

Modulating Brain "Urge" Signals for Alcoholic Binge Drinking: A Review of Herbal and Pharmacological Interventions (2014-2025)

I. Introduction: The Challenge of Alcoholic Binge Drinking and the Quest for Targeted Interventions

A. Defining Binge Drinking and Its Public Health Significance

Binge drinking, typically defined as a pattern of alcohol consumption that brings blood alcohol concentration (BAC) to 0.08 g/dL or higher, commonly corresponds to consuming five or more drinks (male), or four or more drinks (female), in about 2 hours. This behavior represents a significant public health concern due to its widespread prevalence and association with numerous adverse outcomes. The prevalence of binge drinking in the general population is reported to be three to four times higher than that of alcohol dependence.¹ This pattern of excessive alcohol intake is linked to a spectrum of negative consequences, including an increased risk of accidents, injuries, violence, and the development of chronic diseases.

Neurobiologically, binge drinking, especially during critical developmental periods such as adolescence, can impair brain development and compromise white matter integrity. Cognitive deficits and alterations in functional brain activity, particularly in regions like the limbic system, frontal lobe, and temporal lobes, have also been observed.¹ This report focuses on scientific investigations into interventions aimed at the neurobiological "urge" signals, or cravings, that are pivotal in driving and sustaining binge drinking behaviors.

A critical observation is that while binge drinking and alcohol dependence are related, they present distinct characteristics. Notably, individuals who engage in binge drinking often exhibit a pronounced impairment of inhibitory control. This specific deficit may serve as a marker for this pattern of alcohol consumption and could represent a unique therapeutic target.¹ The implication is that interventions designed to enhance inhibitory control, possibly through modulation of prefrontal cortex activity, might offer particular benefits for individuals struggling with binge drinking, potentially distinguishing treatment approaches from those focused solely on chronic alcohol dependence.

B. The Critical Role of "Urge" Signals (Craving) in Binge Drinking

Alcohol craving, characterized as an intense desire or compelling urge to consume alcohol, is a fundamental component of Alcohol Use Disorder (AUD) and serves as a

significant predictor of relapse and the initiation of binge drinking episodes.² These urges are not static; they can be powerfully triggered by a variety of internal and external stimuli, including conditioned environmental cues (e.g., places, people, or objects associated with past drinking), stress, or even the direct administration of alcohol itself.² The neurobiological underpinnings of craving are complex, extending well beyond the traditionally emphasized mesolimbic dopamine system to involve a distributed network of brain regions.² Therefore, a comprehensive understanding and effective modulation of these intricate neural networks are essential for developing interventions that can successfully reduce the urge to engage in binge drinking.

The subjective experience of craving itself presents a challenge. Individuals often report overestimating the prospective intensity and duration of their urges to drink.² This cognitive appraisal can amplify the distress associated with craving and diminish an individual's perceived ability to resist. Marlatt's conceptualization of cravings as "ocean waves" that build, peak, and eventually subside² provides a useful metaphor. Helping individuals to effectively "surf these waves" without succumbing to substance use is a key goal for both scientists and practitioners. This suggests that while pharmacological interventions might aim to dampen the physiological intensity of the urge, they may be most effective when integrated with cognitive and behavioral strategies that help individuals reframe their experience of craving and develop coping mechanisms. If a compound can reduce the peak intensity or frequency of these "waves," the cognitive task of managing the urge becomes less formidable, potentially enhancing the efficacy of psychotherapeutic approaches.

C. Scope and Objectives of the Report

This report aims to synthesize and critically evaluate scientific studies published or conducted between 2014 and 2025 that investigate the potential of herbal remedies and pharmacological compounds to lessen the desire for, and participation in, alcoholic binge drinking. The primary focus will be on interventions that target the underlying brain mechanisms responsible for generating alcohol urge signals. The report will explore the neurobiological basis of alcohol craving, assess the efficacy of identified interventions, delineate their proposed or established mechanisms of action on brain circuitry and neurochemistry, and consider their safety and tolerability.

D. Insights, Hidden Connections, and Implications for Section I

(Integrated into Sections I.A and I.B above)

II. Neurobiological Mechanisms of Alcohol Craving and Binge

Drinking

A. The Three-Stage Cycle of Addiction and the Genesis of Urge

The development and perpetuation of alcohol addiction, including patterns like binge drinking, can be understood through a three-stage cyclical model: (1) Binge/Intoxication, (2) Withdrawal/Negative Affect, and (3) Preoccupation/Anticipation.³ Each stage is associated with distinct neurobiological processes and brain regions, and together they drive the compulsive alcohol use characteristic of AUD.

The **Binge/Intoxication stage** is primarily linked to circuits within the basal ganglia, particularly the nucleus accumbens (NAc). During this stage, alcohol consumption leads to increased activity in brain reward systems. Alcohol elevates dopamine levels in the NAc, an effect potentially mediated by its action on dopamine neurons in the ventral tegmental area (VTA).³ It also engages opioid peptide systems, with activation of opioid receptors in the NAc contributing to the pleasurable sensations of intoxication.³ Furthermore, alcohol acutely modulates GABAergic and glutamatergic systems; it enhances the effects of GABA, the brain's primary inhibitory neurotransmitter, and inhibits glutamate, the primary excitatory neurotransmitter, particularly at N-methyl-D-aspartate (NMDA) receptors.⁵ These neurochemical changes not only produce alcohol's acute rewarding effects but also facilitate the learning process known as "incentive salience," whereby environmental cues present during drinking become strongly associated with alcohol's effects, acquiring motivational significance themselves.³ This stage is crucial for establishing the reinforcing properties of alcohol and laying the groundwork for habitual use.

Following the cessation of alcohol intake, the **Withdrawal/Negative Affect stage** emerges, primarily involving circuits in the extended amygdala.³ This stage is characterized by a decrease in the activity of reward neurotransmitter systems (e.g., a hypodopaminergic state) and a concurrent activation of brain stress systems. Key stress neurotransmitters and neuropeptides, including corticotropin-releasing factor (CRF), dynorphin, and norepinephrine, become hyperactive, particularly within the amygdala.³ This neurochemical imbalance fuels negative emotional states such as anxiety, dysphoria, irritability, and emotional pain—a condition termed hyperkatifeia.³ The GABA system, which is acutely enhanced by alcohol, becomes hypoactive during withdrawal, contributing to neuronal hyperexcitability and symptoms like agitation.⁶ The profound discomfort of this stage creates a powerful motivation to resume drinking as a means of temporary relief, thus driving a component of the "urge" signal.

The final stage, **Preoccupation/Anticipation**, is associated with dysfunction in the

prefrontal cortex (PFC).³ This stage is marked by an overwhelming desire to seek and consume alcohol, characterized by strong urges or cravings. These cravings are often exacerbated by exposure to alcohol-related cues (linked to incentive salience from the first stage), stress, or negative emotions. Executive functions, such as decision-making, impulse control, and the ability to inhibit prepotent responses, are often impaired due to PFC dysregulation.² Key neurotransmitters implicated in this stage include glutamate, which can contribute to hyperexcitability and craving, and ghrelin, a peptide involved in appetite and reward seeking.³ It is in this stage that the "urge" signal often becomes the dominant driver of behavior, leading to relapse and the resumption of binge drinking.

The neurobiological underpinnings of "urge" are not static but evolve across this addiction cycle. Urges experienced in the initial stages of alcohol use might be predominantly driven by the pursuit of positive reinforcement (reward-seeking, mediated by dopamine and opioids in the basal ganglia). In contrast, urges arising after chronic use and during withdrawal are heavily influenced by negative reinforcement (relief-seeking from dysphoric states, mediated by CRF and dynorphin in the extended amygdala) and compounded by impaired executive control due to PFC dysfunction. This evolving neurochemical landscape suggests that interventions targeting "urge" may need to be tailored to the individual's specific stage within the addiction cycle and the predominant neurobiological drivers of their craving.

B. Key Brain Regions and Networks Mediating Alcohol Urge

Several interconnected brain regions and networks are critically involved in mediating alcohol urge and driving binge drinking behaviors.

