# Breaking the Cycle: Pharmacologic Prevention of Alcohol Use Disorder in PTSD

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## Abstract

The comorbidity of Post-Traumatic Stress Disorder (PTSD) and Alcohol Use Disorder (AUD) is a critical public health issue.

**Current interventions are predominantly reactive, addressing AUD only after onset and leaving a major prevention gap.** Psychotherapies such as Cognitive Processing Therapy, Prolonged Exposure, and CBT demonstrate preventive potential, yet pharmacological approaches remain underexplored.

**Drawing on a synthesis of prevalence data, risk factor studies, and pharmacological safety evidence, this work introduces an original framework that reconceptualizes PTSD–AUD comorbidity as a trajectory that can be interrupted.** By targeting shared neurobiological pathways and intervening during high-risk periods, it may be possible to reduce AUD incidence among PTSD patients. Pharmacological therapy should be considered as a potential adjunct to psychotherapy.

**This new framework highlights the preventive potential of agents such as naltrexone and topiramate**, which are well studied in prevention of AUD and have demonstrated safety in PTSD.

While prevention-specific trials are limited, **the scale of the problem supports consideration of early pharmacological strategies** in high-risk populations, alongside ongoing research.

This prevention-centered perspective aims to advance discussion and **encourage future study of proactive interventions.**

## Introduction

PTSD–AUD comorbidity is highly prevalent, affecting up to 30% of veterans and contributing $50–100 billion in annual costs, and contributing to significantly elevated mortality. Psychotherapies such as Cognitive Processing Therapy, Prolonged Exposure, and CBT already show preventive benefit, reducing alcohol risk. Preventive pharmacological strategies aimed at halting the PTSD-to-AUD trajectory are notably absent.
The magnitude of the problem supports the ethical rationale to initiate prevention based on this framework while pursuing additional studies.

## Objectives

- **Measure PTSD–AUD comorbidity prevalence and risk factors in high-risk groups.**
- **Evaluate safety and efficacy of pharmacological prevention in PTSD patients.**
- **Propose a preventive pharmacotherapy approach for high-risk patients based on evidence.**
- **Advocate for clinical trials to test pharmacological prevention in high-risk PTSD cases.**

## Rationale

This poster **synthesizes existing literature on PTSD–AUD** comorbidity to address the absence of preventive pharmacological strategies.
It leverages peer-reviewed data to quantify prevalence, assess pharmacological potential, and **propose a new framework**.
The goal is to **guide future clinical trials**, supporting the conference's empirical focus by highlighting a $50–100 billion burden and research gaps.
This synthesis lays the **groundwork for targeted pharmacological studies** in high-risk PTSD patients.

## Methods

This framework is based on a narrative review of peer-reviewed clinical trials, cohort studies, systematic reviews, and pharmacologic research retrieved through PubMed, Semantic Scholar, and Google Scholar. Keywords included "PTSD," "AUD," "pharmacologic prevention," "naltrexone," "topiramate," and "as-needed medication for alcohol use."

## RESULTS

**PTSD Is a Strong Predictor of AUD, Especially in High-Risk Subgroups and Conditions**

WHO IS AT HIGHEST RISK?
EVIDENCE HIGHLIGHTS

- Prior alcohol/drug use disorders
- Family history of AUD
- Co-occurring mood/anxiety disorders
- Childhood adverse experiences
- Severe interpersonal trauma/polyvictimization
- PTSD with externalizing, anxious/dysphoric arousal, and sleep disturbance
- Lower income, homelessness, lack of social support/unpartnered status
- Male gender

