SYSTEMATIC REVIEW OPEN

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Modulating the endocannabinoid system in alcohol use disorder: A translational systematic review and meta-analysis of preclinical and human studies

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Alcohol use disorder (AUD) is a chronic condition with a staggering global burden and yet limited pharmacological treatments. Convergent evidence implicates the endocannabinoid system (ECS) as a potential therapeutic target due to its broad regulatory role across reward, stress, and affective processes. We conducted a systematic review and meta-analysis of 63 preclinical and human studies evaluating ECS modulators for AUD. Preclinical studies were synthesized by mechanism of action, and meta-analyses were conducted for cannabinoid receptor (CB-1R) antagonists and inverse agonists, CB-1R agonists, and cannabidiol (CBD). Human studies were narratively synthesized due to methodological heterogeneity. Preclinical data meta-analyses demonstrated that CB-1R inverse agonists (SMD = −1.21) and CBD (SMD = −0.70) reduced alcohol intake, while CB-1R agonists increased consumption (SMD = +0.66). Dose–response analyses identified non-linear effects for CB-1R inverse agonists and CBD. In contrast, human studies showed inconsistent and generally null effects, with limited studies examining newer ECS modulators beyond rimonabant or CBD. While preclinical evidence supports ECS modulation, particularly CB-1R antagonism and CBD, as promising strategies for reducing alcohol use behaviors, clinical translation has been limited by safety concerns, methodological inconsistencies, and under-investigation of novel compounds. Mechanistically informed trials of novel compounds, including next-generation CB-1R antagonists and CBD, are needed to bridge this translational gap and yield new treatments for AUD.

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INTRODUCTION

Alcohol use disorder (AUD) is characterized by compulsive alcohol consumption, diminished control over alcohol intake, and negative emotional states during withdrawal [1], leading to significant public health, social, and economic consequences. AUD is a prevalent and debilitating condition, affecting approximately 27.9 million adults in the United States alone in 2024 [2, 3].

Currently, there are only three U.S. Food and Drug Administration (FDA)-approved pharmacological treatments for AUD: naltrexone, acamprosate, and disulfiram. Each drug primarily targets a distinct aspect of AUD and demonstrates clinically meaningful benefits, though response varies substantially across patients [4–6]. Naltrexone reduces craving and heavy drinking but not withdrawal symptoms [7]. Acamprosate supports abstinence maintenance but is less effective for suppressing craving or reducing drinking behavior [7, 8]. Disulfiram relies heavily on patient adherence and does not address the core motivational or withdrawal-related symptoms of AUD [9]. Most importantly, treatment response is heterogeneous. These medications appear to benefit only a subset of patients, and population-level reductions in alcohol consumption remain modest [4, 10]. Together, the heterogeneity of response and the limited number of treatment options—with no new medication approved for AUD since acamprosate in 2004 —underscore the urgent need for more effective and personalized therapeutic strategies.

Emerging research suggests that the endocannabinoid system (ECS), which includes cannabinoid receptors (primarily CB-1 and CB-2), endogenous ligands such as 2-arachidonoylglycerol (2-AG) and anandamide (AEA), and metabolic enzymes, including fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) [11], may represent a therapeutic target for AUD. CB-1 receptors (CB-1R)—the most abundant G-protein coupled receptors in the brain [12]—function as presynaptic inhibitory modulator that dynamically regulate neurotransmitter release across limbic and cortical circuits [11].

Convergent evidence links ECS dysregulation to AUD: while endocannabinoid signaling boosts alcohol reward initially, chronic exposure induces adaptive changes—such as reduced CB-1R availability and lower FAAH levels during early abstinence—that correlate with consumption severity. Moreover, Cannabinoid Receptor 1 (CNR1)/FAAH polymorphisms are associated with AUD risk [13–20]. Because the ECS simultaneously modulates

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reward, stress, and affect circuits [21], all of which are disrupted in AUD, pharmacological interventions targeting the ECS could address multiple dimensions of the disorder.

Although interest in alternative treatments for AUD is growing, ECS-targeted strategies require rigorous translational evaluation to bridge preclinical findings and therapeutic applications. This review synthesizes evidence from both experimental preclinical models and human studies to evaluate the ECS as a potential therapeutic target for AUD. We examine how ECS modulators influence clinically relevant outcomes, such as alcohol consumption, abstinence duration, withdrawal symptoms, relapse risk, treatment retention, craving, and cue reactivity. This translational approach aims to optimize clinical trial design and guide the development of novel therapeutics by identifying ECS mechanisms with the greatest translational potential.