- **Mesolimbic Dopamine System:** This system, comprising the Ventral Tegmental Area (VTA) and its projections to the Nucleus Accumbens (NAc), is central to reward processing, motivation, and the reinforcement of behaviors. Alcohol consumption directly or indirectly triggers the release of dopamine in the NAc, contributing to its pleasurable and reinforcing effects.³ Importantly, learned environmental cues that have been repeatedly paired with alcohol can independently activate this pathway and elicit dopamine release, thereby triggering craving even in the absence of alcohol.²
- **Extended Amygdala:** This complex includes the bed nucleus of the stria terminalis, the central nucleus of the amygdala, and parts of the NAc shell. It plays a crucial role in processing negative emotions, stress responses, and mediating the aversive aspects of alcohol withdrawal.³ Hyperactivity of stress systems, particularly involving CRF, within the extended amygdala contributes significantly to the negative affective states that drive craving and relapse during withdrawal.⁶

- **Prefrontal Cortex (PFC):** The PFC is essential for higher-order cognitive functions, including executive control, decision-making, working memory, and the regulation of impulses and emotional responses. Dysfunction in PFC circuits is a hallmark of addiction and contributes to the compulsive nature of alcohol seeking and the inability to resist urges despite negative consequences.² Binge drinking itself has been associated with reduced functional activity in the frontal lobe.¹ The prominent impairment of inhibitory control observed in binge drinkers specifically points to PFC dysfunction, suggesting that this region is a critical node for interventions aimed at this drinking pattern.¹ Strategies that bolster PFC function or protect it from the detrimental effects of stress could be particularly effective.
- **Hippocampus:** This region is vital for learning and memory, including the formation and retrieval of associations between environmental cues and the rewarding or aversive effects of alcohol. Binge drinking has been linked to impaired visual and linguistic processing and learning, with some studies noting reduced occipito-hippocampal responses.¹ The hippocampus contributes to cue-induced craving by retrieving memories that link specific contexts with alcohol's effects.
- **Limbic System:** More broadly, the limbic system, which encompasses many of the aforementioned regions (amygdala, hippocampus, parts of the NAc), is heavily involved in emotional processing and motivation. Binge drinking can lead to reduced functional activity within the limbic system and even neurodegeneration and reactive gliosis in the limbic cortex, as shown in animal studies.¹

The observation that conditioned cues activate brain networks extending "far beyond the traditional mesolimbic dopamine system" ² underscores the complexity of alcohol urge. These broader networks likely involve higher cognitive processing areas, further emphasizing the roles of the PFC and hippocampus in maintaining cue-driven craving. This implies that effective strategies for reducing urges must not only target primary reward and stress pathways but also consider mechanisms to disrupt these deeply ingrained, cue-associated learned responses, potentially through extinction-based behavioral therapies or pharmacological agents that modulate memory reconsolidation.

C. Critical Neurotransmitters and Receptors

A multitude of neurotransmitter systems and their receptors are implicated in the complex neurobiology of alcohol craving and binge drinking.

- **Dopamine (DA):** As discussed, dopamine is a primary neurotransmitter in the brain's reward system, crucial for motivation, reinforcement, and the attribution of

incentive salience to alcohol and its associated cues.²

- **Gamma-Aminobutyric Acid (GABA):** The principal inhibitory neurotransmitter in the brain. Ethanol acutely enhances GABAergic transmission, often by acting as an indirect GABA agonist at GABAA receptors, contributing to alcohol's sedative, anxiolytic, and motor-impairing effects.⁵ Chronic alcohol exposure leads to adaptive changes in the GABA system, such that during withdrawal, there is a state of reduced GABA function. This GABAergic hypoactivity contributes to neuronal hyperexcitability, anxiety, and withdrawal seizures.⁶ Studies have indicated lower GABA levels in the anterior cingulate cortex (ACC) of individuals at high risk for AUD who are actively drinking, compared to recently detoxified alcohol-dependent patients, suggesting dynamic changes in this system.⁷
- **Glutamate:** The brain's primary excitatory neurotransmitter. Alcohol acutely inhibits the function of glutamate receptors, particularly NMDA receptors.⁵ This contributes to cognitive impairment and some of alcohol's rewarding effects. During withdrawal from chronic alcohol use, the glutamate system can become hyperactive, leading to excitotoxicity, seizures, and contributing to craving.⁶ Glutamate is specifically implicated as a key neurotransmitter in the preoccupation/anticipation stage of addiction.³
- **Opioid Peptides (Endorphins, Enkephalins, Dynorphins):** These endogenous peptides modulate pain, stress, and reward by acting on different opioid receptor subtypes (mu, delta, kappa). Activation of mu and delta opioid receptors, particularly in the NAc, contributes to the rewarding and reinforcing effects of alcohol.³ Conversely, the dynorphin/kappa opioid receptor (KOP) system is often associated with the negative affective states experienced during withdrawal and stress. Activation of KOPs can induce dysphoria and aversive states, and this system is implicated in stress-induced relapse to alcohol seeking.⁶
- **Serotonin (5-HT):** This neurotransmitter is involved in regulating mood, sleep, appetite, and impulsivity. Alcohol can acutely increase serotonin release.⁶ Dysregulation of the serotonin system has been linked to depression and anxiety, conditions often comorbid with AUD. Some antidepressant medications that target the serotonin system (SSRIs) may help reduce alcohol consumption, particularly in individuals with co-occurring depression.¹⁰
- **Corticotropin-Releasing Factor (CRF):** A key peptide in the brain's stress response system. While acute alcohol administration can reduce CRF levels, chronic alcohol use leads to a hyperactive CRF system, especially within the extended amygdala.⁶ This heightened CRF activity during withdrawal and protracted abstinence is a major driver of negative emotional states, anxiety, and stress-induced relapse, thereby fueling the urge to drink.³
- **Other Neurotransmitters and Neuromodulators:** Several other neurochemical

systems are also involved. Acetylcholine plays a role in cognitive functions and reward.⁵ Norepinephrine is involved in arousal and stress responses.³ Various neuropeptides, including Neuropeptide Y (NPY, often anxiolytic and may reduce alcohol intake), Neuropeptide S (NPS, can modulate anxiety and arousal), and Oxytocin (involved in social bonding and stress modulation, with some studies exploring its potential to reduce craving), are also being investigated for their roles in AUD.¹² Ghrelin, a hormone primarily known for stimulating appetite, also influences reward pathways and has been implicated in the preoccupation/anticipation stage of addiction.³

The interplay between these neurotransmitter systems is intricate and changes dynamically with the progression from initial alcohol use to binge drinking and dependence. Understanding these interactions is paramount for developing targeted pharmacological interventions.

D. Insights, Hidden Connections, and Implications for Section II

(Integrated into Sections II.A and II.B above)

III. Herbal Interventions for Mitigating Alcohol Urge: Evidence from 2014-2025

The search for effective interventions to reduce alcohol urge and binge drinking has included the investigation of various herbal remedies, some with long histories in traditional medicine. This section reviews the evidence for selected herbs from studies and reviews published or focusing on research conducted between 2014 and 2025.

A. Kudzu (*Pueraria lobata* / *Pueraria montana*)

Background and Traditional Use: Kudzu, a vine native to East Asia, has been utilized for centuries in traditional Chinese medicine for various ailments, including efforts to reduce alcohol cravings and alleviate some symptoms associated with alcohol withdrawal.¹⁰ The primary active compounds in kudzu root are isoflavones, including daidzin, puerarin, and daidzein.¹⁰

Proposed Mechanisms of Action: Several mechanisms have been proposed for kudzu's effects on alcohol consumption. Biochemical studies suggest that its isoflavones may alter the activity of mitochondrial aldehyde dehydrogenase (ALDH2) or monoamine oxidase-B, enzymes involved in acetaldehyde metabolism.¹³ Inhibition of ALDH2 would lead to an accumulation of acetaldehyde after alcohol ingestion, potentially causing unpleasant physiological reactions (e.g., flushing, nausea), similar

to the effects of disulfiram. This could create a learned aversion to alcohol or blunt its rewarding effects. However, one study noted that the reduction in alcohol consumption with kudzu extract was not due to a kudzu-induced increase in alcohol's intoxicating effects, suggesting mechanisms beyond simple ALDH2 inhibition.¹³ Another hypothesis is that kudzu isoflavones may increase cerebral blood flow, thereby affecting how alcohol interacts with various neurotransmitter systems.¹⁰ Regardless of the precise mechanism, isoflavones in kudzu are generally considered effective in reducing alcohol intake in several mammalian species.¹³

The potential for an ALDH2 inhibition mechanism is noteworthy. If this is a primary mode of action, any reduction in "urge" might be a secondary consequence of learned aversion or a diminishment of alcohol's rewarding properties due to mild aversive reactions, rather than a direct modulation of core craving neurocircuits in areas like the PFC or amygdala. Clarifying the dominant mechanism—whether it's primarily aversive, related to direct neurotransmitter effects, or a combination—is crucial for understanding its therapeutic potential for urge reduction.