**EVIDENCE BY CLUSTER PRIOR HISTORY/COMORBIDITY**

| Risk factor | Tier | Effect size | Authors | Study type | Limitations |
|---|---|---|---|---|---|
| Other substance use disorder including drug use disorder | Tier 1 | ~200–300% | Straus 2020 | Prospective national veteran cohort | Large prospective |
| Prior alcohol use pattern including higher baseline use | Tier 1 | ~100–200% | Straus 2020 | Prospective national veteran cohort | Large prospective |
| Family history of alcohol use disorder | Tier 1 | ~100% | Sartor 2011 | Twin study and family history epidemiology | Consistent across cohorts |
| Co-occurring mood or anxiety disorders | Tier 1 | ~50-80% | Petrakis and Simpson 2017 | Narrative and epidemiologic syntheses | Multiple cohorts |
| Chronic pain burden and pain interference | Tier 1 | ~30-60% | Morasco 2013, Ilgen 2011 | Cross sectional and longitudinal veterans | Clinic cohorts replicated |
| Nicotine use disorder | Tier 1 | ~50-80% | Petrakis and Simpson 2017 | Epidemiologic review | Linked administrative and cohort data |
| Comorbid attention deficit symptoms and impulsivity | Tier 2 | ~30-100% | Wilens 2011, Capusan 2016 | Epidemiologic and clinical cohorts | Single cohort |
| Medication exposures including benzodiazepines, opioids | Tier 2 | ~20-60% | VA and DoD 2023, Baldwin 2013 | Guideline synthesis and observational studies | Observational |

**EVIDENCE BY TRAUMA CHARACTERISTICS**

| Risk factor | Tier | Effect size | Authors | Study type | Limitations |
|---|---|---|---|---|---|
| Childhood maltreatment and adverse experiences | Tier 1 | ~100–300% | Dube 2002 | Retrospective cohort | Large health plan cohort |
| Interpersonal trauma and polyvictimization | Tier 1 | ~50-100% | DellAquila 2023 | Cross sectional national sample with ordered onset | Large national samples |
| Younger age at trauma or at post-traumatic stress onset | Tier 1 | ~20-60% | Veteran trajectories 2023 | Prospective cohort trajectory models | Trajectory cohorts |
| Combat exposure and high intensity trauma in military and first responders | Tier 2 | ~30-120% | Kehle 2012, Miller 2016 | Prospective cohorts after deployment | Prospective military cohorts some single unit |
| Adult sexual trauma | Tier 2 | ~150–200% | Kaysen 2014, Kelley 2019 | Epidemiologic studies | Some cohorts single sample |

**PTSD PHENOTYPES, GENETICS, AND BIOCHEMICAL STUDIES**

| Risk factor | Tier | Effect size | Authors | Study type | Limitations |
|---|---|---|---|---|---|
| post-traumatic stress symptom phenotypes externalizing anxious arousal dysphoric arousal | Tier 1 | ~50-120% | Armour 2015, Contractor 2018 | Factor analytic and cohort studies | Multiple veteran and trauma cohorts |
| Sleep disturbance and insomnia with nightmares | Tier 1 | ~30-70% | Kline 2014, Babson 2015, Short 2025 | Longitudinal and prospective cohorts | Longitudinal links and prospective cohorts |
| Genetic and epigenetic markers beyond family history ADH1B ALDH2 FKBP5 CRHR1 BDNF methylation | Tier 2 | ~30-60% | Polimanti 2019 and genomma consortia | GWAS and epigenetic studies | High precision molecular study limited replication |
| Neuroendocrine dysregulation low basal cortisol and altered stress reactivity | Tier 2 | ~20-50% | Yehuda and colleagues 2006 to 2020 | Prospective and cross sectional | Assay and timing sensitive mixed replication |
| Neurocognitive impairment executive and inhibitory control deficits | Tier 2 | ~15-40% | Aupperle 2012, Scott 2017 | Neuropsychological studies | Cross sectional or small longitudinal |
| Traumatic brain injury | Tier 2 | ~30-50% | Brenner 2023 | Prospective administrative cohort | Effect attenuates when post-traumatic stress is modeled |

