How Alcohol Use Modifies Pain

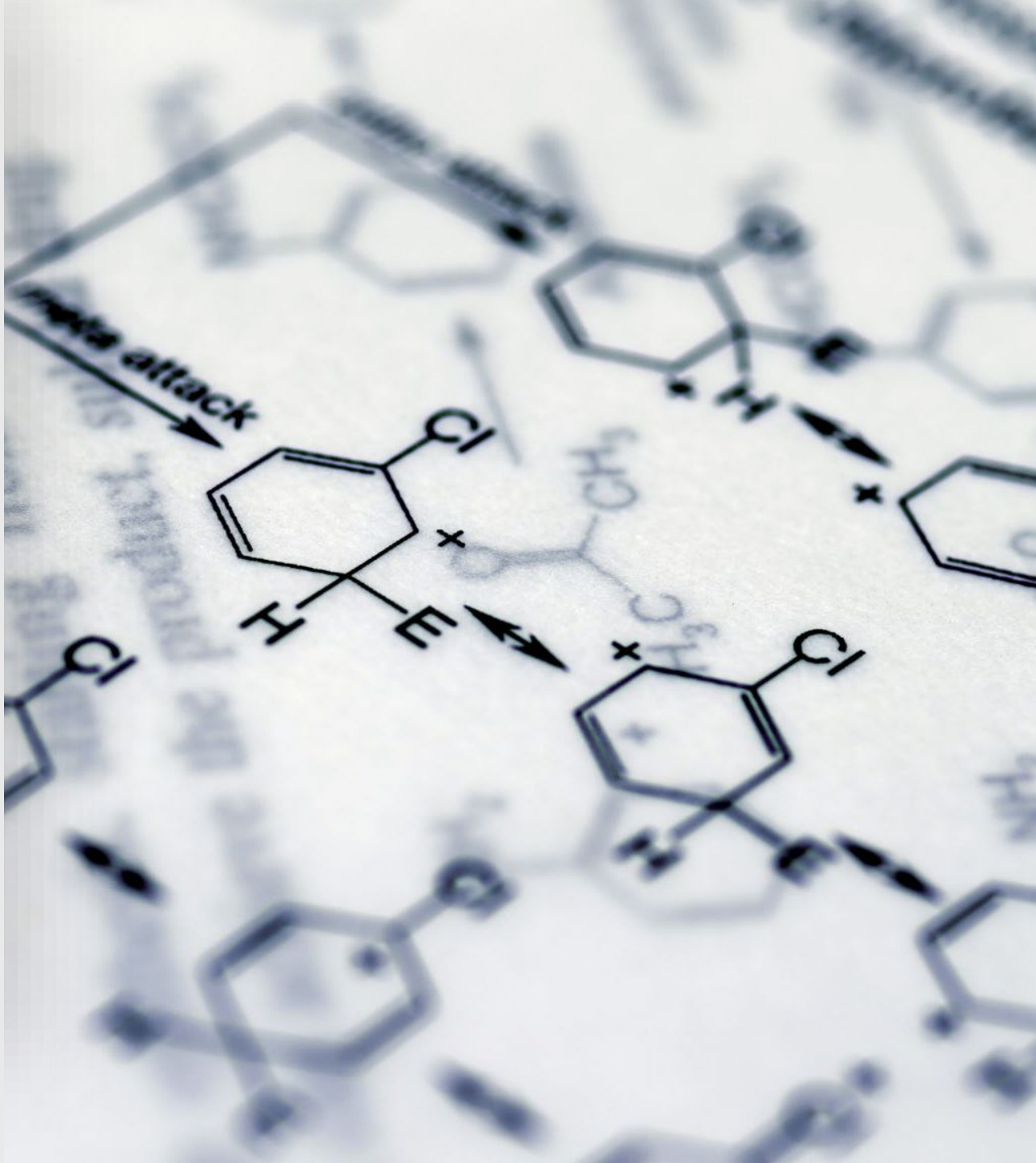
R. Corey Waller MD, MS

Executive Advisor, Shore Capital Partners

Editor in Chief, The ASAM Criteria 4th Edition

Objectives

- Clarify receptor- and circuit-level actions of ethanol relevant to nociception
- Connect acute ethanol effects to short-term antinociception and sedation
- Explain chronic-use adaptations that produce hyperalgesia and allodynia
- Translate mechanisms to perioperative, trauma, and chronic pain management