Evidence from 2014-2025 (and relevant background):

Research interest in kudzu for alcohol-related problems has continued, with a notable systematic review falling within the 2014-2025 timeframe.

- A Cochrane systematic review and meta-analysis abstract, presented in 2019 (with literature searches up to January 2019), evaluated kudzu for reducing alcohol consumption and dependence.¹⁵ This review included seven randomized controlled trials (RCTs), though most were small and had an unclear risk of bias. Among these, four RCTs reported that kudzu was favored over placebo in reducing the number of drinks consumed, normalizing drinking behavior, and increasing the number of abstinent days. Significantly, a meta-analysis of three of these trials indicated that kudzu *may reduce alcohol cravings*, with an odds ratio (OR) of 2.97 (95% Confidence Interval [CI] 1.37 to 6.46), supported by moderate-certainty evidence.¹⁵ This finding directly addresses the "urge" component of the user's query and represents a key piece of evidence from the specified period.
- Earlier human studies provided important context for this review. For instance, a study by Lukas et al. (2013, published prior to 2014 but cited as background in ¹³) involving non-treatment-seeking male heavy drinkers found that four weeks of treatment with a standardized kudzu extract (containing 250 mg of isoflavones, three times daily) led to a significant reduction in the number of alcoholic drinks consumed per week by 34–57%. It also reduced the number of heavy drinking days and significantly increased both the percentage of days abstinent and the number of consecutive days of abstinence. However, this particular study

reported *no significant effect on the self-reported desire to use alcohol (craving)*.¹³

- Similarly, an even earlier study by Lukas et al. (2005, cited in ¹³) demonstrated that a 7-day treatment with kudzu extract significantly reduced alcohol consumption by heavy drinkers in a naturalistic laboratory setting, again without a reported significant impact on the urge to drink.
- A study by Penetar et al., published in July 2015, investigated the effects of a single dose of kudzu extract on alcohol consumption in a human laboratory binge drinking paradigm.¹³ This study is highly relevant as it falls squarely within the 2014-2025 timeframe and specifically addresses a binge drinking context. The findings suggested that a single pretreatment dose of kudzu root extract may reduce alcohol consumption in such a paradigm.¹⁴
- The discrepancy between individual earlier studies not finding an effect on craving and the 2019 meta-analysis suggesting a potential reduction in craving is significant. It may be that the aggregate evidence from multiple trials is more robust, or that different study designs, populations, or craving measures used in the trials included in the meta-analysis were more sensitive to detecting changes in urge. It is also possible that kudzu's impact on consumption might indirectly lead to a reduction in craving over time or specifically in binge-drinking scenarios.
- Reflecting ongoing research interest, an intervention study titled "Addressing heavy alcohol use consumption with kudzu (A-HACK)" (ClinicalTrials.gov identifier: NCT03709043), which began in 2018, is currently examining the efficacy of kudzu in reducing alcohol consumption.¹⁸ The results of such ongoing trials will be crucial for further clarifying kudzu's role.

Safety and Tolerability: Kudzu extract is generally reported as well-tolerated. The Lukas et al. (2013) study found minimal side effects, with excellent medication adherence and no adverse changes in vital signs, blood chemistry, or renal/liver function.¹³ The 2019 Cochrane review noted that while three trials reported no adverse events, two other RCTs reported a low frequency of adverse effects (ranging from 1.7% to 3%), with headaches being the most common.¹⁵ Due to the estrogen-mimicking effects of its isoflavone content, caution is advised for individuals with hormone-sensitive conditions, such as certain types of breast cancer.¹⁰

B. Ashwagandha (*Withania somnifera*)

Background and Traditional Use: Ashwagandha is an adaptogenic herb prominently used in traditional Ayurvedic medicine, primarily to help the body manage stress and promote overall well-being.¹⁰

Proposed Mechanisms of Action: Ashwagandha is believed to exert its effects by modulating the body's stress-response system, notably by reducing cortisol levels.¹⁰ It is also thought to support neurotransmitter balance, with preclinical research indicating potential GABAergic activity.¹⁰ A 2020 preclinical study demonstrated that ashwagandha extract was effective in controlling seizure and agitation in a rat model of alcohol withdrawal, suggesting direct effects on withdrawal neurobiology, possibly via GABAergic mechanisms.²⁰ Additionally, ashwagandha possesses anti-inflammatory, antioxidant, and neuroprotective properties that could be beneficial in the context of alcohol-related brain changes.¹⁹

The primary relevance of ashwagandha to reducing alcohol urge likely arises from its well-documented anti-stress and anxiolytic effects. These actions can mitigate "relief-craving," which is the urge to drink to alleviate negative emotional states or withdrawal symptoms—a key driver in the withdrawal/negative affect stage of addiction.³ By modulating the HPA axis and potentially enhancing GABAergic inhibition, ashwagandha may reduce the motivation to use alcohol as a form of self-medication for stress or anxiety.

Evidence from 2014-2025:

- Ashwagandha is primarily recognized for its capacity to reduce stress and anxiety, which are common triggers for alcohol consumption and relapse.¹⁰ Clinical trials, reviewed in sources like ¹⁹ (a 2021 review, though dates of individual trials cited therein would need specific verification for the 2014-2025 window), have demonstrated ashwagandha's ability to lower anxiety scores and reduce cortisol levels in stressed individuals.
- A significant preclinical study by Kalra et al. (2020) investigated the effects of ashwagandha extract (standardized to 3.75 mg/kg of withanolide glycosides) on alcohol withdrawal syndrome in rats.²⁰ The findings showed that ashwagandha was significantly effective in controlling both seizures and agitation during alcohol withdrawal, with efficacy in some measures comparable to diazepam. This study, falling within the 2014-2025 timeframe, points to a direct modulatory effect on the neurobiological disturbances associated with alcohol withdrawal, a period of intense craving and high relapse risk. The observed GABAergic action is particularly pertinent, as alcohol withdrawal involves significant dysregulation of the GABA system.⁶ By alleviating the severity of acute withdrawal, ashwagandha could reduce the powerful urges that drive immediate relapse.
- While not a direct test of ashwagandha, a 2023 study (publication date noted as Oct 2024 in snippet ⁷, likely a prospective or typo, actual publication probably 2023/2024) examined GABA levels in the anterior cingulate cortex (ACC) in

relation to alcohol use. It found that actively drinking individuals at high risk for AUD had significantly lower GABA levels in the ACC compared to recently detoxified alcohol-dependent subjects. This highlights the ongoing relevance of GABAergic system alterations in AUD, a system that ashwagandha is proposed to modulate.

- Specific human clinical trials investigating ashwagandha directly for reducing alcohol craving or binge drinking as primary outcomes within the 2014-2025 period are not clearly detailed in the provided information, although its role in stress reduction, a key factor in AUD, is well-supported.¹⁹

Safety and Tolerability: Ashwagandha is generally considered safe and well-tolerated when used appropriately. Some individuals may experience mild side effects such as gastrointestinal upset or drowsiness.¹⁰ It is typically advised to be avoided by individuals with hyperthyroidism or those taking sedative medications due to potential interactions or additive effects.¹⁰ Clinical safety studies, including a 2023 publication on repeated intake in healthy males, support its safety at typical dosages.²¹

C. Passionflower (*Passiflora incarnata*)

Background and Traditional Use: Passionflower has a history of use as a traditional remedy for nervousness, anxiety, and as a mild sedative.²²

Proposed Mechanisms of Action: The anxiolytic and sedative effects of passionflower are primarily attributed to its modulation of the GABA neurotransmission system. *In vitro* studies suggest that extracts of *P. incarnata* can inhibit the synaptic reuptake of GABA and may also bind to both GABAA (ionotropic) and GABAB (metabotropic) receptors.²³ Binding to the GABA site on the GABAA receptor is considered a likely contributor to its pharmacological effects.²³

Similar to ashwagandha, passionflower's potential utility in reducing alcohol urge is likely mediated by its anxiolytic properties stemming from GABAergic mechanisms. Anxiety is a frequent comorbidity with AUD and a significant trigger for alcohol consumption.³ By enhancing GABAergic inhibition or helping to restore balance in this system (which is notably affected by alcohol), passionflower could reduce anxiety levels and thereby lessen the "urge" to use alcohol as a means of self-medication.

Evidence from 2014-2025:

- A non-interventional study conducted by Gibbert et al. and published in 2017 investigated the effects of a dried ethanolic extract of passionflower over 12

weeks in adult patients diagnosed with nervous restlessness (not specifically an AUD population).²³ The study reported significant improvements in measures of resilience and quality of life, along with reductions in accompanying symptoms such as inner restlessness, sleep disturbance, and fear. The treatment was rated as having good tolerability. These findings support its general anxiolytic and calming effects.

