Prevalence And Psychotherapeutic Treatment Of PTSD & Substance Use Disorders

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The ASAM State of the Art Course in Addiction Medicine
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Disclosure Information

Emma Barrett, PhD
Australian-American Fulbright Commission – Postdoctoral Scholarship
PTSD According To DSM-IV

**DSM-IV Criteria**

**A1:** Experienced, witnessed, confronted with an event that involved actual or threatened death or serious injury.

**A2:** Response must involve intense fear, helplessness or horror.

**B(5):** Re-experiencing – intrusive recollections, distressing dreams, flashbacks, intense psychological distress, physiological reactivity to reminders (> 1)

**C(6):** Avoidance – avoid thoughts/feelings/conversations, avoid activities/places/people that remind, inability to recall trauma, diminished interest in activities, feeling detached, restricted affect, foreshortened future (> 3)

**D(5):** Arousal – difficulty sleeping, irritability /outbursts of anger, difficulty concentrating, hypervigilance, exaggerated startle (> 2)

**E:** Duration of symptoms is at least 1 month

**F:** Causes clinically significant distress or impairment in functioning
PTSD According To DSM-V

**DSM-V Criteria**

A1: Experienced, witnessed, learned that trauma occurred to others, or experienced repeated or extreme exposure to aversive details.

A2: Response must involve intense fear, helplessness or horror.

B(5): Re-experiencing – intrusive memories, distressing dreams, flashbacks, intense psychological distress, physiological reactivity to reminders (≥ 1)

C(2): Avoidance – avoid memories/thoughts/feelings, avoid external reminders (activities/places/people) (≥ 1)

D(7): Negative cognitions and mood – inability to remember trauma, persistent negative beliefs or expectations about oneself/others/world, distorted blame-based cognitions about cause/consequence of trauma, negative emotional state (fear, horror, anger, guilt, shame), diminished interest in activities, feeling detached, inability to experience positive emotions (≥ 2)

E(6): Arousal – irritability /outbursts of anger, reckless or self-destructive behaviour, hypervigilance, exaggerated startle, difficulty concentrating, sleep disturbance (≥ 2)

F: Duration of symptoms is more than 1 month

G: Causes clinically significant distress or impairment in functioning
Prevalence of PTSD and SUD

- Nearly half (46%) of people with PTSD meet criteria for any substance use disorder (SUD) 4
- Individuals with PTSD are 5 times more likely to have SUD compared to those without PTSD 5

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTSD</td>
<td>6%</td>
</tr>
<tr>
<td>Alcohol Use Disorder</td>
<td>29%</td>
</tr>
<tr>
<td>Drug Use Disorder</td>
<td>10%</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTSD</td>
<td>100%</td>
</tr>
<tr>
<td>Alcohol Use Disorder</td>
<td>42%</td>
</tr>
<tr>
<td>Drug Use Disorder</td>
<td>22%</td>
</tr>
</tbody>
</table>

2. Grant et al. (2015) JAMA Psychiatry, 72(8), 757-766
Prevalence of PTSD+SUD

- **SUD treatment samples**
  - **80 - 92%** have been exposed to trauma¹,²
  - **30% - 60%** have lifetime PTSD³

- **Military samples**
  - Among OEF/OIF Veterans, post-deployment prevalence rates are **15% - 20%** for PTSD and **21%** for SUD⁴
  - Among Veterans serving in the Vietnam era or later, **41%** of those with SUD are also diagnosed with PTSD⁵

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¹ Dore et al. (2012) *Drug Alcohol Rev*, 31(3), 294-0392
² Mills et al. (2005) *Drug Alcohol Depend*, 77(3), 243-249
³ Torchalla et al. (2012) *J Subst Abuse Treat*, 42, 65-77
⁴ Bray et al. (2007); Hoge et al. (2004); Seal et al (2007); Thomas et al.(2010)
⁵ Petrakis et al. (2011) *Am J Addict*, 20(3), 185-189
Harms Associated With PTSD+SUD

PTSD+SUD
- More polysubstance use
- Earlier age onset substance use
- Poorer mental health
- Poorer physical health
- Poorer psychosocial functioning

More severe clinical profile

Poorer treatment outcomes

Substance use & mental health

Psychosocial

Physical health

Mills et al. (2005) Drug and Alcohol Dependence, 77, 243-249.
How Should We Treat Co-occurring PTSD+SUD?