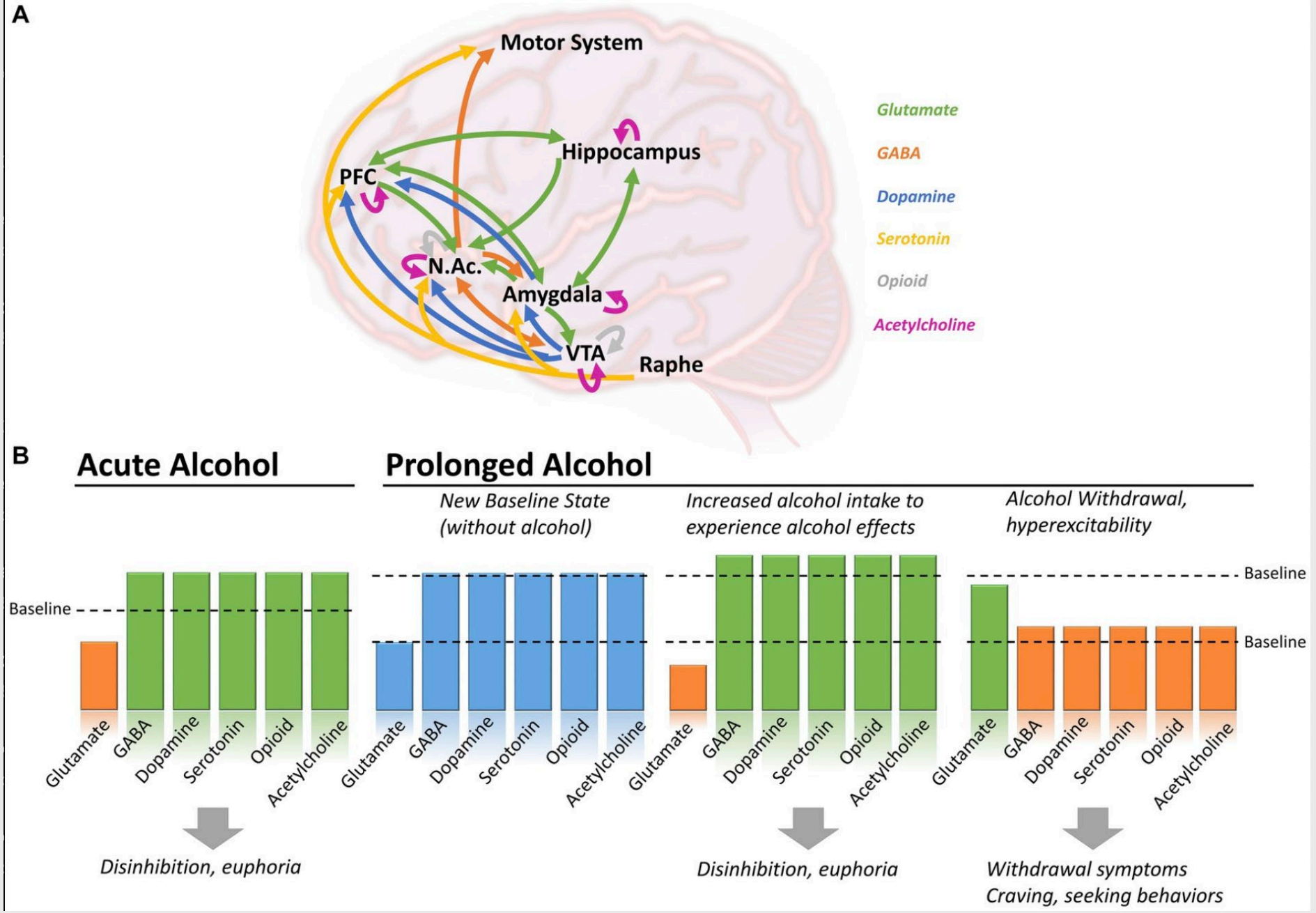


Definitions and Epidemiology

- Alcohol use spectrum: low-risk, risky use, Alcohol Use Disorder (AUD) (NIAAA, 2021, DSM-5-TR, 2022).
- Prevalence: AUD ~10% adults; higher in trauma/perioperative and chronic pain settings (SAMHSA, 2024; Zale et al., 2015).
- Bidirectional relationship: pain elevates hazardous drinking risk; alcohol use elevates risk of pain chronification (Zale et al., 2015; Boissoneault et al., 2018).
- Self-medication: up to one-third of chronic pain patients report using alcohol for analgesia (Riley & King, 2009).

Basic Neurobiology: How Alcohol Interacts with Pain Pathways

- **Acute ethanol:** potentiates inhibitory tone and dampens excitatory signaling (Abrahao et al., 2017).
- **Chronic exposure/withdrawal:** glutamatergic upshift, GABAergic downshift, neuroimmune activation → central sensitization and hyperalgesia (Egli et al., 2012; Coller & Hutchinson, 2012).



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Mechanistic deep dive

- GABA-A receptors
  - **Acute:** Enhanced GABA-A currents, especially δ-subunit extrasynaptic receptors → increased tonic inhibition in spinal dorsal horn and brainstem pain modulatory nuclei (Abrahao et al., 2017).
  - **Chronic:** Subunit reconfiguration (↓δ, ↑α4/α5), PKC/PKA-mediated phosphorylation changes, benzodiazepine insensitivity → decreased inhibitory efficacy and withdrawal hyperexcitability (Abrahao et al., 2017; Koob & Volkow, 2016).
- NMDA receptors
  - **Acute:** Inhibition of NR2B-containing NMDA channels → reduced Ca2+ influx and CaMKII/PKC signaling → transient antinociception (Abrahao et al., 2017).