- A systematic review published in 2020 (literature search up to October 2019) evaluated the neuropsychiatric effects of *Passiflora incarnata*.²⁴ This review included nine clinical trials of varying durations (from one day to 30 days) involving adult participants. The majority of these studies reported reduced anxiety levels following the administration of passionflower preparations. Importantly, no significant adverse effects, such as memory loss or impairment of psychometric functions, were observed.
- While one source mentions passionflower as being proposed as an aid for alcohol withdrawal, this is primarily based on studies related to opiate addiction, and strong, specific evidence from the 2014-2025 period directly linking passionflower to reduced alcohol urge or binge drinking in humans is not prominent in the provided materials.²²
- A study on a different species, *Passiflora tripartita* var. *mollissima*, conducted in mice (with a prospective publication date of 2025, suggesting recent research activity, likely 2024) demonstrated anxiolytic effects at doses of 100 mg/kg and 200 mg/kg.²⁵ While this is not *P. incarnata* and is a preclinical animal study, it lends further support to the general neuropharmacological activity of the *Passiflora* genus in modulating anxiety.
- Despite a plausible mechanism of action via the GABA system, a significant gap exists in direct clinical trial evidence from the 2014-2025 period specifically evaluating passionflower's efficacy for alcohol urge or binge drinking in AUD populations. This highlights an area where further research is warranted.

Safety and Tolerability: Passionflower is generally regarded as safe and well-tolerated. The 2017 study by Gibbert et al. reported only mild adverse events, such as tiredness, in a few cases.²³ The 2020 systematic review also concluded that no significant adverse effects were observed in the clinical trials it analyzed.²⁴

D. St. John's Wort (*Hypericum perforatum*)

Background and Traditional Use: St. John's Wort is a well-known herbal remedy, primarily recognized for its antidepressant effects, particularly in cases of mild to moderate depression.¹⁰

Proposed Mechanisms of Action: The antidepressant effects of St. John's Wort are thought to be related to its ability to modulate neurotransmitter levels in the brain, including potentially elevating serotonin.¹⁰ Some preclinical studies (conducted before 2014, such as one cited in²⁶ and a 2005 study by Perfumi et al.²⁷) indicated that St. John's Wort extract could reduce voluntary ethanol intake in alcohol-preferring rats, and that this effect might be synergistic when combined with naltrexone.

The primary relevance of St. John's Wort for reducing alcohol urge, based on evidence within the 2014-2025 timeframe, appears to be indirect, through its established efficacy in treating co-occurring depression. If an individual's binge drinking is substantially driven by an attempt to self-medicate depressive symptoms, then alleviating the underlying depression with St. John's Wort could consequently reduce the urge to drink that stems from this specific cause.

Evidence from 2014-2025:

- It is suggested that because depression and AUD frequently co-occur, an herb like St. John's Wort that supports a more stable mood could be beneficial during recovery by reducing the urge to self-medicate with alcohol.¹⁰
- A meta-analysis published in 2017³ compared the efficacy and safety of St. John's Wort with standard selective serotonin reuptake inhibitors (SSRIs) for the treatment of *depression*.²⁸ This analysis, which included 27 clinical trials with a total of 3808 patients, found that St. John's Wort demonstrated comparable response and remission rates to SSRIs in patients with mild-to-moderate depression, and had a significantly lower discontinuation/dropout rate. While this is important for its use in depression, it does not directly address alcohol urge in individuals without a primary depressive disorder.
- The provided information lacks specific human clinical trials conducted between 2014 and 2025 that investigate St. John's Wort directly for the purpose of reducing alcohol urge or binge drinking in individuals whose primary diagnosis is AUD without significant co-occurring depression. The promising rat study by Perfumi et al.²⁷ dates to 2005 and is thus outside the specified timeframe for primary research.

Safety and Tolerability: A significant concern with St. John's Wort is its potential for numerous drug interactions. It can affect the metabolism of various medications, including other antidepressants, birth control pills, and blood thinners, by inducing cytochrome P450 enzymes.¹⁰ This considerable interaction profile is a major limiting factor for its widespread or unmonitored use, especially in individuals with AUD who may be taking other medications for co-occurring physical or mental health

conditions. Its use would necessitate a thorough review of all current medications by a healthcare professional.

E. Milk Thistle (*Silybum marianum*)

Background and Traditional Use: Milk thistle is widely recognized for its hepatoprotective (liver-protective) properties and has a long history of use for liver ailments.¹⁰ The primary active constituent group is silymarin, a complex of flavonolignans.

Proposed Mechanisms of Action (for AUD context): In the context of alcohol use, milk thistle's benefits are primarily attributed to its ability to promote liver cell repair and protect the liver from toxins, including those generated by alcohol metabolism.¹⁰ It is suggested that improved liver function might lead to reduced fatigue and gastrointestinal issues, which could indirectly bolster an individual's resolve when attempting to reduce or quit alcohol.¹⁰ However, there is no strong indication from the provided materials that milk thistle directly modulates brain neurochemistry involved in urge signals.

Evidence from 2014-2025:

- Much of the information on milk thistle and alcohol-related liver disease refers to studies and systematic reviews published *before* the 2014 cutoff (e.g., Cochrane reviews from 2003 and 2005 are mentioned or form the basis of summaries in ²⁹).
- One source states that the evidence supporting its effectiveness, even for liver protection in the context of alcohol abuse, remains inconclusive, and that abstinence from alcohol is proven to be more effective.²² This source does not mention any role for milk thistle in reducing alcohol "urge."
- A systematic review published in February 2022 (thus within the 2014-2025 scope) by Rambaldi et al. (revisiting earlier Cochrane work) concluded that it "could not demonstrate significant effects of milk thistle on mortality or complications of liver diseases in patients with alcoholic and/or hepatitis B or C liver diseases combining all trials or high-quality trials".³² While this review is recent, its focus is on liver outcomes and mortality, not on alcohol craving or binge drinking behavior itself.
- Based on the provided information, milk thistle's role appears to be primarily adjunctive, aimed at supporting liver health in individuals who consume alcohol, rather than directly targeting the neurobiological mechanisms of alcohol urge or binge drinking.

Safety and Tolerability: Milk thistle is generally considered safe, though some

individuals may experience mild gastrointestinal side effects such as diarrhea, nausea, or bloating. It can also interact with certain medications, particularly those that are metabolized by the liver, due to potential effects on liver enzymes.¹⁰

F. Other Herbal Candidates

- **Prickly Pear Cactus (*Opuntia ficus indica*):** An older study (Wiese et al., 2004, cited in ²² and detailed in ³³), thus pre-dating the 2014-2025 focus for primary research, found that an extract of prickly pear cactus significantly reduced some alcohol hangover symptoms (nausea, dry mouth, anorexia) and the risk of a severe hangover. The proposed mechanism was a reduction in the inflammatory response to alcohol consumption, as evidenced by lower C-reactive protein levels.³³ There is no direct evidence within the provided 2014-2025 materials suggesting it reduces alcohol urge or binge drinking behavior itself.
- **Psilocybin:** Derived from certain species of mushrooms, psilocybin is a psychedelic compound that has garnered renewed research interest for various psychiatric conditions, including addiction. One source mentions that psilocybin has been proposed as a treatment for alcohol addiction, citing a study (likely pre-2014 in its original context) where two doses of psilocybin combined with psychotherapy led to over 80% of participants decreasing their drinking habits.²² More recently, and critically within the 2014-2025 timeframe, a Phase 2 randomized clinical trial (NCT04141501), which recruited participants between June 2020 and August 2023, investigated psilocybin-assisted therapy for relapse prevention in individuals with AUD.³⁴ The abstract, with a prospective publication eCollection date of April 2025, reported on 37 participants who completed a 4-week follow-up. The study found no significant differences between the psilocybin (25 mg single oral dose) plus brief psychotherapy group and the placebo (mannitol) plus brief psychotherapy group in terms of abstinence duration or mean alcohol use per day at the 4-week mark. However, participants in both groups reported reduced craving and temptation to drink alcohol after the dosing visit, with an additional reduction observed in the psilocybin group.³⁴ The authors concluded that a single dose of psilocybin with limited psychotherapy might not be sufficient to reduce relapse rates in severely affected AUD patients but noted the limited sample size and the need for larger trials. This recent finding, though mixed regarding primary outcomes, does suggest a potential signal for craving reduction with psilocybin that warrants further investigation. The mechanism of psilocybin is thought to involve serotonin 2A(5-HT_{2A}) receptor agonism, leading to altered states of consciousness, potential "resetting" of neural circuits, and profound psychological insights, rather than targeting typical

urge pathways in the same manner as conventional AUD medications.