- Reluctance to address PTSD among SUD clients
  - Too vulnerable
  - Need to address SUD first (sequential model)
- Psychotherapeutic treatment models for SUD+PTSD
  - Majority of clients prefer an integrated treatment approach
  - More efficient use of time and resources

Back et al. (2006) *Addict Behav.*, 31, 351-4
Back et al. (2014) *Addict Behav.*, 39(2), Epub
Symptom Interplay

- When substance use is reduced, PTSD symptoms can intensify, increasing risk of relapse\(^1,2\)

- PTSD must be treated to achieve lasting improvements in substance use outcomes

- \textit{Reductions in PTSD are more likely to lead to reductions in substance use, than the reverse}\(^3,4\)

\begin{itemize}
  \item Back et al. (2006) \textit{Addict Behav.} 31, 351-4
  \item Back et al. (2006) \textit{J Nerv Ment Dis.} 194, 690-6
  \item Back et al. (2009) \textit{Am J Addict.}, 18(1), 15-20.
  \item Hien et al. (2010) \textit{Am J Psychiat.}, 167(1), Epub
\end{itemize}
PTSD treatment responders had significantly fewer
• % days drinking (11% vs 31%)
• % heavy drinking days (9% vs 21%)
• average drinks per day (.77 vs. 2.39) vs. treatment non-responders
Minimal Evidence ↓ SUD Associated With ↓ PTSD

- No significant differences between AUD treatment responders vs. non-responders
  - IES (28.6 vs. 34.4)
  - CAPS (29.8 vs. 40.0, $p = 0.08$)
  - MISS (98.4 vs. 101.9)

Back et al. (2006) J Nerv Ment Dis. 194, 690-6
Overview of PTSD+SUD Connection

Khantzian (1985) *Am J Psychiatry*, 142(11), 1259-64
Overview Of Integrated Treatment Of PTSD+SUD

1. Treat PTSD and SUD
2. Manage PTSD without substances
3. Recovery from PTSD and SUD
4. Long term relief
## Evidence-based Integrated Psychotherapies

<table>
<thead>
<tr>
<th>Individual</th>
<th>Non-trauma-focused</th>
<th>Trauma-focused/exposure-based</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Seeking Safety</strong>: 25 sessions, twice weekly.</td>
<td><strong>Prolonged Exposure</strong>: Imaginal exposure only or imaginal plus in vivo exposure (e.g. COPE)</td>
<td></td>
</tr>
<tr>
<td>Psychoeducation, coping and interpersonal effectiveness skills, cognitive processing and restructuring</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Integrated CBT</strong>: 8 modules over 8–12 individual sessions. Psychoeducation, anxiety reduction skills (breathing retraining), cognitive processing and restructuring</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Seeking Safety: as above</th>
<th>TARGET: 8-9 gender-specific group sessions. Psychoeducation, cognitive processing, emotion regulation skills, and personal narrative work</th>
</tr>
</thead>
</table>

Roberts et al. (2016) *Cochrane Database of Systematic Reviews*, Issue 4. Art. No.: CD010204

Evidence-based Integrated Psychotherapies

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<tr>
<th>Non-trauma-focused</th>
<th>Trauma-focused/exposure-based</th>
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<tr>
<td><strong>Individually</strong></td>
<td></td>
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<tr>
<td>Seeking Safety</td>
<td>Prolonged Exposure (e.g. COPE)</td>
</tr>
<tr>
<td>Integrated CBT</td>
<td></td>
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<tr>
<td><strong>Group</strong></td>
<td></td>
</tr>
<tr>
<td>Seeking Safety</td>
<td></td>
</tr>
<tr>
<td>TARGET</td>
<td></td>
</tr>
</tbody>
</table>

- Little evidence to support non-trauma-focused therapies (individual & group)
- **Integrated treatment models with trauma-focused therapy** are recommended
- But... drop out rates high and effect sizes modest → need more research

Roberts et al. (2016) *Cochrane Database of Systematic Reviews*, Issue 4. Art. No.: CD010204
The COPE Therapy

- COPE: Concurrent Treatment of PTSD and Substance Use Disorders using Prolonged Exposure¹
- Synthesis of two theory-based, empirically-validated CBT Txs
  - Prolonged Exposure (PE) for PTSD²
  - Relapse Prevention for SUD³

Primary goals

1. Educate clients about the functional relationship between PTSD and SUD
2. Decrease PTSD symptom severity via PE (in-vivo and imaginal exposure)
3. Decrease substance use, initiate and maintain abstinence using CBT

2. Foa et al. (2007) Prolonged Exposure Therapy for PTSD. NY: Oxford University
COPE Therapy Overview

- 12, individual, 60-90 minute sessions
- Contents
  - Introduction, psychoeducation about PTSD+SUD, develop goals
  - Coping with cravings and thoughts about using
  - Identify triggers for cravings (both trauma- and substance-related triggers)
  - Managing high-risk thoughts (both trauma- and substance-related thoughts) (e.g., escape, relaxation, testing control, nostalgia)
  - Seemingly irrelevant decisions
  - Drink/drug refusal skills
  - Managing anger (symptom of PTSD, trigger for use)
  - In-vivo exposures (sessions 3-11) and imaginal exposures (sessions 4-11)

