Alcohol Use Disorder, PTSD, and TBI in Veterans: New Research

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Case: Veteran with PTSD, TBI & AUD

- 33 yo married male Iraq combat veteran, college
- PTSD
  - Nightmares, insomnia, hypervigilance, irritability, trouble concentrating
- Alcohol Use Disorder
  - 3-5 drinks/night weekdays; 25-30 drinks/night weekends; total 65-85 drinks/week
  - Numerous efforts to cut down to “social drinking”
  - unable to control impulsive drinking
  - Intoxication associated with risky sexual behavior, other drug use, self-laceration
- TBI
  - Severe headaches, forgetfulness, irritability
- Irregular adherence to medications and psychological tx, missed visits -- related to alcohol use and cognitive disorganization
- Asks for “something to help” calm down, to sleep, not need to drink so much
Triad of Co-occurring Disorders

Each alone, and in combination, are associated with high-risk behaviors:

Impulsivity, violence, suicide, accidents, marital disruption, work impairment and health problems.
Postdeployment Alcohol Use, Aggression, and Post-Traumatic Stress Disorder

Over 16,000 postdeployment military personnel,

• Relation between cutoff scores on the PCL and high-risk behaviors:
  • Alcohol use, heavy use, driving after drinking, verbal & physical aggression, impulsiveness

• In active duty (AD) personnel, for every outcome examined → significantly greater odds for each problem behavior when PCL scores were higher
  • 20% of AD personnel with PCL scores in the 17 to 29 range engaged in heavy alcohol use compared to 31% of those with PCL scores > 50
  • Driving after drinking was 2-3x higher for those with PCL scores in the 44 - 49 range compared to those with PCL scores in the 17 - 29 range
Alcohol and Suicide Risk

Risk Factors Associated With Suicide in Current and Former US Military Personnel (Leard Mann *JAMA*. 2013;310(5):496-506)

• Over 150,000 Millennium cohort participants

• Individuals with increased risk for suicide:
  men (hazard ratio [HR], 2.14; 95% CI, 1.17-3.92; \( P = .01 \)); depression (HR, 1.96; 95% CI, 1.05-3.64; \( P = .03 \)); manic-depressive disorder (HR, 4.35; 95% CI, 1.56-12.09; \( P = .005 \)); alcohol-related problems (HR, 2.56; 95% CI, 1.56-4.18; \( P < .001 \)).

• Suicide deaths could potentially be reduced by approximately 18% in this population as a whole, by preventing or eliminating alcohol-related problems.
The Problem of Co-occurring Alcohol Use Disorder and PTSD/TBI

- Clinicians face difficult challenges in treating veterans with co-occurring alcohol use disorder (AUD) and chronic PTSD and/or mild TBI (mTBI).

- Effective and integrated treatments are needed for veterans with both AUD and PTSD/mTBI who may not be adequately managed with current therapies.
PTSD, TBI, & SUDs Comorbidity

• Common
• May share common neurobiological underpinnings
• Problematic
  – Assessment
  – Morbidity
  – Treatment
  – Outcome
Epidemiology of co-occurring PTSD/SUDs

Schaefer and Najavits (2007)

• In patients with lifetime PTSD, lifetime SUD is 21-43%, compared to 8-25% in those without PTSD (Jacobsen et al 2001)

• In SUD patients, the prevalence of lifetime PTSD ranges from 26-53% and for current PTSD 15-41%
PTSD and Alcohol Use Disorders: Co-Occurrence at SFVAMC

SFVAMC (Ft. Miley & CBOCs)

<table>
<thead>
<tr>
<th>Year</th>
<th>PTSD Diagnoses</th>
<th>Substance and PTSD Diagnoses</th>
<th>Alcohol and PTSD Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>FY07</td>
<td>33.1%</td>
<td>11.3%</td>
<td></td>
</tr>
<tr>
<td>FY08</td>
<td>34.2%</td>
<td>12.6%</td>
<td></td>
</tr>
<tr>
<td>FY09</td>
<td>34.1%</td>
<td>13.1%</td>
<td></td>
</tr>
<tr>
<td>FY10</td>
<td>34.9%</td>
<td>13.6%</td>
<td></td>
</tr>
<tr>
<td>FY11</td>
<td>37.9%</td>
<td>15.5%</td>
<td></td>
</tr>
</tbody>
</table>
Combat Also Increases the Rate of Alcohol Use Disorder, not just PTSD and TBI

- Reserve/Guard troops with combat exposure:
  - high rates of alcohol misuse after deployment
  - risk for new-onset alcohol misuse (Jacobson et al. 2008)
    - heavy weekly drinking:
      post-deployment 12.5%; new onset rate 8.8%
    - binge drinking:
      post-dep 53%; new onset rate 25.6%
  - alcohol-related problems:
    post-dep 11.9%; new onset rate 4.8%
Relationships between posttraumatic stress disorder and substance-use disorder


• **PTSD can lead to SUDs or moderate/exacerbate SUDs**
  – childhood traumatic stress $\rightarrow$ ↓ ↓ self-regulatory mechanisms $\rightarrow$ risk for SUD.
  – PTSD $\rightarrow$ may ‘self-medicate’ with substances to cope w PTSD xs.