MATERIALS AND METHODS

This systematic review protocol was registered with PROSPERO (CRD42024593040) and adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [22].

Search strategy and information sources

We searched Ovid MEDLINE (PubMed), Embase, PsycINFO, Web of Science Core Collection, Scopus, and the Cochrane Library in September 2024 and updated it in July 2025. Reference lists of relevant articles and reviews were manually checked. Full search strategies are available in Supplementary eMethods.

Eligibility criteria

Preclinical studies were eligible if they were controlled laboratory experiments using animal models of alcohol-related behaviors with prior alcohol exposure and designed to assess alcohol preference or self-administration.

Human studies were eligible if they were either controlled trials or experimental studies involving adults (≥18 years), including healthy volunteers, heavy drinkers, or individuals diagnosed with AUD. Primary outcomes were alcohol consumption (amount, frequency), pharmacokinetic interactions, subjective effects, performance/behavioral effects, and physiological measures.

Study selection process

Search results were pooled in EndNote 21 and deduplicated using the Reference Deduplicator tool [23]. Two reviewers (G.C., M.C.M.) independently screened titles and abstracts. Similarly, full texts of potentially eligible studies were subsequently retrieved and assessed. Discrepancies at any stage were resolved through discussion with a third reviewer (J.D.A.). A list of reasons for exclusion at this stage is available in Supplementary Table S1.

Data extraction

Data extraction was performed by two independent reviewers (G.C., M.C.M.) using standardized, pre-piloted forms tailored separately for preclinical and human studies.

Data synthesis

Data synthesis was organized by cannabinoid mechanism of action, separating preclinical and clinical evidence.

Preclinical studies. For preclinical studies measuring alcohol intake proxies (voluntary drinking or operant responding), meta-analyses were conducted, allowing us to statistically pool results from multiple studies to estimate an overall effect. Studies were grouped by mechanism (CB-1R antagonists/inverse agonists, CB-1R agonists, CBD). We calculated the standardized mean difference (SMD), an effect size measure that expresses the magnitude of a treatment effect in standard deviation units, allowing comparison across studies using different scales, for each experiment and estimated pooled effects using random-effects models due to expected heterogeneity. Dose–response relationships for compounds tested at multiple doses were assessed using linear and non-linear (quadratic) meta-regression models. Heterogeneity was assessed using standard statistics (Cochran's Q, tau^2, and I^2). Detailed statistical procedures are provided in Supplementary eMethods.

Human studies. Quantitative meta-analysis of human studies was precluded by substantial heterogeneity in study design (e.g., laboratory-based administration, therapeutic trials, naturalistic observation), intervention type, dosing, administration route, population (from healthy volunteers to AUD), and outcome measures (pharmacokinetics, subjective effects, alcohol use metrics). The limited number of studies per specific intervention-outcome pairing further precluded quantitative synthesis. As such, clinical evidence was synthesized narratively, categorized by mechanism of action and structured around key outcome domains: pharmacokinetic effects, performance/behavioral outcomes, and subjective effects.

Quality assessment

For preclinical studies, we extracted key methodological details but did not apply formal risk-of-bias ratings due to the lack of a widely accepted tool applicable across heterogeneous animal models.

For human studies, risk of bias was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool for randomized controlled trials and the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I V2) [24] for observational [25] (Supplementary Table S2).

RESULTS

Our initial search in September 2024 yielded 7,879 potentially relevant records. An updated search in July 2025 identified an additional 963 records, of which 939 were unique and added to screening. One additional record [26] was identified through manual searching of recently published literature. After deduplication, a total of 4,002 unique records were screened for eligibility. Of these, 3,869 were deemed irrelevant based on title and abstract screening. The remaining 133 studies underwent full-text assessment, resulting in 63 studies meeting inclusion criteria for the review [7, 26–87], such that 44 were preclinical studies and 19 were human (Fig. 1).