Back et al. (2014) COPE Therapist Guide. Oxford University Press, USA
In-vivo Exposure

- Occur in between therapy sessions
- Repeated (2-3 times)
- Prolonged (≥ 30-45mins)
- Common examples
  - Walmart (or other crowded stores)
  - Sitting in middle of restaurant
  - Going to a sporting event or a movie theatre
  - Driving during rush hour, being stopped at a stop light
  - Watching or reading the news

Back et al. (2014) COPE Therapist Guide. Oxford University Press, USA
Imaginal Exposure

- Repeated revisiting of trauma memory (30min per session x 8 sessions) leads to extinction
- Learn to discriminate between past and present
- Learn that anxiety behaves like a wave, no feeling is final
- Learn that *thinking* about event is not dangerous
- Trauma memories more organized, and maladaptive beliefs are addressed/corrected

Back et al. (2014) *COPE Therapist Guide*. Oxford University Press, USA
Prolonged Exposure Therapy: The Wave Of Anxiety (And Craving)
Dr. Edna Foa
Univ. of Pennsylvania

Drs. Markus Heilig, Anna Persson & Asa Magnusson
Linköping Univ.
Stockholm, Sweden

Dr. Denise Hien & colleagues
Adelphi Univ.

Dr. Kathleen Carroll
Yale Univ.

Drs. Sudie Back, Kathleen Brady, Therese Killeen & Julianne Flanagan
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Drs. Katherine Mills, Maree Teesson & Emma Barrett
Univ. of New South Wales
Sydney, Australia

COPE Collaborators
COPE Studies

- United States
  - PTSD + cocaine: N=39\(^1,2\)
  - Military PTSD + SUD; COPE vs Relapse Prevention (N=84)\(^3\)
  - PTSD + SUD; COPE vs Relapse Prevention (N=110)\(^4\)
  - Military PTSD + SUD; COPE vs Seeking Safety (ongoing)\(^5\)
  - Military PTSD + SUD (ongoing)\(^6\)
- Australia
  - PTSD + SUD; COPE vs Treatment-as-usual (N=103)\(^7\)
- Sweden
  - PTSD + alcohol (N=22)\(^8\)

2. Brady et al. (2001) *JSAT*, 21(1), 47-54
3. Back et al. (in preparation)
4. Hien et al. (in preparation)
5. Norman et al. (ongoing)
6. Roache et al. (ongoing)
8. Heilig et al. (under review)
Integrated Exposure-Based Therapy for Co-occurring Posttraumatic Stress Disorder and Substance Dependence: A Randomized Controlled Trial

Katherine L. Mills, PhD
Marcy Yovovic, PhD
Sadie E. Bush, VMD
Kathleen T. Brady, MD, PhD
Amanda L. Baker, PhD
Sally Hagenom, MPH, Psych (Clin)
Charles Sussman, PhD
Erin L. Barnett, PhD
Sallie M. Morr, MPH
Julia Essesveld, MPH, Psych (Clin)
Phyllis L. Dyer, MPH (North)

Prolonged exposure therapy, a cognitive-behavioral therapy (CBT) involving exposure to traumatic reminders and recollections of past trauma, has long been regarded as standard treatment for posttraumatic stress disorder (PTSD). Although there are no other evidence-based treatments for PTSD, such as eye movement desensitization and reprocessing therapy, there is strong evidence for the efficacy of prolonged exposure therapy for other posttraumatic stress disorders (PTSD). This study used a randomized controlled trial (RCT) design to evaluate the efficacy of prolonged exposure therapy for PTSD in a community sample of veterans with PTSD.

Objective: To determine whether an integrated treatment for PTSD and substance dependence, concurrent treatment of PTSD and substance use disorders using prolonged exposure (COPE), can achieve greater reductions in PTSD and substance dependence symptoms severity compared with usual treatment for substance dependence.

Design, Setting, and Participants: Randomized controlled trial enrolling 267 participants who met DSM-IV TR criteria for both PTSD and substance dependence. Participants were recruited from 2002 to 2009 in Sydney, Australia. Outcome measures were assessed at 9-month postbaseline, with interim measures collected at 6 weeks and 3 months postbaseline.

Interventions: Participants were randomized to receive COPE plus usual treatment (n=60) or usual treatment alone (control, n=60). COPE consists of 15 individual 90-minute sessions (6, 19.5 hours) with a clinical psychologist.

Main Outcome Measures: Change in PTSD symptom severity as measured by the Clinician-Administered PTSD Scale (CAPS), total score (n=240) and change in severity of substance dependence as measured by the number of dependence criteria met according to the Composite International Diagnostic Interview—version 3.0 (CIDI—version 3.0) (n=240).