• **SUD known to heighten likelihood of trauma exposure $\rightarrow$ ↑↑risk of PTSD (the high-risk hypothesis).**

• **SUD $\rightarrow$ increases probability of developing PTSD after trauma exposure,**
  – due to higher psychological/biological vulnerability in pts w chronic SUD (the susceptibility hypothesis).

• The PTSD/SUD relationship may be mediated by a 3$^{rd}$ variable, such as deficits in coping skills
Edna Foa on Relationship of PTSD & AUD

“The two disorders .... form a *vicious cycle*

in which PTSD leads to abuse of alcohol;

alcohol abuse impedes recovery from the traumatic experience thus contributing to the maintenance of PTSD;

and PTSD in turn further escalates and entrenches alcohol abuse.”

from: 5R01 AA012428: NALTREXONE AND CBT FOR PATIENTS WITH ALCOHOLISM AND PTSD
Relationships Between PTSD & Alcohol Dependence

• Alcohol:
  • most common substance of abuse in veterans with PTSD.
  • may be an attempt to “self-medicate” insomnia, anxiety & hyperarousal.
    • However, heavy alcohol use → exacerbates problems.

• Alcohol & substance use ↔ bidirectional relationship with PTSD.
  • risk factors for development of PTSD,
  • moderators of PTSD symptom severity
  • potential consequences of PTSD

• AUDs & PTSD share some common neurobiological mechanisms, e.g. elevations/dysregulation in norepinephrine & glutamate.

• Co-occurrence of AUDs & PTSD is associated with:
  • worse psychosocial & medical outcomes,
  • higher rate of relapse to substance use,
  • higher rates of hospitalization.
Cortico-limbic circuitry dysregulation

↑ Amygdala (AMY)
↓ Medial PFC (mPFC)

Lack of “top down” regulation necessary to effectively manage maladaptive thoughts (intrusive memories, cravings) or repetitive behaviors (avoidance, substance use).

Significant PFC-AMY uncoupling at rest and during symptom provocation.

Attenuated PFC-AMY connectivity shown to be a marker of early relapse risk.

Adapted from Back S (2015) Research Society on Alcoholism

Goldstein & Volkow, 2011; Huang et al., 2014; Holmes et al, 2012; McHugh et al., 2014; Pitman et al., 2012
Psychological Treatments for Concurrent PTSD & SUDs Review

• 17 studies identified, evaluating 10 tx protocols
  – 6 trauma-focused; 4 non-trauma-focused

• Trauma-focused
  – Imaginal Exposure [IE] integrated with CBT for SUDs (Coffey et al., 2006)
  – Concurrent Tx PTSD & Coc Dep [CTPCD/COPE]: Imaginal In vivo + add-on coping skills tx for SUDs (Back et al, 2001)

• Non-Trauma-focused

• studies showed pre-post reductions in PTSD and/or SUD sx

• Most treatments did not prove superior to regular SUD tx
  – But some preliminary evidence suggests pts may benefit from trauma-focused txs

• “Lack of methodologically sound tx trials makes it difficult to draw firm conclusions”
Do Treatment Improvements in PTSD Severity Affect Substance Use Outcomes? A Secondary Analysis From a Randomized Clinical Trial in NIDA’s Clinical Trials Network
Hien et al. Am J Psychiat 2010

Method:
Participants were 353 women randomly assigned to 12 sessions of either trauma-focused or health education group treatment. PTSD and substance use assessments were conducted during treatment and posttreatment at 1 week and after 3, 6, and 12 months.

Conclusions: PTSD severity reductions were more likely to be associated with substance use improvement, with minimal evidence of substance use symptom reduction improving PTSD symptoms.
- Results support the self-medication model of coping with PTSD symptoms and an empirical basis for integrated interventions for improved substance use outcomes in patients with severe symptoms.
Why Use Medications in AUD & PTSD?

1. To reduce alcohol use and its sequelae in PTSD

2. To reduce PTSD symptoms
   1. Intrusive re-experiencing of trauma
   2. Avoidance
   3. Hyperarousal
   4. irritability, anxiety
Some Possible Medications to Treat PTSD and Alcohol Use Disorder: Most established

<table>
<thead>
<tr>
<th>Known Alcohol Pharmacotherapies</th>
<th>Known PTSD Pharmacotherapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Disulfiram (Antabuse)</td>
<td>• SSRIs</td>
</tr>
<tr>
<td>• Naltrexone po and IM</td>
<td>• SNRIs</td>
</tr>
<tr>
<td>• Acamprosate (Campral)</td>
<td>• Prazosin</td>
</tr>
<tr>
<td>• Topiramate</td>
<td>• Possibly Topiramate</td>
</tr>
</tbody>
</table>
PHARMACOTHERAPY FOR ALCOHOL DEPENDENCE IN PTSD: SSRIs/SNRI