G. Table 1: Summary of Herbal Interventions for Alcohol Urge Reduction (2014-2025)

Herb Name	Key Active Compounds	Proposed Neurobiological Mechanism(s) related to Urge/Binge Drinking	Summary of Key Findings (2014-2025, Study Type)	Evidence Strength for Urge/Binge Reduction & Limitations
Kudzu (<i>Pueraria lobata/montana</i>)	Isoflavones (daidzin, puerarin, daidzein)	May alter ALDH2/MAO-B (acetaldehyde metabolism); may affect neurotransmitter interaction via cerebral blood flow changes. ¹⁰	2019 Cochrane review (meta-analysis of 3 RCTs): <i>May reduce alcohol cravings</i> (OR 2.97); 4 RCTs showed reduced consumption/increased abstinence. ¹⁵ 2015 human trial (Penetar et al.): Single dose reduced alcohol consumption in a binge drinking paradigm. ¹³ Ongoing A-HACK trial (NCT03709043). ¹⁸	Moderate (for craving, per 2019 review); Moderate (for consumption in binge paradigm, per 2015 trial). Limitations: Earlier individual studies often didn't find craving effect; quality of trials in review varied; mechanism needs full elucidation.
Ashwagandha (<i>Withania somnifera</i>)	Withanolides	Adaptogenic (reduces cortisol, HPA axis modulation); potential GABAergic action; anti-inflammatory	2020 preclinical (rat) study: Effective in controlling alcohol withdrawal seizures/agitation. ²⁰ Human trials support	Low (direct for alcohol urge/binge in humans); Preclinical evidence for withdrawal. Limitations: Human evidence

		y, antioxidant. ¹⁰	anti-stress/anxiolytic effects. ¹⁹ No direct large human AUD trials for urge in 2014-2025 snippets.	for AUD urge/binge is indirect (via stress/anxiety reduction); needs direct AUD trials.
Passionflower (<i>Passiflora incarnata</i>)	Flavonoids, alkaloids (exact contribution unclear)	Modulation of GABA system (GABA reuptake inhibition, GABAA/GABAB receptor binding). ²³	2017 human non-interventional study: Improved resilience/QoL in nervous restlessness. ²³ 2020 systematic review (9 trials): Majority reported reduced anxiety. ²⁴ No direct large human AUD trials for urge in 2014-2025 snippets.	Low (direct for alcohol urge/binge in humans). Limitations: Human evidence for AUD urge/binge is indirect (via anxiolysis); needs direct AUD trials.
St. John's Wort (<i>Hypericum perforatum</i>)	Hypericin, hyperforin	May elevate serotonin levels. ¹⁰	2017 meta-analysis (27 trials): Comparable to SSRIs for mild-moderate depression. ²⁸ No direct human AUD trials for urge (non-depressed) in 2014-2025 snippets.	Low (direct for alcohol urge/binge in non-depressed AUD). Limitations: Relevance mainly for co-occurring depression; significant drug interaction potential.
Psilocybin	Psilocybin	5-HT2A receptor agonism;	2020-2023 Phase 2 RCT (NCT04141501,	Low to Moderate (for craving signal,

		potential neural network resetting, enhanced neuroplasticity, psychological insight.	pub. 2025): No significant effect on primary outcomes (abstinence, mean use) vs placebo at 4 wks. Both groups had reduced craving; <i>additional reduction in psilocybin group.</i> ³⁴	needs confirmation). Limitations: Small sample size in recent trial; primary outcomes not met; requires psychotherapy integration; long-term effects unclear.
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IV. Pharmacological Compounds Targeting Brain Urge Signals: Developments from 2014-2025

The development and evaluation of pharmacological compounds for AUD, including those targeting urge signals related to binge drinking, have continued to evolve. This section examines recent evidence for established and off-label medications, as well as novel compounds emerging from preclinical and early clinical research between 2014 and 2025.

A. Re-evaluation of Established and Off-Label Pharmacotherapies

Recent systematic reviews and meta-analyses have provided updated perspectives on the efficacy of medications commonly used for AUD.

- **Naltrexone (Opioid Antagonist):**

- **Mechanism:** Naltrexone is an opioid receptor antagonist, primarily acting at mu-opioid receptors. By blocking these receptors, it is thought to reduce the rewarding, euphoric effects of alcohol and may also diminish alcohol craving.³
- **Evidence**³⁵:
 - Oral naltrexone (typically 50 mg/day) demonstrated **moderate-strength evidence** for reducing the risk of returning to *any drinking* (Number Needed to Treat = 18) and for reducing the risk of returning to *heavy drinking* (NNT = 11) compared to placebo. There was also moderate-strength evidence that it reduces the percentage of drinking days and the percentage of heavy drinking days. The evidence for its effect on reducing the number of drinks per drinking day was rated as low strength.

- Injectable naltrexone (long-acting formulation) showed **low-strength evidence of no effect** on return to any drinking or return to heavy drinking. There was low-strength evidence for a reduction in the percentage of drinking days and heavy drinking days.
 - Naltrexone remains a first-line pharmacotherapy for AUD, with current evidence supporting the efficacy of the oral formulation in reducing overall alcohol consumption and relapse to heavy drinking, outcomes intrinsically linked to the successful management of alcohol urges.
- **Acamprosate (Glutamate Modulator):**
 - **Mechanism:** Acamprosate's precise mechanism is not fully elucidated, but it is thought to restore the balance between GABAergic and glutamatergic neurotransmission, which is disrupted by chronic alcohol use. It may act by attenuating the hyperactivity of NMDA glutamate receptors that occurs during alcohol withdrawal and protracted abstinence, thereby reducing withdrawal symptoms and craving.¹¹
 - **Evidence (Jonas et al., 2023³⁵):**
 - Acamprosate demonstrated **moderate-strength evidence** for reducing the risk of returning to *any drinking* (NNT = 11) compared to placebo. There was also moderate-strength evidence that it reduces the percentage of drinking days. However, the review found **moderate-strength evidence of no significant effect** on the risk of returning to *heavy drinking*. Evidence was deemed insufficient to determine its effects on the percentage of heavy drinking days or the number of drinks per drinking day.
 - Acamprosate is also considered a first-line therapy, particularly useful for supporting abstinence. Its potential to mitigate the glutamatergic hyperexcitability and negative affective states associated with withdrawal may indirectly reduce urges driven by these factors.
- **Disulfiram (Aldehyde Dehydrogenase Inhibitor):**
 - **Mechanism:** Disulfiram works as an aversive agent by irreversibly inhibiting the enzyme aldehyde dehydrogenase (ALDH). This leads to an accumulation of acetaldehyde if alcohol is consumed, causing a highly unpleasant constellation of symptoms (e.g., flushing, nausea, vomiting, palpitations, headache) known as the disulfiram-ethanol reaction.¹¹ It does not directly target neurobiological urge signals but relies on deterrence.
 - **Evidence (Jonas et al., 2023³⁵):**
 - The review found **low-strength evidence of no effect** for disulfiram in preventing a return to any drinking compared with placebo. Historically, evidence supporting its effectiveness has been inconsistent.¹¹

- Due to its mechanism, disulfiram is less relevant for directly modulating brain-based urge signals and is more suited for individuals highly motivated to maintain abstinence under supervision.
- **Topiramate (Anticonvulsant):**
 - **Mechanism:** Topiramate has multiple neurochemical actions, including enhancement of GABAergic activity (via GABAA receptors), antagonism of AMPA/kainate glutamate receptors, and inhibition of carbonic anhydrase and voltage-gated sodium channels. These actions may collectively reduce the rewarding effects of alcohol and mitigate withdrawal-related neuronal hyperexcitability.¹¹
 - **Evidence (Jonas et al., 2023³⁵):**
 - When used off-label for AUD, topiramate showed **moderate-strength evidence** for improving (reducing) the percentage of drinking days, the percentage of heavy drinking days, and the number of drinks per drinking day. An earlier review also noted it may decrease alcohol intake (Evidence rating B).¹¹
 - Topiramate shows considerable promise as an off-label treatment by targeting key neurotransmitter systems (GABA and glutamate) critically involved in alcohol urge and consumption patterns.
- **Gabapentin (Anticonvulsant, GABA analogue):**
 - **Mechanism:** Gabapentin is structurally related to GABA and is thought to modulate GABAergic transmission, potentially by increasing GABA synthesis or release, and may also affect calcium channels, thereby reducing neuronal hyperexcitability. It is used to treat seizures, neuropathic pain, and anxiety.¹¹
 - **Evidence (Jonas et al., 2023³⁵):**
 - The review found **low-strength evidence** that gabapentin was not significantly associated with lower rates of return to any drinking and **low-strength evidence** for reducing return to heavy drinking. An earlier source suggested it may reduce alcohol ingestion (Evidence rating B), particularly in selected patient subpopulations with significant withdrawal symptoms or anxiety.¹¹
 - The evidence for gabapentin in AUD is somewhat mixed, but its mechanism of action remains relevant to modulating systems involved in alcohol urge and withdrawal.
- **Ondansetron (Serotonin 5-HT3 Antagonist):**
 - **Mechanism:** Ondansetron selectively blocks serotonin 5-HT3 receptors. These receptors are found in the peripheral and central nervous system, including areas involved in reward processing. By antagonizing 5-HT3 receptors, ondansetron may modulate dopamine release in the mesolimbic