Results from baseline to 9-month follow-up, significant reductions in PTSD symptom severity were found for both the treatment group (mean difference = .12, 95% CI: -.07 to -.25, P < .01), and the control group (mean difference = -.12, 95% CI: -.26 to 0.02, P = .16). However, the intervention group also reported significantly greater reductions in PTSD symptom severity (mean difference = -.16, 95% CI: -.26 to .04, P < .01). No significant between-group differences were found in relation to improvements in severity of substance dependence (0.43 vs 0.52, incidence rate ratio = 0.85, 95% CI: 0.60 to 1.17), nor were there any significant between-group differences in relation to changes in substance use, depression, or anxiety.

Conclusion: Among patients with PTSD and substance dependence, the combined use of COPE plus usual treatment, compared with usual treatment alone, resulted in improvement in PTSD symptom severity without an increase in severity of substance dependence.

Total Registration: nctn.org identifier: NCT02395671

JAMA. 2013;309(1):81-89

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Both groups received treatment as usual for their substance use in the community (e.g., detox, residential rehabilitation, maintenance pharmacotherapies, counselling)

Funded by the National Health and Medical Research Council
Mills et al. (2012). JAMA, 308(7), 690-99
<table>
<thead>
<tr>
<th>Substance use characteristics</th>
<th>N=103</th>
<th>Trauma/PTSD characteristics</th>
<th>N=103</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of first intoxication</td>
<td>13yrs (6-29)</td>
<td>Age of first trauma</td>
<td>8yrs (1-44)</td>
</tr>
<tr>
<td>History of injecting drug use</td>
<td>80%</td>
<td>History of childhood trauma</td>
<td>77%</td>
</tr>
<tr>
<td>Prior substance use treatment</td>
<td>93%</td>
<td>Prior PTSD treatment</td>
<td>35%</td>
</tr>
<tr>
<td>Past-month substance use</td>
<td></td>
<td>Number of traumas</td>
<td>6 (2-10)</td>
</tr>
<tr>
<td>- Benzodiazepines</td>
<td>73%</td>
<td>Trauma types</td>
<td></td>
</tr>
<tr>
<td>- Cannabis</td>
<td>69%</td>
<td>- Physical assault</td>
<td>93%</td>
</tr>
<tr>
<td>- Alcohol</td>
<td>67%</td>
<td>- Threatened or held captive</td>
<td>89%</td>
</tr>
<tr>
<td>- Heroin</td>
<td>45%</td>
<td>- Witnessed injury or death</td>
<td>79%</td>
</tr>
<tr>
<td>- Amphetamines</td>
<td>42%</td>
<td>- Sexual assault</td>
<td>78%</td>
</tr>
<tr>
<td>- Cocaine</td>
<td>21%</td>
<td>- Accident or disaster</td>
<td>66%</td>
</tr>
<tr>
<td>Main drug of concern</td>
<td></td>
<td>- Torture</td>
<td>24%</td>
</tr>
<tr>
<td>- Heroin</td>
<td>21%</td>
<td>- Combat experience</td>
<td>2%</td>
</tr>
<tr>
<td>- Cannabis</td>
<td>20%</td>
<td>Median duration of PTSD symptoms</td>
<td>10yrs (1-40)</td>
</tr>
<tr>
<td>- Amphetamines</td>
<td>18%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Benzodiazepines</td>
<td>16%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Alcohol</td>
<td>12%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Cocaine</td>
<td>7%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mills et al. (2012). *JAMA*, 308(7), 690-99
Severity of Dependence

Severity of PTSD

Mills et al. (2012). *JAMA*, 308(7), 690-99
Factors Associated With Reductions In PTSD

**Individual baseline characteristics**

Demographics:
- age, sex, place of birth, education+, employment, prison history
Substance use:
- age of onset, history of IDU, number of substances used, main drug of concern
Trauma and PTSD:
- age of first & worst trauma, childhood trauma, types of trauma, number of traumas, baseline PTSD severity+*
Mental health:
- depression, anxiety, BPD
Treatment history:
- SUD treatment, PTSD treatment, current treatment, antidepressants)

**COPE treatment characteristics**

Therapist
Started COPE therapy+
Number of COPE sessions+
Received imaginal and/or in vivo exposure+

Events over follow up
Time spent in SUD treatment
Use of antidepressants
New trauma exposure

* baseline PTSD severity
* number of traumas
* number of COPE sessions

*Mills et al. (under review)*

Course In Addiction Medicine

*ASAM*
COPE US Military RCT

N = 81

COPE (n=54)

Relapse Prevention (n=27)