Preclinical studies

All preclinical studies utilized rodent models (mice and rats) (n = 44) [7, 27–30, 35–37, 39–43, 45–49, 52–58, 60–70, 72, 74–77, 80, 81, 83]. Among them, CB-1R antagonists and inverse agonists were the most studied (n = 23) candidate intervention, primarily utilizing SR141716A (Rimonabant) (n = 16 studies), which acts as an inverse agonist at CB-1R [88]. Newer compounds including AM4113 (n = 2), AM6527 (n = 1), and SR147778 (n = 2) also featured in investigations. Other candidate interventions studied included: CB-1R agonists (n = 13 studies total), such as WIN 55,212-2 (n = 6) and CP55,940 (n = 3); Δ9-THC (n = 4 studies); CBD (n = 9 studies); and alternative cannabinoid modulators targeting FAAH, diacylglycerol lipase (DAGL), and CB-2 receptors (CB-2R) (n = 4 studies in this category) (Table 1)

CB-1R antagonists/inverse agonists. Twenty-three studies examined CB-1R antagonists/inverse agonists on alcohol intake and related behaviors in rodent models. Most experiments utilized SR141716A (Rimonabant) [29, 36, 37, 41, 55, 61, 67, 68, 70], while others employed newer compounds including the CB-1R neutral antagonists AM4113 [30, 40] and AM6527 [66], SR147778 [45, 53], and RTICBM-74 [58].

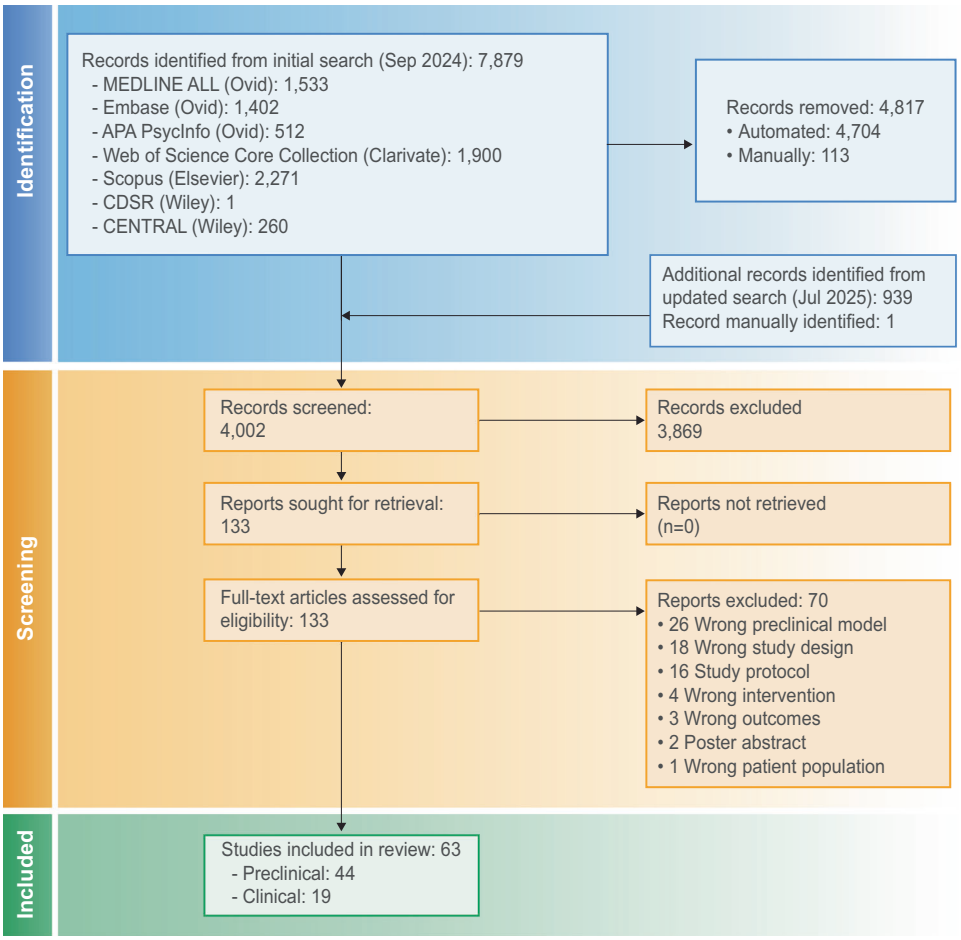

Fig. 1 PRISMA Flowchart illustrating the systematic search and selection process for studies included in this systematic review and meta-analysis. The flowchart details the number of records identified, screened, excluded, and included, along with reasons for exclusion at the full-text assessment stage.

Across 37 experiments in 13 studies, SR141716A significantly reduced alcohol intake (SMD = −1.21; 95% CI: −1.59 to −0.83, Fig. 2). A dose-response analysis (Supplementary Figure S1) indicated a non-linear (quadratic) relationship between SR141716A (Rimonabant) dose and effect size ($p = 0.002$), suggesting biphasic effects with potential optimal efficacy at intermediate doses (2-5 mg/kg).