• **Sertraline** Brady 2005, N = 94: Significant decrease in alcohol use in both the SERT & PLA; only a trend for PTSD improvement
  - SERT Ss with less severe AUD and early-onset PTSD
    - *had significantly fewer drinks per drinking day* (*p* < 0.001) than PLA
  - SERT Ss with more severe alcohol dependence and later onset PTSD
    - *had significantly more drinks per DD* (*p* < 0.01) than PLA

  (NOTE: Kranzler (2011): moderating effect of AUD age of onset on SSRI treatment outcome only present in late onset AUD Ss who are L’ homozygotes at 5-HTTLPR.)

• **Sertraline** Hien (2015 JCCP): Seeking safety + sertraline vs placebo
  - PTSD Sx reduction: SERT > PLA
  - Alcohol use reduction: SERT = PLA
  - No difference in early vs late-onset AD

• **Paroxetine** or **Desipramine [SNRI]** + Naltrexone/PLA Petrakis
  - PTSD Sx: DMI = PAR; both groups reduced from baseline
  - Alcohol use reduction: DMI superior to PAR (each combined with NTX/PLA)
PHARMACOTHERAPY FOR AUD IN PTSD: Naltrexone

- **Naltrexone** or **disulfiram** vs PLA
  NTX or DSF each reduced alcohol use in veterans with & without PTSD; also Beneficial effects on PTSD sx

- **Naltrexone/PLA + Paroxetine or Desipramine** (Petrakis 2012)
  - NTX superior to PLA only for craving/retention
  - No effect on PTSD

- **Naltrexone/PLA** (Foa JAMA 2013) N= 165
  - NTX or PLA combined with prolonged exposure vs supp couns
  - NTX > PLA in reducing %DD; no diff in PTSD sx
  - PE was no better than supportive tx; but didn’t exacerbate alcohol use
PHARMACOTHERAPY FOR ALCOHOL DEPENDENCE IN PTSD: Adrenergic agents

- **Prazosin**
  - Simpson 2015; N=30
    - Alcohol: Prazosin > PLA in reducing use
    - PTSD: Prazosin = PLA
  - Ralevski, Petrakis N~100
    - no apparent benefit

- **Others:**
  - ?doxazosin, ?propranolol
PHARMACOTHERAPY FOR ALCOHOL DEPENDENCE IN PTSD: Anticonvulsants

- **Topiramate:**
  - Batki N=30, (Batki 2014 ACER)
  - Fischer N=30 ongoing (NCT 01408641);
  - Batki N=150 ongoing

- **Zonisamide**
  - Petrakis, in progress
    - N= 30 Veterans PTSD & AUD
Examples of other Novel Pharmacotherapies

• **N-acetylcysteine**
  – N= 35 Veterans PTSD & SUD
  – Positive results for substance craving (some alcohol) & PTSD sx reduction, Back/Kalivas, MUSC
Topiramate Tx of AUD in PTSD (TAP1)
Study Background/Rationale

- Topiramate has shown promise in separate studies:
  - reducing alcohol use
  - ameliorating symptoms of PTSD

- First controlled trial to explore use of topiramate for both AUD and PTSD, with minimal psychosocial treatment
Research Question/Hypotheses

The overall goal was to improve the care of veterans with PTSD and AUD

1. PRIMARY AIM:
To obtain a preliminary assessment of the efficacy of topiramate in decreasing the % days drinking as compared to placebo.

The *primary hypothesis* was that there would be a “signal” (trend) toward a significantly greater percent of days abstinent from alcohol use *in the topiramate treatment group compared to the placebo group*.

2. SECONDARY AIM:
To obtain a preliminary assessment of the efficacy of topiramate in reducing *PTSD symptom severity* in veterans with chronic PTSD and AUD.
Design and Methodology

**Methods**
- DB placebo-controlled pilot study
- 30 Veterans with PTSD & alcohol dependence
- 12-week treatment
- Topiramate or placebo up to 300 mg/d
- Weekly manualized alcohol counseling (NIAAA Medical Management)

**Measures**
- Alcohol measures: TLFB, EtG, craving
- PTSD Measures: PCL
- Impulsivity and Decision-Making
- Study powered to detect a “signal” (trend) for between-group differences
<table>
<thead>
<tr>
<th>Participant Characteristics at Baseline (mean ± SD)</th>
<th>Topiramate</th>
<th>Placebo</th>
<th>Top. vs. Pla. p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (female)</td>
<td>14 (1)</td>
<td>16 (1)</td>
<td>-</td>
</tr>
<tr>
<td>Age [years]</td>
<td>49.5 ± 13.9</td>
<td>50.4 ± 12.8</td>
<td>NS</td>
</tr>
<tr>
<td>Education [years]</td>
<td>12.9 ± 3.1</td>
<td>14.4 ± 1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Race</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Caucasian (Hispanic/Latino)</td>
<td>8 (2)</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>African American</td>
<td>2</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Combat Exposed (%)</td>
<td>10 (71)</td>
<td>12 (75)</td>
<td>NS</td>
</tr>
<tr>
<td>Comorbid Substance Use Disorder, n (%)</td>
<td>5 (36)</td>
<td>5 (32)</td>
<td>NS</td>
</tr>
<tr>
<td>Residential TX, n (%)</td>
<td>4 (29)</td>
<td>2 (13)</td>
<td>NS</td>
</tr>
<tr>
<td>Outpatient TX, n (%)</td>
<td>7 (50)</td>
<td>8 (50)</td>
<td>NS</td>
</tr>
<tr>
<td>BDI</td>
<td>23.4 ± 11.6</td>
<td>26.3 ± 12.3</td>
<td>NS</td>
</tr>
<tr>
<td>BAI</td>
<td>20.4 ± 12.7</td>
<td>27.4 ± 13.3</td>
<td>NS</td>
</tr>
<tr>
<td>AUDIT Score</td>
<td>27.1 ± 7.9</td>
<td>23.0 ± 7.5</td>
<td>NS</td>
</tr>
<tr>
<td>Avg. Drinks$^$ per DD</td>
<td>11 ± 6</td>
<td>11 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>Avg. Drinks$^$ per Week</td>
<td>52 ± 34</td>
<td>58 ± 25</td>
<td>NS</td>
</tr>
<tr>
<td>Avg. DD per Week</td>
<td>5 ± 2</td>
<td>6 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Avg. HDD per Week</td>
<td>4 ± 2</td>
<td>5 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline CAPS Total</td>
<td>72.8 ± 14.3</td>
<td>83.1 ± 17.3</td>
<td>NS</td>
</tr>
<tr>
<td>Intrusion</td>
<td>18.2 ± 4.3</td>
<td>21.9 ± 6.9</td>
<td>NS</td>
</tr>
<tr>
<td>Avoidance</td>
<td>31.1 ± 6.1</td>
<td>34.8 ± 8.9</td>
<td>NS</td>
</tr>
<tr>
<td>Arousal</td>
<td>23.5 ± 6.7</td>
<td>26.4 ± 4.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: DD, Drinking Day; HDD, Heavy Drinking Day (>4 standard alcoholic drinks for men, >3 standard alcoholic drinks for women). Note-drink consumption is average over past 90 days prior to study consent.$^\$ standard alcoholic drink defined as containing 13.6 g of pure alcohol
# Percent Drinking Days

## Table 2. Topiramate Within Group Change (Baseline to 12 Weeks) and Between Group Differences

<table>
<thead>
<tr>
<th>Alcohol Measures</th>
<th>WITHIN GROUP ANALYSIS</th>
<th>BETWEEN GROUP ANALYSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (Past 90)</td>
<td>Active TX (Week 1-12)</td>
</tr>
<tr>
<td></td>
<td>Mean ± Std. Dev.</td>
<td>Mean ± Std. Dev.</td>
</tr>
<tr>
<td>% Drinking Days</td>
<td>71.3 ± 30.6</td>
<td>20.8 ± 34.2</td>
</tr>
<tr>
<td>% HDD</td>
<td>59.0 ± 35.0</td>
<td>11.9 ± 27.3</td>
</tr>
<tr>
<td>Std. Drinks per Week</td>
<td>53.7 ± 35.3</td>
<td>9.3 ± 18.0</td>
</tr>
<tr>
<td>Drinks per DD</td>
<td>11.7 ± 6.1</td>
<td>4.6 ± 4.2</td>
</tr>
</tbody>
</table>

Abbreviations: DD, Drinking Day; HDD, Heavy Drinking Day (>4 standard alcoholic drinks for men, >3 standard alcoholic drinks for women). (standard alcoholic drink defined as containing 13.6 g of pure alcohol) - Controlled for baseline drinking in all between group models. – No sig group by week interactions.

### Mean Percent Drinking Days Per Week

![Mean Percent Drinking Days Per Week](chart1)

### Median Percent Drinking Days Per Week

![Median Percent Drinking Days Per Week](chart2)
# Drinks/Drinking Day

## Table 2. Topiramate Within Group Change (Baseline to 12 Weeks) and Between Group Differences

<table>
<thead>
<tr>
<th>Alcohol Measures</th>
<th>WITHIN GROUP ANALYSIS</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (Past 90)</td>
<td>Active TX (Week 1-12)</td>
</tr>
<tr>
<td></td>
<td>Mean ± Std. Dev.</td>
<td>Mean ± Std. Dev.</td>
</tr>
<tr>
<td>% Drinking Days</td>
<td>71.3 ± 30.6</td>
<td>20.8 ± 34.2</td>
</tr>
<tr>
<td>% HDD</td>
<td>59.0 ± 35.0</td>
<td>11.9 ± 27.3</td>
</tr>
<tr>
<td>Std. Drinks per Week</td>
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Abbreviations: DD, Drinking Day; HDD, Heavy Drinking Day (>4 standard alcoholic drinks for men, >3 standard alcoholic drinks for women). (standard alcoholic drink defined as containing 13.6 g of pure alcohol) – Controlled for baseline drinking in all between group models. – No sig group by week interactions.