  - **Chronic/withdrawal:** Upregulated NR2A/NR2B, increased Src/Fyn phosphorylation, enhanced synaptic trafficking → increased CaMKII/ERK/CREB signaling and potentiation in dorsal horn/amygdala → hyperalgesia (Egli et al., 2012; Haller et al., 2014).
- Glycine receptors
  - **Acute:** Positive allosteric modulation of α1 GlyRs in spinal cord → augmented inhibition (Abrahao et al., 2017).
  - **Chronic:** Desensitization/altered subunits → diminished inhibitory control (Abrahao et al., 2017).

Mechanistic deep dive

- Serotonergic and nicotinic systems
  - **Acute:** 5-HT3 modulation acutely; chronic use reduces serotonergic tone in PAG/RVM, weakening descending inhibition (Benarroch, 2012; Heinricher & Fields, 2013).
  - **Chronic:** nAChRs (α4β2, α7): Chronic exposure disrupts cholinergic antinflammatory/antinociceptive signaling (Picciotto & Zoli, 2008).
- Opioid system
  - **Acute:** β-endorphin release and modest MOR activation → antinociception (Koob & Volkow, 2016).
  - **Chronic:** MOR desensitization/internalization (GRK/β-arrestin), dynorphin/KOR upregulation → dysphoria/pronociception; cross-tolerance with opioids (Kampman, 2019; Koob & Volkow, 2016).
- Endocannabinoid system
  - **Acute:** Elevated anandamide/2-AG → CB1-mediated antinociception (Pava & Woodward, 2012).
  - Chronic: CB1 downregulation → reduced descending inhibition (Pava & Woodward, 2012).
- Ion channels and excitability
  - **Acute:** Mild suppression of Nav/Cav; chronic: increased Nav1.7/1.8 availability and Cav function → peripheral sensitization (Black et al., 2012).
  - **Chronic:** GIRK/HCN modulation alters dorsal horn excitability and descending control