CB-1R antagonists/inverse agonists consistently reduced voluntary alcohol intake in 20 of 23 studies (Table 1), with dose-dependent efficacy typically ranging from 30-60% reduction compared to vehicle treatment. One study observed complete abolition of the alcohol deprivation effect across all tested doses of SR141716A (0.3-3 mg/kg) [70]. Newer neutral CB-1R antagonists, such as AM4113 and AM6527, showed comparable efficacy to SR141716A while potentially avoiding adverse effects associated with inverse agonism [30, 66]. Specifically, two preclinical studies [30, 66] reported that these neutral antagonists did not induce nausea-related behaviors, depressive-like symptoms, or anxiogenic effects.

Beyond reducing alcohol intake, CB-1R antagonists mitigated motivational aspects of alcohol seeking, with several studies demonstrating reductions in cue-induced reinstatement of alcohol seeking [36, 39, 41], though effects on stress-induced reinstatement were less consistent [41].

CB-1R agonists. Studies investigating CB-1R agonists ($n = 13$) predominantly demonstrated facilitative effects on alcohol intake (Table 1). Our meta-analysis of nine experiments from five studies using the agonist WIN 55,212-2 showed a significant overall effect, indicating increased alcohol intake compared to controls (SMD = 0.66, 95% CI [0.30, 1.02]) (Fig. 3). Dose-response analysis (Supplementary Figure S2) suggested no significant dose-dependent effects ($p = 0.202$).

Among included studies, WIN 55,212-2 was shown to significantly increase alcohol relapse during deprivation periods [56, 57], with higher doses producing stronger and more persistent effects.

Some studies suggested potential dose-dependent biphasic effects. Low doses of WIN55,212-2 (0.5-1 mg/kg) increased alcohol intake while higher doses produced mixed effects [62]. Similarly, lower doses of CP 55,940 (10-50 µg/kg) increased alcohol-seeking during relapse and alcohol preference [46, 74], while higher doses sometimes decreased responding, potentially due to non-specific motor suppression. One study showed that CP55,940 (10, 30 and 50ug/kg doses) significantly increased motivation for beer intake, and this effect was reversed by CB-1R inverse agonist SR 141716 [42].

Delta-9-Tetrahydrocannabinol (Δ9-THC). Δ9-THC demonstrated distinct temporal effects compared to synthetic CB-1R agonists. Acute Δ9-THC administration reduced alcohol drinking dose-dependently (3-30 mg/kg), but intake increased significantly after cessation of Δ9-THC treatment [63], suggesting development of compensatory neuroadaptations following chronic cannabinoid exposure. Δ9-THC exacerbated the severity and prolonged the recovery period of alcohol withdrawal seizures [52]. It also increased alcohol preference on non-exposure days in a two-

Table 1. Preclinical studies examining the effects of cannabinoid modulators on alcohol-use related behaviors.