---

![Mean Standard Alcohol Drinks Per Drinking Day](image1.png)

**Group**
- Placebo
- Topiramate

![Median Standard Alcohol Drinks Per Drinking Day](image2.png)

**Group**
- Placebo
- Topiramate

---
### Obsessive Compulsive Drinking Scale

**Table 3. Topiramate Within Group Change and Between Group Differences**

<table>
<thead>
<tr>
<th>Craving Measures</th>
<th>WITHIN GROUP ANALYSIS</th>
<th>BETWEEN GROUP ANALYSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (Past 90)</td>
<td>Active TX (Week 1-12)</td>
</tr>
<tr>
<td></td>
<td>Mean ± Std. Dev.</td>
<td>Mean ± Std. Dev.</td>
</tr>
<tr>
<td>OCDS Total</td>
<td>16.9 ± 8.7</td>
<td>5.5 ± 6.6</td>
</tr>
</tbody>
</table>

- Effect Size was calculated by dividing the mean difference between the group means by the standard deviation of the mean value for each participant averaged over weeks. –No significant Group-by-Week interactions.
# PTSD Total and Arousal

## Table 4. Topiramate Within Group Change and Between Group Differences

<table>
<thead>
<tr>
<th>PTSD Measures</th>
<th>WITHIN GROUP ANALYSIS</th>
<th>BETWEEN GROUP ANALYSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (Past 90)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean ± Std. Dev.</td>
<td>Active TX (Week 1-12)</td>
</tr>
<tr>
<td></td>
<td>Mean ± Std. Dev.</td>
<td>p-value Linear Mixed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Group Mean ± Std. Dev.</td>
</tr>
<tr>
<td>PCL TOTAL SCORE</td>
<td>57.2 ± 13.4</td>
<td>.001 -26%</td>
</tr>
<tr>
<td></td>
<td>42.3 ± 16.4</td>
<td>42.3 ± 16.0</td>
</tr>
<tr>
<td>PCL B-Intrusion</td>
<td>15.9 ± 5.2</td>
<td>.026 -23%</td>
</tr>
<tr>
<td></td>
<td>12.3 ± 5.5</td>
<td>12.3 ± 5.4</td>
</tr>
<tr>
<td>PCL C-Avoidance</td>
<td>23.9 ± 5.7</td>
<td>.002 -26%</td>
</tr>
<tr>
<td></td>
<td>17.6 ± 7.4</td>
<td>17.6 ± 7.2</td>
</tr>
<tr>
<td>PCL D-Arousal</td>
<td>17.3 ± 4.8</td>
<td>.000 -30%</td>
</tr>
<tr>
<td></td>
<td>12.4 ± 4.9</td>
<td>12.4 ± 4.9</td>
</tr>
</tbody>
</table>

- Effect Size was calculated by dividing the mean difference between the group means by the standard deviation of the mean value for each participant averaged over weeks.
- No significant Group-by-Week interactions.

![PCL Total Score (mean)](image1)

![PCL Arousal (mean)](image2)

![PCL Total Score (mean)](image3)

![PCL Arousal (mean)](image4)
Learning and Memory

Table 6. HVLT-R: Linear Mixed Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Topiramate Group Mean ± Std. Dev.</th>
<th>Group Mean ± Std. Dev.</th>
<th>Group p-value</th>
<th>Effect Size</th>
<th>Week p-value</th>
<th>Group x Week p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Recall</td>
<td>35.9 ± 9.3</td>
<td>44.0 ± 14.3</td>
<td>.002</td>
<td>.69</td>
<td>NS</td>
<td>.018</td>
</tr>
<tr>
<td>(Learning)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed Recall</td>
<td>33.9 ± 10.3</td>
<td>44.0 ± 15.8</td>
<td>.031</td>
<td>.77</td>
<td>.021</td>
<td>NS</td>
</tr>
<tr>
<td>(memory)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Effect Size was calculated by dividing the mean difference between the group means by the standard deviation of the mean value for each participant averaged over weeks.
- Models covaried for baseline scores.
TAP1 Study Final Results

- Topiramate compared to placebo resulted in:
  - lower frequency and amount of alcohol use (trends)
  - significantly reduced alcohol craving

- Trends for lower PTSD symptoms in the topiramate group:
  - lower hyperarousal
  - lower total PCL

- Topiramate was also associated with higher retention and medication adherence.

- Emergent AEs not significantly different.

- But significant mid-study memory impairment which decreased over time.
TAP2: Design and Methodology, 1: Overview

Subjects
- 150 Veterans with AUD and PTSD

Methods
- 12-week outpatient clinical trial
- Topiramate/Placebo up to 300 mg/d
- Weekly alcohol counseling (NIAAA Medical Management)

Analysis
- Negative binomial, linear mixed, ANCOVA

Measures
- Alcohol measures: TLFB, EtG, PEth, craving
- PTSD Measures: PCL, sleep
- Cognitive measures:
  - Risk -taking
  - Impulsivity
  - Decision-Making
  - Neurocognitive testing
TAP2 Study Progress/Results Alcohol & PTSD Measures

Mean Drinks Per Week

Mean OCDS Total

Mean PCL Total Score

Mean Insomnia Severity Index
Conclusions

• Psychological treatments are a main tx approach for co-occurring conditions
• Proven pharmacotherapies exist for each condition independently
• But no proven pharmacotherapies for co-occurring conditions as of yet
• Potential agents exist
  – More research needs to be done to confirm initial findings with disulfiram, topiramate
  – Other new therapies need to be investigated
Traumatic Brain Injury (TBI)

a traumatically induced physiologic disruption of brain function, as manifested by one of the following:

- Loss of consciousness
- Loss of memory for events immediately before or after the accident
- Alteration of mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused)
- Focal neurological deficit(s) that may or may not be transient

"TBI" refers to original injury or etiology. Symptoms following injury are referred to as post concussive symptoms (PCS)

(From Kristine Burkman, Ph.D., UCSF/SFVAMC 2016)
Traumatic Brain Injury (TBI), 2.

**Specifiers:** Mild, Moderate, Severe

Refers to 24-48 hours following injury.

Severity of initial injury ≠ impairment in functioning

Prognosis often related to:
- Length of loss of consciousness
- Length of post traumatic amnesia

(From Kristine Burkman, Ph.D., UCSF/SVFAMC 2016)
What is Mild Traumatic Brain Injury? (mTBI -- also known as concussion)
American Congress of Rehabilitation Medicine (Kay et al., 1993)

• Approximately 80% of patients who sustain TBIs had mild TBI (Alexander, 1995).

• Mild TBI: Severity does not exceed:
  – Altered or Loss of consciousness (LOC) <30 min
  – Posttraumatic Amnesia (PTA) <24 hrs
  – Normal CT and/or MRI
  – Glasgow Coma Scale score (GCS) range 13-15

(from Beth Manning, PhD, UCSF/SFVAMC)
Problems/Complexities of mTBI diagnosis
(as per Iverson, Hoge, Bryant, Warden, Corrigan, & others)

• There is a broad range of injury severity.

• LOC is very difficult to determine

• PTA is often mistaken for LOC

• PCS symptoms mimic traumatic stress symptoms.

• Difficult to find objective indicators of mTBI: clear structural or functional abnormalities.
  – Majority of mTBI pts have normal structural MRI and CT scans because CT scans have poor sensitivity in detecting underlying abnormalities associated with mTBI.

(from Beth Manning, PhD, UCSF/SFVAMC)
Prevalence of TBI in Veterans

• Estimated 22% of returning servicemembers have reported experiencing TBIs and concussions\(^1\)

• Of those injured, approximately 31% diagnosed w/ TBI\(^2\)

• 77% of all head injuries are mild TBI\(^3\)

\(^1\)Terrio et al., 2005, \(^2\)Hayward, 2008, \(^3\)Fischer, 2010

(From Kristine Burkman, Ph.D., UCSF/SVFAMC 2016)
Risks Associated with TBI

- Persons w/ TBI more likely to have 2\textsuperscript{nd} and 3\textsuperscript{rd} TBI\textsuperscript{1}
- Repeat TBIs increase severity and chronicity of symptoms\textsuperscript{1}
- Twice as likely to screen positive for PTSD or depression\textsuperscript{2}
- Increased risk for suicide\textsuperscript{3}

\textsuperscript{1}Center for Disease Control (CDC); \textsuperscript{2}Maguen, Lau, Madden & Seal, 2012; \textsuperscript{3}Brenner, Ignacio & Blow, 2011

(From Kristine Burkman, Ph.D., UCSF/SFVAMC 2016)
Effects of mTBI (Post Concussional Syndrome (PCS))

• Somatic symptoms:
  – Headache (most commonly reported symptom)
  – Dizziness and/or vertigo
  – Nausea and vomiting
  – Fatigue
  – Blurred vision
  – Light/sound sensitivity
  – Disordered sleep

• Cognitive problems:
  – Decreased concentration/attention
  – Memory difficulty
  – Intellectual impairment

• Psychological problems:
  – Depression; Anxiety
  – Irritability and/or aggression
  – Social withdrawal
  – Apathy and lack of spontaneity
  – Changes in personality

(from Beth Manning, PhD, UCSF/SFVAMC)
Differential diagnosis of PCS and PTSD

• Symptoms found in both PTSD and PCS:
  – Deficits in attention and memory
  – Irritability
  – Sleep disturbance
  – Physiological hyperactivity
  – Fatigue
  – Increased sensitivity to noise and light

• Symptoms more likely to be specific to PCS:
  – Headache
  – Dizziness
  – Balance problems
  – Nausea/vomiting
  – Generalized memory problems
  – Intellectual impairment
TBI and Substance Abuse

• Challenging research question\(^1\)
  – Bi-directional relationship between TBI and SUD
  – Pre-injury pattern of substance use predicts post-injury pattern of use

• Substance use impairs rehabilitation and exacerbates symptoms

  ▪ Increased risk of additional injury, becomes vicious cycle

\(^1\)Taylor et al., 2003
TBI and Alcohol Use Disorder: High Rates of Co-occurrence

Post mTBI injury:

-more service members had diagnoses of alcohol/substance abuse than any other selected condition except headache (Armed Forces Health Surveillance Center (AFHSC) 2013)

Airmen with mTBI:

-increased risk for addiction-related disorders compared with similarly injured non-mild TBI comparison group. Hazards for alcohol dependence... and nondependent abuse of drugs or alcohol were significantly elevated, (Miller 2013)
Veterans Alcohol TBI (VAT) study: Topiramate Treatment for Hazardous and Harmful Alcohol Use in Veterans with Mild TBI (PI Batki)

Goal: To improve the treatment of veterans with mTBI & alcohol use disorder. Specific Aims: obtain a preliminary assessment of TOP effectiveness in reducing alcohol use in veterans with TBI and AUD obtain preliminary assessment of TOP effectiveness in reducing mTBI symptoms 1) assess the feasibility/safety/tolerability of topiramate in these patients; 2) explore the effects of topiramate on impulsivity and cognitive functioning 3) to inform the design of a planned subsequent larger controlled trial of topiramate.
## Participant Characteristics at Baseline (Means ± Standard Deviation)

<table>
<thead>
<tr>
<th></th>
<th>Topiramate</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (female)</td>
<td>15 (1)</td>
<td>17 (1)</td>
</tr>
<tr>
<td>Age [years]</td>
<td>44.5 ± 3.6</td>
<td>48.5 ± 3.4</td>
</tr>
<tr>
<td>Education [years]</td>
<td>13.7 ± .9</td>
<td>14.1 ± 1.9</td>
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<tr>
<td>Race</td>
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<td></td>
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<tr>
<td>Caucasian</td>
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<tr>
<td>Hispanic/Latino</td>
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<td>2</td>
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<tr>
<td>African American</td>
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<td>1</td>
</tr>
<tr>
<td>Mixed Race</td>
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<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Combat Exposed, n (%)</td>
<td>6 (40.0%)</td>
<td>9 (52.9%)</td>
</tr>
<tr>
<td>DD per Week</td>
<td>4.1 ± 2.0</td>
<td>4.7 ± 2.1</td>
</tr>
<tr>
<td>HDD per Week</td>
<td>3.3 ± 2.4</td>
<td>3.3 ± 1.9</td>
</tr>
<tr>
<td>Avg. Drinks per Week</td>
<td>47.7 ± 40.1</td>
<td>52.6 ± 33.8</td>
</tr>
<tr>
<td>Avg. Drinks$^S$ per DD</td>
<td>14.6 ± 16.5</td>
<td>12.6 ± 7.9</td>
</tr>
</tbody>
</table>

### TBI incidence:
- more than 1, n (%): 13 (86.7%) vs. 11 (64.7%)
- 5 or more, n (%): 3 (20.0%) vs. 9 (52.9%)

### TBI: Type of Injury
- Blunt Trauma, n (%): 10 (66.7%) vs. 11 (64.7%)
- Fall, n (%): 10 (66.7%) vs. 6 (53.3%)
- Motor Vehicle Accident, n (%): 7 (46.7%) vs. 7 (41.2%)
- Blast Injury, n (%): 3 (20.0%) vs. 9 (52.9%)

| NSI Total Severity      | 1.83 ± 0.72 | 1.93 ± 0.70 |
| Somatic Sensory Severity| 1.42 ± 0.79  | 1.53 ± 0.52  |
| Affective Severity      | 2.17 ± 1.02  | 2.40 ± 0.74  |
| Cognitive Severity      | 2.08 ± 0.90  | 2.33 ± 1.04  |
| PTSD Positive, n (%)    | 8 (53.3%)    | 10 (58.8%)   |
| Baseline CAPS Total     | 78.8 ± 5.5   | 82.5 ± 5.1   |

**Abbreviations:** CAPS, Clinician Administered PTSD Scale; DD, Drinking Day; HDD, Heavy Drinking Day; NSI, Neurobehavioral Symptom Inventory

*Heavy Drinking Days: >4 standard alcoholic drinks for men, >3 standard drinks for women. Drink consumption was averaged over the 90 days preceding study consent. **standard alcoholic drink = 13.6 g of alcohol*
Preliminary VAT Outcome: Drinks Per Week

- Significant Main Effect for Time: p<.001
- Within group trend for Time in Topiramate: p=.05
- No Significant Group or Interaction of Treatment*Time

Generalized Linear Mixed: Negative Binomial Model with Robust Variance; SPSS Version 23. Model included fixed factors for Treatment Group, Time, and the Interaction of Treatment*Time.
Preliminary VAT Outcome: 
NSI Total Symptoms and Severity

- NSI Total: Significant Main Effect for Time; \( p=.005 \)
  - Trend for within group effect of Time in Topiramate; \( p=.11 \)

- NSI Total Severity: Significant Main Effect for Time; \( p=.015 \)
  - Trend for within group effect of Time in Topiramate; \( p=.055 \)

- No Significant Group or Interaction of Treatment*Time

Linear Mixed Model; SPSS Version 23. Model included fixed factors for Treatment Group, Time, and the Interaction of Treatment*Time. Total Range: 0-22; Total Severity Range: 0-4, 0=None, 4=Very Severe.
VAT Outcome:
Auditory-Verbal Recall and Verbal Fluency

- AV Recall: Trend for a Treatment*Time interaction; p=.083

- Verbal Fluency: Trend for a Treatment*Time; p=.092

Mean Auditory-Verbal Recall (HVLT-R)

Mean Verbal Fluency (COWA)

Linear Mixed Model; SPSS Version 23. Model included fixed factors for Treatment Group, Time, and the Interaction of Treatment*Time.
TBI and AUD/SUD Dysfunction Overlap
Failure of “top-down” control
Alcohol Approach Bias Modification to Decrease Problem Drinking and Impulsivity in Veterans with AUD: A Pilot Study

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Mentor: Steven L. Batki, M.D.
San Francisco Veteran Affairs Medical Center (SFVAMC)
University of California, San Francisco, School of Medicine, Dept. of Psychiatry (UCSF)
Northern California Institute for Research and Education (NCIRE)

NARSAD Young Investigators Grant
January 2016-January 2018
Alcohol Approach Behavior

- Patients with SUD exhibit an *automatic* tendency to approach rather than to avoid drug cues
- The associative process central to alcohol-approach behavior can be measured with a joystick task called the Approach-Avoidance Task (AAT)

**Alcohol AAT:**
- pictures in one format (e.g., left-tilted) are pulled and pictures presented in another format (e.g., right-tilted) are pushed irrespective of the content of each picture
- differences in pulling vs. pushing in relation to the contents category (e.g., alcohol pictures) are interpreted as automatic action tendencies
Alcohol Approach Bias Modification (AABM)

A picture of an alcoholic or non-alcoholic beverage is presented, tilted 3 degrees to the left or to the right.

Participant have to respond as quickly as possible to the format of the picture by pushing all pictures tilted to the left away from them upon which the picture size gradually decreases, as in the examples on the left (alcohol image), and pulling all pictures tilted to the right (non-alcohol image) towards them, upon which picture size gradually increases, as in the examples on the right.

During AABM, all alcoholic images are presented in push format, and all non-alcoholic beverages in pull format.
Alcohol Approach Bias Modification (AABM)

- Two large RCT of AABM vs. Sham
  - 214 inpatients (Wiers et. al., 2011)
    - Reduction in alcohol AAT d-scores (reduced alcohol approach bias)
    - Reduced relapse at 1-year follow-up (>2 days resumed drinking)
  - 509 inpatients (Eberl et. al., 2013)
    - Confirmed lower relapse at 1-year follow-up
    - Confirmed reduced alcohol approach bias

- Limitations:
  - Not well characterized
  - Relatively stable inpatient population (free or low cost admission)
  - Binary clinical outcome (relapse)
Alcohol Approach Bias Modification (AABM) to Decrease Problem Drinking and Impulsivity in Veterans with AUD: A Pilot Study

**Goal:** improve the treatment of veterans who consume alcohol at hazardous or harmful levels

**Specific Aims:**
1) establish the ***feasibility*** of enrolling and retaining heavy drinking veterans with AUD for a 3-week randomized trial of AABM
2) Obtain preliminary assessment of the efficacy of AABM treatment to decrease alcohol approach bias and reduce heavy alcohol use
3) Obtain preliminary assessment of the efficacy of AABM treatment to improve neurocognitive functioning
Future Research Directions

• new medications?
  – Trial of n-Acetylcysteine in AUD/mTBI

• neurocognitive training techniques to increase self-control?

• effects of medications on cognitive control in both PTSD/mTBI and alcohol domains?

• medications and neurocognitive training methods combined?