NIDA grants R01 DA030143, K02 DA039229
Preliminary findings

- Compared to RP, those who received COPE demonstrated:
  - Similar completion rates and reductions in substance use
  - Significantly greater improvement in PTSD symptoms
  - Significantly higher rates of PTSD remission (83% vs 36%)

Symptom interplay:

1. Back et al., (in preparation)
2. Badour et al., (in preparation)

- 56% of change in substance use is mediated by change in PTSD symptoms
- 5% of change in PTSD symptoms is mediated by change in substance use
Summary

- PTSD and SUD often co-occur, this comorbidity is associated with a much more severe clinical profile.
- Studies among men and women, civilian and combat-related PTSD, multiple SUDs and multiple traumas show that integrated exposure-based treatments are safe, feasible and effective.
- Substance use does not increase with exposure-based PTSD treatment.
- PTSD symptom change may be driving SUD change in integrated therapies.
Where do we go from here?

- **Who** does integrated therapy work best for (gender, military vs. civilians) and **what** are the mechanisms?
- **How** can we enhance PTSD and AUD treatment outcomes (accelerate extinction learning, increase retention) via behavioral or pharmacological interventions, or neurostimulation devices?
- **How early** can we apply integrated treatments (during adolescence, subclinical diagnoses)?
Thank you!!

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Quiz Questions

Q1. Between 30 – 60% of people seeking treatment for substance use meet criteria for a lifetime diagnosis of PTSD
   • A. True
   • B. False
Quiz Questions \textit{cont'd}

\textbullet{} Q2. Based on the recent Cochrane Review published by Roberts et al. (2016), what treatment approach for co-occurring PTSD and SUD has the most empirical support?

\textbullet{} A. Sequential treatment model with non-trauma focused PTSD therapy

\textbullet{} B. Sequential treatment model with trauma-focused PTSD therapy

\textbullet{} C. Integrated treatment model with non-trauma focused PTSD therapy

\textbullet{} D. Integrated treatment model with trauma-focused PTSD therapy
Quiz Questions *cont’d*

- **Q3.** Which statement most accurately reflects symptom interplay between PTSD and substance use?
  - A. Reductions in PTSD symptoms are associated with *increases* in substance use
  - B. Reductions in PTSD symptoms are associated with *reductions* in substance use
  - C. There is no symptom interplay between PTSD and substance use
  - D. Reductions in substance use are *always* associated with reductions in PTSD symptoms
Co-occurring Bipolar Disorder, Schizophrenia & Substance Use Disorders

E. Sherwood Brown, MD, PhD

Professor, Aradine S. Ard Chair in Brain Science
Vice Chairman for Clinical Research
Co-Editor-in-Chief, Journal of Dual Diagnosis
Department of Psychiatry, The University of Texas Southwestern Medical Center
The ASAM Review Course in Addiction Medicine
October 7, 2016

Disclosure Information

E. Sherwood Brown, MD, PhD

Genentech– Honorarium
Prevalence of Substance Use Disorders (SUDs) in Schizophrenia and Bipolar Disorder (BPD)

- Lifetime prevalence of substance-use disorder (SUD) from epidemiologic study
  - Schizophrenia 47%
  - Major depressive disorder 27%
  - Bipolar I disorder 61%
  - Bipolar II disorder 48%

- A more recent population-based study found a 58% and 37.5% lifetime rate of SUDs in bipolar disorder

- In clinical populations lifetime rates of SUD of 31-80% are reported for schizophrenia
Impact of Substance use on BPD

- Increased hospitalization (although the literature is mixed)
- Violence toward self and others
- Poor treatment adherence
- Possibly poorer response to substance use treatment
Impact on Schizophrenia

- CATIE study observed moderate/severe drug use was associated with poorer outcomes related to psychotic symptoms, depression, and QOL, and criminal justice system involvement

- SUD associated with greater hospital readmission

- Possible early onset psychosis identified associated with violence and substance use

- Increased risk of being the victim of violence

Huber CG, et al. *Schizophr Res.* 2016;175:198-203
Mechanisms

- Why do people with BPD and schizophrenia have such high rates of SUDs?

Mechanisms cont’d

- *Schizophrenia or BPD cause SUDs*
  - Self-medication, impaired judgment, mood swings, psychosis, environment
Mechanisms cont’d

- **Substance use disorders cause schizophrenia or BPD**
  - Cannabis and schizophrenia?
  - The literature suggesting cannabis use as a risk factor for the development of psychosis is growing
  - Adolescent substance use may even be associated with a distinct set of symptom characteristics in people with psychosis that includes better cognition.