CB-1R Antagonists/Inverse Agonists					
Study	**Species/Strain**	**Compound (Dose)**	**Administration Method**	**Effect on Alcohol-Use Related Behaviors**	**Key Findings**
Serra 2002	Adult male Sardinian alcohol-preferring rats	SR141716A (Rimonabant) (0.3–3 mg/kg)	Two-bottle choice	Positive	All doses significantly suppressed alcohol deprivation effect; complete abolition of elevated intake in deprived rats; Significantly decreased food intake without any difference between alcohol-deprived and -nondeprived rats.
Colombo 1998	Adult male Sardinian alcohol-preferring rats	SR141716A (Rimonabant) (2.5–10 mg/kg)	Two-bottle choice	Positive	Dose-dependent reduction (35–50%) of voluntary alcohol intake; effect persisted throughout 4-hour sessions
Arnone 1997	Adult male C57BL/6 mice	SR141716A (Rimonabant) (0.1–3 mg/kg)	Two-bottle choice	Positive	Reduction in alcohol consumption at 0.3–3 mg/kg; no effect on water intake; Dose-dependently reduced sucrose intake and drinking and had no effect on water drinking.
Economidou 2006	Male Wistar rats (age unknown)	SR141716A (Rimonabant) (0.3–3 mg/kg)	Operant self-administration	Positive	Dose-dependent reduction in alcohol self-administration and seeking behaviors; reduced progressive ratio responding; reduced cue-induced but not stress-induced reinstatement; Significantly decreased sucrose self-administration but only modestly reduced NaCl self-administration at the highest dose.
Maccioni 2009	Adult male Sardinian alcohol-preferring rats	SR141716 (Rimonabant) (0–3 mg/kg)	Operant self-administration	Positive	Dose-dependent reduction in alcohol responses (~20–60%); increased latency to first alcohol response at the highest dose; Did not alter operant responding for water.
Gessa 2005	Adult male Sardinian alcohol-preferring rats	SR147778 (0.3–3 mg/kg)	Two-bottle choice and operant self-administration	Positive	In two-bottle choice test: Repeated administration suppressed acquisition of alcohol drinking in alcohol-naïve rats; acute administration reduced alcohol intake by 25–55% and all doses significantly suppressed alcohol deprivation effect in alcohol-experienced rats; In operant paradigm: Acute administration suppressed motivational properties of alcohol in extinction; Had no significant effect on water, food, or sucrose consummatory behaviors.
Raghav 2024	Adult male and female C57BL/6 J mice	AM6527 (1–10 mg/kg)	One bottle DID & two bottle choice IAA models and Operant self-administration	Positive	In DID: Dose-related reductions in alcohol intake in both sexes without sex differences; effects sustained with repeated administration of 3 mg/kg dose. In IAA: Dose-, sex-, time-dependent reductions at 2-h, 4-h, and 24-h post injections. In DID & IAA: significantly reduced alcohol withdrawal in males and non-statistical trend in‘ reduction in females In operant paradigm: Dose-related reduction in self-administration and alcohol intake; Increased water intake and but did not alter preference for sucrose or quinine.

Table 1. continued

CB-1R Antagonists/Inverse Agonists					
Study	**Species/Strain**	**Compound (Dose)**	**Administration Method**	**Effect on Alcohol-Use Related Behaviors**	**Key Findings**
Balla 2018	Adult male C57BL/6 J mice	AM4113 (1–3 mg/kg)	Two-bottle DID paradigm	Positive	Dose- and time-dependent reduction in binge-like alcohol consumption; reduced alcohol-induced dopamine release
Lovelock 2022	Adult male Wistar & adult male and female Long-Evans rats	RTICBM-74 (5–10 mg/kg), SR141716A (Rimonabant) (1–3 mg/kg)	Operant self-administration	Positive	Reduced alcohol self-administration across all doses
Rodriguez De Fonseca 1999	Male young adult Wistar rats	SR141716A (Rimonabant) (0–3 mg/kg)	Operant self-administration and alcohol vapor exposure	Positive	3 mg/kg decreased operant responses in alcohol-dependent but not non-dependent animals; Had no effect on operant responding for food or water in both ethanol dependent and nondependent rats.
Rubio 2008	Adult male Wistar rats	SR141716A (Rimonabant) (0.5 mg/kg)	Forced alcohol intake	Positive	Reduced anxiety in alcohol-abstinent rats; reversed GABA loss and reduced glutamate imbalances
Santos-Molina 2021	C57BL/6 J & Cnr1-/- mice (Age and sex unknown)	S-MRI-1867, SR141716A (Rimonabant), JD5037 (1–10 mg/kg)	Two-bottle choice & DID	Positive	Oral administration of compounds reduced alcohol drinking in wild-type but not CB-1R knockout mice; Did not affect total liquid consumption or food intake.
Cippitelli 2005	Young adult male Wistar & Sardinian alcohol-preferring rats	SR141716A (Rimonabant) (0.3–3 mg/kg)	Operant self-administration	Positive	Dose-dependent reduction in alcohol self-administration; greater sensitivity in alcohol-preferring rats; Reduced operant responding for sucrose but did not affect responding for food reinforcement.
Alvarez-Jaimes 2009	Young adult male Wistar rats	SR141716A (Rimonabant) (1–3 µg/side)	Operant self-administration	Positive	Intra-NAc and posterior VTA infusion dose-dependently reduced alcohol self-administration
Dulman 2021	Adult male C57BL/6 J mice	AM4113 (1 mg/kg)	Two-bottle choice	Positive	Significantly reduced alcohol consumption over three treatment days; showed anxiolytic effect
Malinen 2008	Adult male AA rats	SR141716A (Rimonabant) (1–10 mg/kg)	Operant self-administration	Positive	Dose-dependent reduction in alcohol intake when given systemic or intra-VTA but reduction in alcohol intake without dose relation when given intra-accumbal; effective at both systemic and direct brain injections; