assume such EBTs would be safe for individuals with PTSD and psychosis?

Prolonged Exposure Therapy for PTSD

Exposure Therapy has been shown to reduce or eliminate symptoms of PTSD for:
- Victims of physical assault
- Combat
- Rape
- Torture
- Motor vehicle accidents
- Terrorist attacks
- Natural/human-made disasters, medical emergencies
- Geriatric patients
- Adolescent patients
- Patients with substance abuse
- Traumatic brain injury
- Patients living in rural areas via telehealth technology
- As well as in United States, New Zealand, Canada, Israel, Korea, much of Europe, and Japan

*Effect size (d) is a standardized measure of how well a treatment works. The standard conventions are: 0.2 = small; 0.5 = medium; 0.8 = large.

<table>
<thead>
<tr>
<th>Prolonged Exposure Therapy in Effectiveness Settings Total N: &gt; 3000</th>
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<tbody>
<tr>
<td><strong>PE Studies Completers</strong></td>
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<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>Rauch et al (2009)</td>
</tr>
<tr>
<td>Wolf et al (2012)</td>
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<td>Thorp et al (2012)</td>
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<td>Necasich et al (2011)</td>
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<tr>
<td>Yoder et al (2012)</td>
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<tr>
<td>Schmier et al (2007)</td>
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<td>Efthekari et al (2012)</td>
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*Effect size (d) is a standardized measure of how well a treatment works. The standard conventions are: 0.2 = small; 0.5 = medium; 0.8 = large.
Exacerbation of Symptoms

- Minority of patients in treatment show a temporary exacerbation of symptoms
  - 10.5% in PTSD symptoms
  - 21.1% in Anxiety symptoms
  - 9.2% in Depressive symptoms
- Temporary exacerbation of symptoms typically does not go over baseline levels
- Temporary exacerbation of symptoms is not associated with:
  - Treatment dropout
  - Poorer treatment outcome

PTSD Treatment Literature for PTSD with SMI

- There are only a handful of published PTSD treatment outcome studies for those with SMI
- They all include a case-mix of individuals with SMI (i.e., not exclusively psychotic disorder)
  - Cognitive group treatment, open trials, single arm:
    - 35% of completers were responders (Rosengberg SD, et al. American Journal of Psychiatric Rehabilitation. 2006;9(2):171-180.)
  - Cognitive group treatment vs TAU, RCT:
  - Exposure Treatment, open trial, single arm:
    - 92% of completers were responders (Frueh BC, et al. J Anxiety Disord. 2009;23(5):665-675.)
    - 20-point reduction in CAPS scores post-treatment
    - 65% of completers were responders (Grubaugh AL, et al. Behav Res Ther. 2016;78:1-12.)
    - 27-point reduction in CAPS scores post-treatment

Sample: Grubaugh et al (2016) Intent-to-Treat (N = 34)

<table>
<thead>
<tr>
<th>Age</th>
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<tr>
<td>Gender (male)</td>
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<td>Employment:</td>
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<td>Full-time</td>
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</tr>
<tr>
<td>Part-time</td>
<td>9%</td>
</tr>
<tr>
<td>Unemployed</td>
<td>74%</td>
</tr>
<tr>
<td>Combat era</td>
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<tr>
<td>Vietnam</td>
<td>38%</td>
</tr>
<tr>
<td>Post-Vietnam</td>
<td>12%</td>
</tr>
<tr>
<td>Gulf War</td>
<td>27%</td>
</tr>
<tr>
<td>OEF/OIF</td>
<td>24%</td>
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<tr>
<td>Service connected disability</td>
<td>80%</td>
</tr>
<tr>
<td>Psychiatric hospitalization</td>
<td>27% (past 12 months)</td>
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Exacerbation of Symptoms (continued)

- PE = Prolonged Exposure
- PE + comb = PE with cognitive restructuring
- WL = Waitlist

<table>
<thead>
<tr>
<th></th>
<th>PE</th>
<th>PE + comb</th>
<th>WL</th>
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<tbody>
<tr>
<td>Improve on PTSD</td>
<td>93%</td>
<td>91%</td>
<td>36%</td>
</tr>
<tr>
<td>Worsening on PTSD</td>
<td>0</td>
<td>0</td>
<td>8%</td>
</tr>
<tr>
<td>Improve on Depression</td>
<td>84%</td>
<td>83%</td>
<td>37%</td>
</tr>
<tr>
<td>Worsening on Depression</td>
<td>2%</td>
<td>3%</td>
<td>12%</td>
</tr>
</tbody>
</table>

Worsening and improvement = increase or decrease in symptoms by 2 Standard Error of the Difference, based on SD and test-retest reliability (7.5 points in the PSSI, 11.4 points on the CAPS; 4.5 points on the BDI). Combination treatments = PE/BI, PE/CR, CPT, EMOR.

TAU = Treatment as usual.
Overview of Treatment Findings: PE for PTSD in Patients with SMI

- Emerging evidence base for effectiveness/efficacy
- Patients appear to be experiencing PTSD symptom reduction
- They do not appear unduly distressed or overwhelmed
- Little evidence of differential response to treatment by SMI diagnosis
- Dropout rates perhaps a little higher but not that different from other PTSD trials
- In PE studies, no study related adverse events

Overview of Treatment Findings: PE for PTSD in Patients with SMI (continued)

- Most patients can reasonably navigate the exposure-oriented protocol
- However some challenges include:
  - Patients at times struggle with accurately anchoring their SUDS ratings
  - Many patients have unstable circumstances that can create interfering noise
  - Patients often need reassurance they are ready for treatment

SUDS = Subjective Units of Distress Scale.
Overview of Treatment Findings:
PE for PTSD in Patients with SMI

- Most patients can reasonably navigate the exposure-oriented protocol
- However some challenges include:
  - Marginally higher dropout, not reliably higher
  - Patients are sometimes overly sedated

Unlike sedation that is associated with benzodiazepines in non-SMI PTSD population, stopping or reducing the medication that is causing sedation in SMI patients may have severe adverse consequences.

Lessons Learned:
PE for PTSD in Patients with SMI

- A period of stabilization is helpful with regards to recent psychiatric hospitalization and or suicidality
- Coordination with other providers can improve patient stability and decrease irrelevant noise from interfering with treatment sessions
- Not surprisingly, transportation incentives decrease attrition
- No consistent pattern as to dropouts—most occur before Session 2
- The addition of more sessions to the standard PE protocol may not improve treatment response for non-responders

Lessons Learned:
PE for PTSD in Patients with SMI

- It is hard to predict which patients will benefit from PTSD services—sometimes the least likely candidate does really well in treatment
- Overall, it appears that few modifications are needed to the PE protocol if the patient is relatively stable and able to focus on session content
- Current data are promising and suggest that intensive PTSD interventions are unlikely to exacerbate patients’ functioning and can result in significant PTSD symptom decreases
- Cost-benefit ratio seems to favor PTSD research with this population given toll of PTSD and likelihood of symptom improvement

Future Directions

- There is a need for studies designed to better understand the role of PTSD treatment on patients’ primary symptoms of SMI and overall quality of life
- Need to promote screening and treatment efforts for PTSD within public-sector settings that serve patients with SMI