pathway, thereby potentially reducing alcohol's rewarding effects and craving.¹¹

- **Evidence:** Ondansetron may reduce alcohol use, particularly in selected subpopulations, such as individuals with early-onset AUD (Evidence rating B from ¹¹). It is listed among compounds investigated for AUD.¹²
- Ondansetron holds potential for specific patient subgroups, highlighting a move towards more personalized approaches.
- **Baclofen (GABA-B Agonist):**
 - **Mechanism:** Baclofen is an agonist at GABAB receptors. Activation of these receptors can reduce neuronal excitability and has been shown to decrease dopamine release in reward pathways. It is also used as a muscle relaxant and has anxiolytic properties.¹²
 - **Evidence (Jonas et al., 2023 ³⁵):**
 - The review found **low-strength evidence** for baclofen reducing the rates of return to any drinking (though this finding was noted for imprecision and inconsistency) and **low-strength evidence of no effect** for reducing return to heavy drinking.
 - Despite initial enthusiasm for baclofen in AUD treatment, recent comprehensive reviews suggest its efficacy is limited for broad application in reducing drinking.

B. Novel Targets and Emerging Compounds (2014-2025 Preclinical & Early Clinical)

Research beyond established medications has focused on novel neurobiological targets to address alcohol urge and binge drinking.

- **Kappa Opioid Receptor (KOP) Antagonists (e.g., LY2444296):**
 - **Mechanism:** The endogenous dynorphin/KOP system is implicated in the negative affective states associated with stress and alcohol withdrawal. Activation of KOPs can induce dysphoria and anxiety, contributing to relapse. KOP antagonists aim to block these effects, thereby reducing the motivation to drink for relief from negative emotional states.⁸
 - **Evidence:** A study published in *Scientific Reports* in March 2024 by Flores-Ramirez and colleagues provided significant preclinical findings.⁸ They demonstrated that LY2444296, a selective, short-acting, orally administered KOP antagonist, significantly reduced alcohol self-administration and attenuated physical signs of withdrawal in both male and female Wistar rats with a history of alcohol dependence. Notably, these effects were observed specifically at 8 hours of abstinence, a period corresponding to acute withdrawal symptoms. The compound did not affect alcohol intake in

non-dependent rats, suggesting selectivity for the dependent state. Researchers plan further investigations into LY2444296's ability to block stress- and cue-induced relapse and to identify the specific brain regions mediating its effects.⁸

- These findings are highly promising, as they target the stress-related component of urge and withdrawal, directly addressing the negative reinforcement pathway that perpetuates alcohol use.

- **Nociceptin Receptor (NOP) Modulators (e.g., PPL-138):**

- **Mechanism:** The nociceptin/orphanin FQ (N/OFQ) system and its receptor, the NOP receptor (also known as ORL-1), are widely distributed in the brain and involved in modulating stress, reward, pain, anxiety, and learning. PPL-138 is a compound described as being similar to buprenorphine (a partial mu-opioid agonist and kappa-opioid antagonist used for opioid dependence and pain) but with a unique profile that includes stronger activation of the NOP receptor. This NOP agonism is hypothesized to relieve pain and stress-induced anxiety and potentially block the rewarding effects of alcohol, without itself possessing significant addictive properties.³⁸
- **Evidence:** News from November 2023 reported on an ongoing preclinical trial testing PPL-138 for co-occurring Post-Traumatic Stress Disorder (PTSD) and AUD.³⁸ Initial findings in male rat models of PTSD indicated that PPL-138 reduces PTSD-like symptoms, such as anxiety and increased pain sensitivity, while also decreasing alcohol consumption. The effect on alcohol consumption was noted to be particularly evident in animals prone to drink more due to anxiety. Future research will include testing in female models.³⁸
- PPL-138 represents a potential dual-acting therapy for individuals with co-occurring PTSD and AUD, conditions where stress and anxiety are major drivers of alcohol urge and consumption.

- **Phosphodiesterase-4 (PDE4) Inhibitors (e.g., Apremilast):**

- **Mechanism:** Phosphodiesterases (PDEs) are enzymes that regulate intracellular second messengers like cyclic AMP (cAMP). PDE4 is highly expressed in the brain and plays a role in inflammation and neuronal signaling. PDE4 inhibitors, such as apremilast (an FDA-approved drug for treating inflammatory conditions like psoriasis and psoriatic arthritis), are being investigated for their potential in AUD. They may reduce neuroinflammation associated with chronic alcohol use and modulate neurotransmission in key brain regions involved in addiction, such as by enhancing GABAergic transmission in the central amygdala.³⁹
- **Evidence:** A preclinical study, with results anticipated for publication in *JCI Insight* around April 2025 (as reported in news releases from April/May 2025,

suggesting very recent research activity likely in 2024 or early 2025), found that apremilast significantly decreased alcohol intake and reduced pain sensitivity in both male and female rats, including a strain genetically predisposed to high alcohol consumption and a standard laboratory strain.³⁹ The study also observed that apremilast enhanced GABAergic transmission in the central amygdala of standard strain rats and that alcohol exposure led to increased brain expression of PDE4 genes.

- The repurposing of an existing anti-inflammatory drug like apremilast offers a novel therapeutic strategy, linking neuroinflammatory processes to AUD and associated pain, both of which can significantly contribute to alcohol urges.
- **Other Investigated Compounds:** A review from 2023 lists numerous other medications that have been investigated for AUD, including varenicline, aripiprazole, quetiapine, various antidepressants, lithium, neuropeptide Y, neuropeptide S, CRF antagonists, oxytocin, memantine, ifenprodil, samidorphan, ondelopran, and ABT-436.¹² The extent of research specifically on *urge/binge drinking* for these compounds within the 2014-2025 timeframe varies. One notable recent study is the ON-ICE trial (Zimmermann et al., 2022), which is investigating the combined effects of oxytocin and naltrexone on stress-induced and alcohol cue-induced craving in AUD.⁸

C. Insights, Hidden Connections, and Implications for Section IV

The landscape of pharmacological research for AUD reveals several important trends and considerations. There is a discernible shift towards developing compounds that target the neurobiological systems underlying stress, negative affect, and withdrawal, such as KOP antagonists (LY2444296), NOP modulators (PPL-138), and potentially PDE4 inhibitors (apremilast). This moves beyond a sole focus on modulating the primary dopamine-driven reward pathway. This evolution in strategy reflects a more nuanced understanding of the addiction cycle, recognizing that particularly in later stages or in patterns of binge drinking aimed at alleviating dysphoria, the negative reinforcement pathways (driven by systems in the extended amygdala and stress responses) become critical drivers of urges.³ Addressing this "dark side" of addiction is increasingly seen as crucial.

The strategy of repurposing drugs already approved for other medical conditions, exemplified by apremilast, is an efficient approach that could accelerate the development and availability of new treatments for AUD.³⁹ Because these drugs have already undergone extensive safety testing for their original indications, their path to potential approval for AUD could be shorter and less costly than developing entirely new chemical entities. This allows for the relatively rapid introduction of novel

mechanistic approaches, such as anti-inflammatory strategies, into the AUD treatment armamentarium.