Mechanisms cont’d

- SUDs lead to misdiagnosis of schizophrenia or BPD
  - Substance-induced mood or psychotic symptoms
Mechanisms cont’d

- SUDs and schizophrenia or BPD share a common etiology or risk factors
  - Impulsivity

- Genetics, non-random mating

Treatment of Dual Diagnosis Patients

- The literature is limited perhaps due to 1) complicated patient population with changes in psychiatric symptoms and substance use occurring concurrently and 2) large industry-sponsored clinical trials generally exclude participants with current substance use.
Treatment – BPD and SUD Pharmacotherapy

- 11 randomized, double-blind, placebo-controlled trials in peer-reviewed literature
- Two positive studies of citicoline, and one more mixed study of lamotrigine for BPD and cocaine use disorder
- Three negative quetiapine studies for BPD and alcohol use disorder and one small pilot for cocaine
- Positive study of lithium in adolescents with BPD and SUD
- Positive study of valproate for BPD and AUD
- Somewhat positive study of naltrexone and a more negative study of acamprosate for BPD and AUD.

Valproate for Bipolar Disorder and Alcohol Use

- 59 outpatients with bipolar I disorder and alcohol dependence and receiving lithium therapy were randomized to valproate or placebo for 24 weeks

- Valproate group had significantly fewer heavy drinking days and a trend toward fewer drinks per heavy drinking day than the group receiving placebo

- Higher serum valproate levels were associated with decreases in alcohol use

Citicoline

- Non-prescription nutritional supplement that may work though cholinergic systems and phospholipids

- 44 outpatients with bipolar or schizoaffective disorder and cocaine abuse/dependence randomized to 12 weeks of citicoline (2000 mg/day) add-on therapy or placebo

- Citicoline group had lower likelihood than placebo of cocaine-positive urine at exit (OR 6.41) and greater improvement in memory

- Retention in the citicoline group was much better

Citicoline for BPD and Cocaine use

- 130 outpatients with bipolar I disorder and cocaine dependence received citicoline or placebo add-on therapy for 12 weeks.

- All participants had a cocaine-positive urine drug screen at baseline.
Urine Drug Screens Positive For Cocaine In Citicoline & Placebo Groups

- Treatment group comparison of urine drug screens positive for cocaine (with missing data imputed as positive) 
  \( p = 0.022 \)

- Treatment group comparison of urine drug screens positive for cocaine (without imputation) \( p = 0.035 \)
Treatment-Schizophrenia and SUD Pharmacotherapy

- 10 randomized, controlled trials of medications
- Many used an active comparator rather than a placebo control
- Many of the studies had small sample sizes (<40)
- Clozapine may be a promising drug for schizophrenia and SUD
- Naltrexone may decrease alcohol use in this dual diagnosis population

Psychotherapy for BPD and SUD

- An integrated group therapy that addresses both bipolar disorder and SUD was associated with fewer days of substance use than group drug counseling focusing on substance use.

- An individual CBT specific for BPD and SUD was compared to medication management. The CBT improved attendance (60% vs. 33% 12 week completion), and tended to improve medication adherence and mood but did not decrease substance use.


Psychotherapy for Schizophrenia and SUD

- Somewhat mixed results with motivational interviewing and cognitive behavioral therapy
- Promising findings in patients with a variety of psychiatric illnesses given a social learning intervention that included MI, contingency management and social skills training
- A family intervention was superior to an education and problem solving control for psychiatric symptoms and functioning, but not for substance use
- Cognitive enhancement therapy may improve cognition and reduce alcohol use

Barrowclough C, et al. BMJ. 2010;341:c6325

Integrated Therapy

- 327 people with schizophrenia, schizoaffective or schizophreniform disorders and SUD randomized to integrated motivational interviewing (MI) and cognitive behavioral therapy (CBT) plus standard care vs. standard care only

- No difference at 24 months on death, readmission, frequency of substance use, but decreased amount of substance use (OR 1.5) as well as readiness to change.

Barrowclaugh C, et al. BMJ. 2010;341:c6325
Summary

- SUD disorders are extremely common in people with schizophrenia or BPD
- When present SUDs in this population appear to be associated with a variety of adverse consequences
- SUD in this population appears to be challenging to treat but some promising pharmacological and psychosocial therapies have been identified
Future directions

- We need to better understand the mechanisms behind the high rates of SUD in people with BPD and schizophrenia
- Additional, large and adequately powered clinical trials of treatments are needed
Further Questions?