Mechanistic deep dive

- Intracellular signaling
  - Chronic/withdrawal: ERK1/2, JNK, p38 MAPK activation; CREB/ΔFosB transcriptional plasticity; epigenetic changes in BDNF/CRF pathways (Haller et al., 2014; Koob & Volkow, 2016).
- HPA axis and CRF
  - Chronic: CRF upregulation in extended amygdala, noradrenergic hyperactivity → sympathetically mediated hyperalgesia (Koob & Volkow, 2016).
- Neuroimmune mechanisms
  - TLR4/NLRP3 activation → TNF-α, IL-1β, IL-6; cytokines enhance NMDA and reduce GABA/glycine currents (Coller & Hutchinson, 2012; Mayfield et al., 2013).
  - Microglial P2X4/P2X7 → BDNF release → TrkB → KCC2 downregulation; GABA becomes less hyperpolarizing → central sensitization (Ferrini et al., 2013; Coull et al., 2005).
  - Oxidative stress via CYP2E1 → ROS/RNS modify NMDA/TRP channels (Cederbaum, 2012).
- Peripheral nociceptor sensitization
  - TRPV1/TRPA1 potentiation and upregulation → burning pain, hyperalgesia (Trevisani et al., 2002; Blednov & Harris, 2009).
  - NGF/BDNF support nociceptor sprouting and synaptic strengthening (Pezet & McMahon, 2006).
- Sleep and circadian effects
  - Disrupted sleep architecture lowers conditioned pain modulation; mechanistically linked to adenosine/orexin alterations (Finan et al., 2013; Thakkar, 2015).

Alcohol and Acute Pain: Perioperative and Trauma

- **Intoxication:** transient antinociception via GABA-A/glycine potentiation and NMDA inhibition but higher sedation/respiratory risk (Abrahao et al., 2017; Hudspith et al., 2016).
- **Chronic use:** higher analgesic requirements due to central sensitization and opioid tolerance (Egli et al., 2012; Hudspith et al., 2016).
- Withdrawal risk and timing: onset 6–24h, peak 24–72h; DTs day 3–5 (ASAM, 2020).

Alcohol and Chronic Pain: Mechanisms Driving Hyperalgesia

Persistent synaptic plasticity and neuroimmune tone maintain pain beyond cessation (Egli et al., 2012; Coller & Hutchinson, 2012).

Mechanistic deep dive

- **Central amygdala/extended amygdala:** CRF and dynorphin/KOR increase aversive-pain states via ERK/p38; KOR antagonism shows antihyperalgesia preclinically (Koob & Volkow, 2016; Bruchas et al., 2010).
- **PAG–RVM:** CB1 downregulation and monoaminergic deficits reduce descending inhibition and CPM (Heinricher & Fields, 2013; Pava & Woodward, 2012).
- **Spinal dorsal horn:** microglial P2X4 → BDNF → KCC2 downregulation; astrocytic D-serine enhances NMDA co-agonism (Ferrini et al., 2013; Raghavendra et al., 2004).
- **Peripheral nerve:** TRPV1/TRPA1 phosphorylation via PKCε/PKA increases open probability → heat/mechanical hyperalgesia (Caterina & Julius, 2001; Trevisani et al., 2002).
- **Endocrine/metabolic:** thiamine deficiency impairs mitochondrial function, increasing oxidative stress and nociception (Victor et al., 1989; Sechi & Serra, 2007).

Okay, then what do I do?

- **Ketamine:** counters NMDA upregulation, dampens CaMKII/ERK; reduces spinal wind-up; glial modulation (Hurley & Hammond, 2000; Bell et al., 2017).
- **α2-agonists:** reduce LC hyperactivity and CRF-driven facilitation; enhance descending inhibition via GIRK (Kamibayashi & Maze, 2000).
- **Lidocaine infusions:** stabilize ectopic discharges; anti-inflammatory modulation of sodium channels and glia (Vadalouca et al., 2016).
- **Regional anesthesia:** reduces afferent drive sustaining microglial activation and central sensitization (Woolf, 2011).