Furthermore, the effectiveness of certain compounds appears to be contingent on specific conditions, such as the timing of administration or particular patient characteristics. For instance, LY2444296 demonstrated efficacy in animal models primarily during the acute withdrawal phase (8 hours of abstinence) but not at later abstinence time points.⁹ Similarly, ondansetron has been suggested to be more effective in specific subpopulations, like those with early-onset AUD.¹¹ This variability underscores the unlikelihood of a "one-size-fits-all" pharmacological solution for AUD. The neurobiological state of an individual's brain (e.g., acute withdrawal versus protracted abstinence, or the predominance of cue-induced craving versus stress-induced craving) and underlying genetic or phenotypic differences are likely to significantly influence treatment response. This points towards the growing importance of precision medicine in AUD treatment, aiming to match patients to the interventions from which they are most likely to benefit, a priority also reflected in NIAAA research funding opportunities.⁴¹

D. Table 2: Summary of Pharmacological Compounds for Alcohol Urge Reduction (2014-2025)

Compound/Class	Primary Brain Target/Mechanism related to Urge/Binge	Summary of Key Findings (2014-2025, Study Type)	Evidence Strength/Stage of Development for Urge/Binge Reduction
Naltrexone (Oral)	Mu-opioid receptor antagonist; reduces alcohol reward/craving ³	2023 systematic review/meta-analysis: Moderate evidence for reducing return to any/heavy drinking & % drinking days. ³⁵	Moderate (Established, FDA Approved for AUD)
Acamprosate	Glutamate (NMDA receptor) modulator; restores GABA/glutamate balance ¹¹	2023 systematic review/meta-analysis: Moderate evidence for reducing return to any drinking & % drinking days; no effect on return to	Moderate (Established, FDA Approved for AUD)

		heavy drinking. ³⁵	
Topiramate	GABA enhancement, glutamate antagonism ¹¹	2023 systematic review/meta-analysis: Moderate evidence for improving % drinking days, % heavy drinking days, drinks/drinking day (off-label). ³⁵	Moderate (Off-label for AUD)
LY2444296 (KOP Antagonist)	Kappa Opioid Receptor antagonist; reduces negative affect/stress response ⁸	2024 preclinical (rat) study: Significantly reduced alcohol self-administration & withdrawal signs at 8h abstinence in dependent rats. ⁸	Promising Preclinical
PPL-138 (NOP Modulator)	Nociceptin/Orphanin FQ Receptor (NOP) agonist; may reduce stress/anxiety, block alcohol reward ³⁸	Ongoing preclinical (rat) trial (news Nov 2023): Reduces PTSD symptoms & alcohol consumption, esp. anxiety-driven drinking. ³⁸	Early Preclinical
Apremilast (PDE4 Inhibitor)	Phosphodiesterase-4 inhibitor; anti-inflammatory, may modulate amygdala GABA ³⁹	Preclinical (rat) study (news Apr/May 2025, for pub. JCI Insight): Decreased alcohol intake & pain sensitivity; enhanced amygdala GABA. ³⁹	Promising Preclinical (Repurposed Drug)
Gabapentin	GABA analogue; modulates GABA, calcium channels ¹¹	2023 systematic review/meta-analysis: Low evidence for reducing return to any/heavy drinking. ³⁵ May help selected populations. ¹¹	Low to Moderate (Off-label for AUD, mixed evidence)

Ondansetron (5-HT3 Antagonist)	Serotonin 5-HT3 receptor antagonist; modulates dopamine reward pathway ¹¹	May reduce alcohol use in selected subpopulations (e.g., early-onset AUD). ¹¹ Investigated compound. ¹²	Low to Moderate (Off-label for AUD, specific populations)
Baclofen (GABAB Agonist)	GABAB receptor agonist; may reduce dopamine release/anxiety ¹²	2023 systematic review/meta-analysis: Low evidence for reducing return to any drinking; no effect on return to heavy drinking. ³⁵	Low (Limited Efficacy)
Oxytocin + Naltrexone	Oxytocin (social bonding, stress) + Naltrexone (opioid antagonism)	Ongoing ON-ICE trial (Zimmermann et al., 2022) investigating effects on stress- & cue-induced craving. ⁸	Early Clinical (Combination)

V. Synthesis, Current Gaps, and Future Research Trajectories

A. Comparative Efficacy and Mechanisms: Herbs vs. Pharmacological Compounds

When comparing herbal interventions and pharmacological compounds for mitigating alcohol urge and binge drinking, several distinctions in their characteristics, mechanisms, and current evidence base emerge.

Herbal remedies often contain a multitude of active phytochemicals, which can result in broader, and sometimes less specific, mechanisms of action compared to single-molecule pharmaceuticals. For example, kudzu is proposed to act via isoflavones that may influence alcohol metabolism (potentially through ALDH2) and also interact with neurotransmitter systems.¹⁰ Ashwagandha's effects are considered adaptogenic, involving modulation of the HPA axis and GABAergic systems, alongside antioxidant and anti-inflammatory properties.¹⁰ The evidence for direct reduction of alcohol urge by herbs is often rated as moderate (as with kudzu, based on a 2019 review ¹⁵) or is more indirect, such as through the anxiolytic effects of ashwagandha or passionflower.¹⁹ Within the 2014-2025 timeframe, the volume and rigor of human clinical trial data specifically focused on alcohol urge or binge drinking as primary outcomes tend to be less abundant for many herbal interventions compared to some

established pharmaceuticals.

Pharmacological compounds, by contrast, are typically single chemical entities designed or selected to interact with more defined molecular targets. Established AUD medications like naltrexone (a mu-opioid antagonist) and acamprosate (a glutamate modulator) have a more substantial body of evidence from numerous human RCTs and meta-analyses supporting their efficacy for various AUD outcomes, including those related to reducing drinking.³⁵ Novel pharmacological compounds currently in development, such as KOP antagonists like LY2444296, NOP modulators like PPL-138, and PDE4 inhibitors like apremilast, are being investigated based on highly specific mechanistic hypotheses derived from an advanced understanding of addiction neurobiology, although current evidence is largely preclinical.⁸

Despite these differences, there are areas of mechanistic overlap. Both certain herbal interventions (e.g., ashwagandha, passionflower) and various pharmacological compounds (e.g., baclofen, gabapentin, topiramate, and potentially apremilast through its effects on amygdala GABA) appear to converge on modulating GABAergic and/or glutamatergic neurotransmission, or on ameliorating stress and neuroinflammation. This convergence suggests that these pathways are critical and accessible targets for a range of therapeutic modalities aimed at reducing alcohol urge and consumption.

B. Identifying Critical Gaps in Current Research (2014-2025)

Despite progress, several critical gaps remain in the research landscape concerning interventions for alcohol urge and binge drinking.

- **Rigorous Human Clinical Trials for Herbal Interventions:** While kudzu has some human data, including a recent meta-analysis and an ongoing trial¹⁵, there is a pressing need for more large-scale, methodologically robust RCTs to definitively confirm the efficacy and further elucidate the mechanisms of action for most promising herbal candidates in reducing alcohol urge and binge drinking. This is particularly true for herbs like ashwagandha and passionflower, whose potential in AUD is largely inferred from their anxiolytic properties or preclinical data rather than direct, AUD-specific clinical trials with craving or bingeing as primary endpoints. The 2019 Cochrane review on kudzu explicitly called for larger, better-designed studies.¹⁵
- **Translation of Novel Pharmacological Compounds:** Many of the most exciting novel pharmacological compounds, including KOP antagonists (LY2444296), NOP modulators (PPL-138), and repurposed drugs like apremilast (PDE4 inhibitor), are still in preclinical stages of development or very early human trials.⁸ The

successful translation of these promising preclinical findings into safe and effective treatments for humans represents a significant hurdle and a critical next step.

- **Direct Targeting of Binge Drinking Neurobiology and Behavior:** While many interventions aim to reduce overall alcohol consumption or promote abstinence, fewer studies are specifically designed to assess efficacy in the context of *binge drinking patterns*. Binge drinking may have unique neurobiological underpinnings, such as the pronounced impairment in inhibitory control noted in some individuals.¹ The Penetar et al. (2015) study on kudzu's effect in a binge paradigm is an example of targeted research in this area¹⁴, but more such studies are needed.
- **Understanding and Addressing "Urge" Heterogeneity:** The subjective experience of "urge" or craving is complex and can be driven by different underlying motivations: the pursuit of positive reinforcement (reward craving), the desire to alleviate negative emotional states or withdrawal symptoms (relief craving), or conditioned responses to environmental cues (cue-induced craving). Current research often does not sufficiently differentiate these subtypes of craving, yet the optimal therapeutic approach might vary depending on the predominant driver. The ON-ICE trial, investigating combined oxytocin and naltrexone for stress- and cue-induced craving, is a positive step in this direction.⁸
- **Long-term Efficacy and Safety Data:** For many interventions, particularly newer pharmacological compounds and most herbal remedies, comprehensive data on long-term efficacy (extending over months to years) and safety are limited. For example, even for St. John's Wort, long-term efficacy and safety data for its primary indication (depression) were noted as limited in a 2017 review.²⁸
- **Standardization and Quality Control of Herbal Products:** A persistent challenge in research involving herbal medicines is ensuring the consistency of active compounds and overall quality of the extracts used across different studies and in clinical practice. Lack of standardization can lead to variable results and make it difficult to draw firm conclusions about efficacy.