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Neurobiology and Pharmacotherapy of Post Traumatic Stress Disorder and Addictions

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Disclosure Information

Thomas Kotsen, MD
No Disclosures
PTSD & SUD in OIF/OEF Rand Study (Dec 2008)

- Binge Alcohol – 50% (twice community rate)
- Tobacco smoking – 50% (2.5 X community rate)
- Opiate abuse – 9% (3 X community rate)
- Acute opiate treatment after trauma reduces the development of PTSD, benzos increase PTSD
- Other drugs – inhalants, sedatives, marijuana
Salient Neurobiology of PTSD
Failure of Extinction

- Hyper-response to reminders of the trauma
  - Amygdalar & locus ceruleus (NA) hyperactivity

- Overgeneralization of stimuli
  - Hippocampal dysfunction (glutamate, NMDA)

- Anger dyscontrol, Failure of extinction
  - Medial prefrontal cortex dysfunction (kappa opioid & glutamate)
Extinction is an Active Cortical Process

- Cortical ablation studies – LeDoux
  - Acquisition of conditioned fear responses requires only subcortical structures
  - Cortical ablation greatly prolongs or prevents extinction of fear responses

- “Indelibility of subcortical emotional memories”
Coordination of Threat Response

Medial Prefrontal Cortex
Anterior Cingulate Cortex

Hippocampus

AMYGDALA

+ → Thalamus

+

Coordination of Threat Response

Sights

Sounds

Smells
Innovative PTSD Treatment: Modulating Extinction & Reducing SUD Learning

- **Adrenergic System** – extinction vs. symptom relief
  - Adrenergic Blockers block extinction (Prazosin)
  - Adrenergic agonists like yohimbine facilitate extinction
- **NMDA receptors** - ? Partial agonist: raise dose
  - NMDA agonists facilitate extinction (low dose partial agonist)
  - NMDA antagonists block extinction, but help addiction
- **Kappa opioid antagonists** – help extinction & SUD
  - KOR blockade produces anti-stress effects & reduces disruptions from chronic stress (PTSD)
  - Pathway from amygdala to medial prefrontal cortex inhibits glutamate release from cortex
Innovative Treatments: Hippocampal Glutamate for Learning & Memory

- High densities of NMDA and AMPA receptors in the hippocampus
- Role for glutamate receptors in long term potentiation
- Glutamate receptor antagonists inhibit LTP and learning and memory;
- AMPA receptor potentiators enhance LTP and learning and memory
Glutamate & Addiction: Addiction as Disordered Learning

- Glutamatergic input to VTA and nucleus accumbens facilitates dopaminergic transmission
- Repeatedly taking abused drugs increases glutamate release in nucleus accumbens
- NMDA antagonists block the rewarding effects of several abused drugs
Effect of Acute versus Chronic Drug Abuse

**ACUTE**

- Limbic Cortex
  - Glutamate
  - Learned Associations

- Basal Ganglia
  - GABA
  - Behavioral Engagement

- Social Exploration

- Dopamine
  - inducing behavioral and neural plasticity

**ADDICTED**

- Limbic Cortex
  - Glutamate
  - Learned Associations

- Basal Ganglia
  - GABA
  - Behavioral Engagement

- Paranoia
- Craving

- Dopamine
  - inducing behavioral and neural plasticity

Course in Addiction Medicine
Pharmacotherapy: PTSD vs SUD

<table>
<thead>
<tr>
<th>PTSD</th>
<th>Addictions</th>
</tr>
</thead>
<tbody>
<tr>
<td>◦ Antidepressants</td>
<td>◦ Alcohol</td>
</tr>
<tr>
<td>◦ Anticonvulsants</td>
<td>◦ Naltrexone</td>
</tr>
<tr>
<td>◦ Antipsychotics</td>
<td>◦ Acamprosate</td>
</tr>
<tr>
<td>◦ Innovations</td>
<td>◦ Disulfiram</td>
</tr>
<tr>
<td>◦ Adrenergic blocker: alpha 1</td>
<td>◦ Opiates</td>
</tr>
<tr>
<td>◦ Glutamate partial agonist</td>
<td>◦ Buprenorphine</td>
</tr>
<tr>
<td>◦ Kappa opioid antagonist</td>
<td>◦ Naltrexone</td>
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</tbody>
</table>
### Sertraline Response in PTSD

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline</th>
<th>Endpoint</th>
<th>Change</th>
<th>Response Rate %</th>
<th>P (vs. placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brady et al (2000)⁶</td>
<td>76.6</td>
<td>43.4</td>
<td>-33.0</td>
<td>53.0</td>
<td>.016</td>
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<tr>
<td></td>
<td>75.1</td>
<td>51.9</td>
<td>-23.2</td>
<td>32.0</td>
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<tr>
<td>Davidson et al (2001)⁷</td>
<td>73.9</td>
<td>40.0</td>
<td>-33.0</td>
<td>60.0</td>
<td>.043</td>
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<tr>
<td></td>
<td>73.5</td>
<td>47.3</td>
<td>-26.2</td>
<td>38.0</td>
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</tbody>
</table>
## Paroxetine Response in PTSD