Acute Pain Algorithm (Mechanism-Informed)

1. Screen for recent use/withdrawal; prophylax with thiamine; manage CIWA-Ar–guided withdrawal (ASAM, 2020).
2. Restore inhibitory–excitatory balance: ketamine or magnesium (NMDA), α2-agonist (NE), gabapentinoid (α2δ-1) (Bell et al., 2017; Sills, 2006).
3. Regional/neuraxial to reduce afferent drive and glial activation (Woolf, 2011).
4. Conservative opioids; avoid sedative stacking; enhanced monitoring (Hudspith et al., 2016).
5. Discharge: short supply if needed; strict alcohol avoidance counseling; close follow-up (CDC, 2022).

Chronic Pain Framework (Mechanism-Informed)

- Emphasize reversal of central sensitization and neuroinflammation:
  - Exercise, CBT/ACT, sleep restoration to improve descending inhibition/HPA regulation (Geneen et al., 2017; Finan et al., 2013).
  - Pharmacology targeting NMDA, α2δ-1, monoamines, and TRP channels; minimize chronic opioids; treat AUD with evidence-based meds/psychosocial care (Jonas et al., 2014; Mason & Heyser, 2010).
- Expect gradual improvement in pain thresholds over weeks–months of abstinence (Egli et al., 2012; Boissoneault et al., 2018).

Key Takeaways

- Acute alcohol: boosts inhibitory (GABA/glycine) and dampens excitatory (NMDA) signaling → transient antinociception (Abrahao et al., 2017).
- Chronic exposure: NMDA upregulation, GABA-A maladaptation, microglial P2X4/BDNF/KCC2 pathway, and HPA/CRF-NE dysregulation → central sensitization and hyperalgesia (Egli et al., 2012; Ferrini et al., 2013; Koob & Volkow, 2016).
- Mechanism-aligned therapies: NMDA antagonists, α2-agonists, gabapentinoids, regional techniques, monoaminergic agents, TRP-targeting topicals; treat AUD to reverse plasticity (Bell et al., 2017; Jonas et al., 2014).

Other References

- American Society of Addiction Medicine. (2020). The ASAM Clinical Practice Guideline on Alcohol Withdrawal Management. Journal of Addiction Medicine, 14(3S), 1–72. https://doi.org/10.1097/ADM.0000000000000669
- Abrahao, K. P., Salinas, A. G., & Lovinger, D. M. (2017). Alcohol and the brain: Neuronal molecular targets, synapses, and circuits. Neuron, 96(6), 1223–1238. https://doi.org/10.1016/j.neuron.2017.10.032
- Backonja, M., Wallace, M. S., Blonsky, E. R., et al. (2008). NGX-4010, a high-concentration capsaicin patch, for painful neuropathy. Lancet Neurology, 7(12), 1106–1112. https://doi.org/10.1016/S1474-4422(08)70228-X
- Barrientos, R. M., et al. (2015). Neuroinflammation and aging: Implications for cognition and pain. Neuropsychopharmacology, 40

Real-World Clinical Scenarios

**The following/remaining slides were created by Dr. Sprintz, not Dr. Waller.

Provider-Patient Conversations

1. Be curious, not accusatory
2. Non-judgmental→ caring but detached
3. Be aware of your own personal bias (+ or -)
4. The goal is to build trust, so you can keep your patient safe
    - Decreases medico-legal risk

Provider-Patient Conversations

“How much alcohol do you drink **a day**?”

Common Patient Responses

- “I never drink alcohol.”
- “I only drink socially.”
- “What? Do you think I’m an alcoholic?!”
- “Alcohol is legal.”

Other Common Scenarios

1. The discussion about positive EtG/EtS on a UDT

2. “I drink because the pain meds you’re giving me don’t help” (or ”I’m still hurting”)