**EVIDENCE BY CLUSTER SOCIAL SUPPORT AND DISADVANTAGE**

| Risk factor | Tier | Effect size | Authors | Study type | Limitations |
|---|---|---|---|---|---|
| Lower income unstable housing homelessness related social needs | Tier 1 | ~100–400% | Tsai 2015 | Systematic review of veteran homelessness risk | Large health system cohorts and reviews |
| Lack of social support or unpartnered status | Tier 1 | ~30-100% | Veteran trajectories 2023 | Prospective cohort with trajectory modeling | Prospective trajectory cohorts |
| Male gender | Tier 1 | ~70% | VA national summaries 2020 | Administrative analyses citing national cohorts | Administrative summaries |
| Racial and ethnic disparities in diagnosis and care access | Tier 1 | ~23-109% | Vickers Smith 2023 | Electronic health record analysis | Large EHR cohort |
| Cultural drinking norms and high alcohol availability in the community | Tier 2 | ~20-80% | Chartier 2010, Room 2005 | Ecological and survey based | Ecological or cross sectional |

**New Framework Rationale**

**PTSD is a strong risk factor for AUD, especially in the highest-risk populations.**

**Pharmacological treatments for AUD *prevention already exist.***

**Available AUD prevention modalities have evidence of safety in PTSD.**

**The magnitude and seriousness of PTSD–AUD comorbidity provide both ethical and moral justification to begin prevention now, in parallel with full clinical research.**

**Effective Treatments and Preventive Strategies for AUD Exist.**

| AUD med | Hits in AUD (from your table) | PTSD/stress biology it also hits | Likely PTSD/stress benefits | Evidence vibe |
|---|---|---|---|---|
| Topiramate | ↑GABA, ↓AMPA/kainate, ↓mesolimbic DA | ↓glutamate hyperexcitability, ↑inhibitory tone in amygdala/PFC | Lower hyperarousal, improve sleep, reduce cue reactivity; helpful if PTSD drives coping-drinking | Best overlap signal among AUD meds; RCTs in AUD, pilot data in PTSD+AUD |
| Gabapentin | α2δ $Ca^{2+}$ modulator, ↑GABA tone | Calms limbic hyperexcitability, improves sleep/anxiety | Eases insomnia, anxiety, irritable arousal in early abstinence or chronic stress | Moderate support for AUD symptoms |
| Pregabalin | α2δ $Ca^{2+}$ modulator (potent) | Similar to gabapentin but stronger anxiolysis | Reduces hyperarousal/anxiety, improves sleep | Smaller AUD dataset |
| Acamprosate | NMDA modulation, slight GABA | Theoretic fit to ↓hyperglutamate | Might blunt arousal, but PTSD is multi-system (NE/CRF/HPA) → effect too narrow | Trials haven't shown clear benefit |
| Naltrexone | μ-opioid antagonism → ↓DA reward | Opioid tone has roles in stress, but PTSD core is NE/CRF/GABA-glu | Indirect: can reduce drinking driven by reward; does not treat PTSD symptoms | Strong for AUD |
| Nalmefene | μ/κ/δ modulation (↑κ affinity) | κ-opioid links to dysphoria/stress exist | Theoretical anti-dysphoria, but PTSD data sparse | Good for drink-reduction |
| GLP-1 RAs | ↓cue reactivity/reward, gut–brain | Hypothalamic–brainstem–VTA nodes overlap with stress–interoception | Possible craving/anxiety effects; metabolic upsides for sedentary, stressed patients | Early for AUD |

**AUD Medications Demonstrate General Safety in PTSD Populations**

| Agent | Study criteria & authors | Study type, key outcome, limits |
|---|---|---|
| Naltrexone | Heavy drinkers (≥5 drinks/occasion, ≥2×/wk); O'Malley 1992 (n=97), Kranzler 2003 (n=150) | RCTs; ↓ relapse & craving; ≤12 wks; mostly men; not PTSD |
| Topiramate | Hazardous drinkers (≥24 drinks/wk men, ≥18 women); Johnson 2003 (n=150), Blodgett 2014 (meta n>1,200) | RCTs/meta; ↓ heavy drinking days; dropout 20–30%; cog side effects |
| Nalmefene | High-risk drinkers (≥60 g/day men, ≥40 g/day women); Mann 2013 (n=600, Europe) | RCTs; ↓ daily consumption; focus on harm reduction not prevention; mostly EU |
| GLP-1 RA (semaglutide) | Heavy drinkers without AUD (≥14 drinks/wk men, ≥7 women); Jensen 2022 (n=127) | Pilot RCT; ↓ intake & craving; 12 wks only; exploratory |
| Gabapentin | At-risk drinkers with insomnia/anxiety; Mason 2014 (n=150) | RCT; mixed: ↓ heavy drinking days, improved sleep; small sample; not PTSD |

**PTSD–AUD Comorbidity Is Severe and Prevention Is Justified**

| Domain | Metric and comparator | Effect size | Study |
|---|---|---|---|
| Life losses | Mortality in veterans with PTSD plus AUD vs PTSD alone | ~55% higher | Boscarino 2006 |
| Family impact | Intimate partner violence in PTSD plus AUD vs either disorder alone | 2–3× higher | Marshall 2005 |
| Economic cost | Annual US economic cost attributable to PTSD plus AUD | $50–100B | Pittman 2019; Schnurr 2009 |
| Family/human harm | Dual alcohol + drug use days in women with IPV and PTSD vs IPV without PTSD | ~15× higher odds | Mehr 2023 |
| Economic burden | Psychotherapy cost per treated patient in PTSD plus SUD/AUD vs overall PTSD sample, 24 months | $3,490 vs $2,501 (~39% higher) | Stanicic 2024 |
| Treatment adherence | Sertraline adherence ≥80% PDC in PTSD plus SUD/AUD vs PTSD without comorbidity | 9.5% vs 14.6% (≈35% lower) | Stanicic 2024 |

| Study | Key Finding | Citation |
|---|---|---|
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| Study | Key Finding | Citation |
|---|---|---|
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## Acknowledgment

This research was conducted under the guidance of Dr. Anne Kever and Dr. Melanie Brion at the Cambridge Center of International Research. I also acknowledge the mentorship of Jen Holmberg, Ph.D., UC Berkeley, in studying addiction vulnerability. My preparation for this work was supported by training through Polygence, the Summer Science@Jefferson Program at Thomas Jefferson School of Medicine, the GATI x BEAM Program at UC Irvine, and the Rosetta Institute of Biomedical Research at UCSD.

## Ethical Considerations

Use shared decision-making, screen contraindications, and start low/monitor. Avoid medicalizing subthreshold cases indiscriminately—restrict to validated high-risk phenotypes.

## Discussion

Integrating pharmacotherapy with behavioral interventions may enhance outcomes, creating a synergistic approach that addresses both biological and psychological drivers of risk.
Naltrexone can be used flexibly on an as-needed basis, aligned with PTSD triggers, particularly during trauma anniversaries or periods of acute stress.
In contrast to commonly prescribed PTSD medications such as steroids, benzodiazepines, and opioids, which can increase misuse risk, targeted pharmacologic prevention holds promise.
Randomized controlled trials are urgently needed to evaluate efficacy, focusing on AUD incidence, PTSD symptom stability, and patient adherence.

## Conclusion

**PTSD is a strong predictor of Alcohol Use Disorder, particularly in high-risk subgroups:**

- Prior alcohol or drug use disorders
- Family history of AUD
- Co-occurring mood or anxiety disorders
- Childhood adverse experiences
- Severe interpersonal trauma or polyvictimization
- PTSD anxious/dysphoric arousal, or sleep disturbance
- Lower income/social support, homelessness
- Male gender

**Evidence shows that medications that are effective for treating AUD and hold promise as preventive strategies, with demonstrated safety in PTSD populations, are:**

- Naltrexone
- Topiramate

**Given the severe human, clinical, and economic burden of PTSD–AUD comorbidity, proactive prevention is justified.**
**Rigorous clinical trials are urgently needed to validate pharmacological prevention strategies and guide their integration into care.**