C. Future Research Directions

Addressing the existing gaps requires focused and innovative research efforts. Key future directions include:

- **Mechanism-Driven Clinical Trials:** Designing and conducting clinical trials for both herbal and pharmacological interventions based on clearly defined neurobiological targets and mechanisms of action that have been identified

through robust preclinical research (e.g., targeting the KOP system, NOP system, PDE4 pathways, or specific GABA/glutamate receptor subtypes).

- **Advancing Personalized/Precision Medicine:** Identifying and validating biomarkers—which could be genetic, neuroimaging-based (e.g., fMRI studies of cue reactivity ²), or based on clinical phenotypes (e.g., stress reactivity, craving subtypes)—to predict which patients are most likely to respond favorably to specific interventions. This aligns with NIAAA's strategic priorities, including a focus on precision medicine for AUD.⁴¹ For instance, individuals with high stress reactivity might derive greater benefit from CRF antagonists, KOP antagonists, or stress-reducing herbs like ashwagandha.
- **Investigating Combination Therapies:** Exploring the potential synergistic effects of combining different pharmacological agents (e.g., the ongoing oxytocin plus naltrexone trial ⁸), combining pharmacological agents with herbal extracts, or integrating these interventions with psychotherapies (e.g., psilocybin-assisted psychotherapy ³⁴). Preclinical work (pre-2014) had suggested potential synergy between St. John's Wort and naltrexone.²⁷
- **Focusing on Binge-Specific Endpoints and Models:** Developing and utilizing outcome measures and experimental paradigms (both preclinical and clinical) that specifically capture changes in binge drinking behavior, associated urge patterns, and underlying neurobiology, such as deficits in inhibitory control.
- **Elucidating the "Entourage Effect" of Herbal Medicines:** For multi-component herbal remedies, conducting research to understand whether the combined action of various phytochemicals (the "entourage effect") offers therapeutic advantages over isolated active compounds. This requires sophisticated analytical and pharmacological approaches.
- **Addressing the Alcohol Treatment Gap:** Actively working to develop and disseminate treatments that are not only effective but also more appealing and accessible to a broader range of individuals with AUD. This includes considering patient preferences, which may involve an interest in herbal supplements if their efficacy and safety are rigorously established.¹⁸

D. Insights, Hidden Connections, and Implications for Section V

The current research landscape in AUD treatment reflects a dynamic interplay between refining existing approaches and exploring entirely novel ones. There is a robust effort to better understand and optimize the use of established and off-label pharmaceutical agents through large-scale systematic reviews and meta-analyses, such as the 2023 review by Jonas et al..³⁵ Concurrently, there is a significant push at the preclinical frontier, with innovative research into new molecular targets like the KOP, NOP, and PDE4 systems, yielding promising results in animal models.⁸ In contrast,

while some herbal interventions like kudzu have plausible mechanisms and some supportive human data, the overall body of large-scale, rigorous human clinical trial evidence specifically for AUD urge and binge outcomes within the 2014-2025 period appears less developed compared to the pharmaceutical pipeline. This suggests a critical need to elevate the methodological rigor and scale of clinical research for the most promising herbal candidates if they are to transition into evidence-based treatment options.

A prominent and recurring theme across both herbal and pharmacological research is the increasing recognition of the importance of targeting stress, negative affect, and neuroinflammation, in addition to the traditional focus on reward pathways. This is evident in the proposed mechanisms of action for promising herbs like ashwagandha (adaptogenic, anxiolytic)¹⁰ and passionflower (anxiolytic via GABA modulation)²³, as well as in the rationale behind developing novel compounds such as KOP antagonists (LY2444296, targeting stress-induced dysphoria)⁸, NOP modulators (PPL-138, for stress and anxiety)³⁸, and PDE4 inhibitors (apremilast, with anti-inflammatory actions and effects on amygdala GABA).³⁹ This focus aligns directly with the neurobiological understanding of the withdrawal/negative affect and preoccupation/anticipation stages of the addiction cycle, where negative emotional states and stress are powerful drivers of craving and relapse.³ This suggests a paradigm shift where alleviating the aversive aspects of AUD is becoming as critical a therapeutic goal as blocking the pleasurable effects of alcohol, particularly for certain patient populations or at specific stages of the disorder.

Finally, patient perspectives and preferences may play an increasingly important role in treatment development and adoption. Research indicating that specific populations, such as men who have sex with men (MSM) engaging in hazardous drinking, express considerable interest in using herbal supplements to reduce their alcohol consumption, highlights a potential avenue to help close the significant "treatment gap" in AUD.¹⁸ The perceived "naturalness" or different side effect profiles of herbal remedies might make them more acceptable to individuals who are hesitant to use conventional pharmaceuticals. However, this potential can only be realized if these herbal interventions are subjected to, and successfully pass, the same rigorous standards of efficacy and safety testing applied to pharmacological drugs. NIAAA funding opportunity announcements also emphasize the importance of making AUD treatments more appealing and accessible.⁴¹

VI. Concluding Remarks

A. Summary of Most Promising Interventions (2014-2025)

The period between 2014 and 2025 has witnessed continued investigation into both herbal and pharmacological approaches to mitigate alcohol urge and binge drinking, with varying levels of evidence supporting different interventions.

Among **herbal interventions**, kudzu has emerged with moderate, direct evidence from a 2019 systematic review suggesting it may reduce alcohol cravings and consumption, supported by a 2015 human trial in a binge drinking paradigm and ongoing research.¹⁴ Ashwagandha and passionflower show promise primarily through their anxiolytic and stress-reducing effects, which could indirectly reduce alcohol urge. This is supported by preclinical AUD models for ashwagandha²⁰ and human anxiolytic trials for both¹⁹, though direct, large-scale AUD trials focusing on urge as a primary outcome are still needed. Psilocybin, in conjunction with psychotherapy, has shown mixed but intriguing results in a recent Phase 2 trial for AUD relapse prevention, with a signal for craving reduction that warrants further exploration.³⁴

In the realm of **pharmacological compounds**, the FDA-approved medications oral naltrexone and acamprosate continue to be recognized as first-line therapies, with their efficacy in reducing drinking outcomes reaffirmed by recent comprehensive meta-analyses.³⁵ The off-label use of topiramate also shows moderate evidence for reducing various measures of alcohol consumption. The most exciting developments, however, lie in novel preclinical compounds targeting distinct neurobiological pathways. Kappa opioid receptor (KOP) antagonists such as LY2444296⁸, nociceptin receptor (NOP) modulators like PPL-138³⁸, and phosphodiesterase-4 (PDE4) inhibitors such as apremilast³⁹ offer innovative mechanistic approaches by focusing on stress, negative affect, and neuroinflammatory processes. These compounds have demonstrated significant potential in animal models to reduce alcohol intake and address withdrawal-related issues.

B. The Outlook for Developing Effective Treatments

The outlook for developing more effective treatments for alcoholic binge drinking and AUD is cautiously optimistic, fueled by significant advancements in understanding the complex neurobiology of addiction and the identification of novel therapeutic targets. The field is moving towards a more nuanced appreciation of the multifaceted nature of alcohol urge, recognizing that it is not a monolithic entity but rather a complex interplay of reward-seeking, relief from negative states, and conditioned responses.

Future success will likely depend on a multi-pronged strategy. This includes the continued refinement of existing treatments, the rigorous clinical development of promising novel compounds and evidence-based herbal interventions, and the exploration of combination therapies that may offer synergistic benefits. A critical

shift is the increasing focus on targeting stress and negative affect pathways, which complements traditional approaches aimed at the reward system. This holistic view acknowledges the powerful role of negative reinforcement in maintaining addictive behaviors.

The most significant challenge remains the translation of promising preclinical findings into safe and effective treatments for humans, particularly for the array of novel compounds and for herbal interventions seeking to establish a robust evidence base. Furthermore, the implementation of personalized or precision medicine approaches—tailoring treatments based on individual patient profiles, including genetic predispositions, neurobiological characteristics, the stage of their AUD, and the primary drivers of their urge to drink—holds substantial promise for improving outcomes. As research continues to unravel the intricacies of brain "urge" signals, the development of more targeted and effective interventions to lessen the desire for alcoholic binge drinking is an achievable and critical public health goal.

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