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline</th>
<th>Endpoint</th>
<th>Change</th>
<th>Response Rate (%)</th>
<th>P (vs. placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marshall et al (2001)</td>
<td>74.3</td>
<td>36.4</td>
<td>-37.9</td>
<td>54.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>74.4</td>
<td>49.1</td>
<td>-25.3</td>
<td>37.0</td>
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<tr>
<td>Tucker et al (2001)</td>
<td>74.3</td>
<td>38.8</td>
<td>-35.5</td>
<td>58.8</td>
<td>&lt;0.001</td>
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<td></td>
<td>73.2</td>
<td>48.5</td>
<td>-24.7</td>
<td>38.0</td>
<td></td>
</tr>
</tbody>
</table>
Reduced Alcohol Abuse with PTSD Response to Sertraline, Back et al 2005

![Graph showing reduced alcohol abuse with PTSD response to Sertraline]

- **Respond**
- **Non-resp**
Open-label Med. Trials In PTSD

- **Anticonvulsants**
  - Carbamazepine
  - Topiramate
  - Gabapentin
  - Tiagabine
  - Valproate
  - Lamotrigine

- **Antipsychotics**
  - Olanzapine
  - Quetiapine
  - Risperidone

- **Adrenergic Blockers**
  - Prazosin/Doxazosin
  - Disulfiram/Nepicastat
# ATYPICAL ANTIPSYCHOTICS IN PTSD

## Controlled Trials – Efficacy

Risperidone 1-6 mg + antidepressant

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>N</th>
<th>Design</th>
<th>Trauma</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartzokis et al (2001)</td>
<td>48</td>
<td>16 weeks, R, DB, PC</td>
<td>Combat</td>
<td>Decreased CAPS, HAM-A</td>
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<tr>
<td>Hammer et al (2003)</td>
<td>37</td>
<td>5 weeks R, DB, PC</td>
<td>Combat with psychotic symptom</td>
<td>Decreased PANSS, CAPS-B</td>
</tr>
<tr>
<td>Krystal (2011)</td>
<td>247</td>
<td>6 months R, DB, PC</td>
<td>Combat</td>
<td>Not better than placebo on CAPS or any outcomes</td>
</tr>
</tbody>
</table>
Alcoholism +/- PTSD Treated with Naltrexone +/- Disulfiram

% Relapsed Over 3 months (n=264, P<0.002)
Depot Naltrexone (Vivitrol)

- The best candidates for naltrexone are those with strong family history and more severe binging or dependence.
- Adherence to naltrexone can be a challenge for PTSD patients with this severe type of alcohol abuse.
- Depot naltrexone given once per month is optimal solution to adherence challenge.
- NO significant contraindications except opiate treatment – addressed next in this talk.
Current Pharmacotherapy of PTSD & Alcoholism

- Sertraline & paroxetine standards
  - Alcohol abuse reduced by PTSD response
- NO added efficacy for anti-convulsants or anti-psychotics (Valproate & Risperidone) with SSRI
- Disulfiram reduces alcohol use in PTSD
- No contra-indication to adding Naltrexone or Acamprosate with other PTSD medications
Innovative PTSD Treatments Modulating Extinction & Reducing SUD Learning

- NMDA receptors - ? Partial agonist: raise dose
  - NMDA agonists facilitate extinction (low dose of partial agonist is an agonist for helping PTSD)
  - NMDA antagonists block extinction, but help addiction
  - As PTSD symptoms resolve, gradual increase to higher doses of partial agonist, where it is antagonist
  - Blocks high glutamate levels and “new learning” of reinforcement from addictive agents with SUD relapse
- Kappa opioid antagonists– help extinction & SUD
  - KOR blockade produces anti-stress effects & reduces disruptions from chronic stress (PTSD)
  - Pathway from amygdala to medial prefrontal cortex inhibits glutamate release from cortex
D-Cycloserine (DCS) enhanced the effectiveness of exposure therapy for acrophobia (fear of heights) in humans.

DCS group had decreased fear in virtual reality & in real-life fear of heights at 1 week and 12 weeks.

Similar studies in PTSD with exposure therapy generally failed, **except** in patients who had reductions in PTSD symptoms during exposure therapy sessions.
Innovations: PTSD & Addictions

- **Adrenergic blockade** is critical to reduce early PTSD symptoms & drug withdrawal
- Other overlapping neural memory circuits engaged with PTSD and addiction (SUD) facilitates **Extinction process** in both disorders
- Glutamate memory pathways may facilitate extinction, then glutamate partial blockade may reduce addiction liability – **Cycloserine**
- **Kappa opioid antagonists** reduce stress related circuits and reduce glutamate activity
Further Questions?

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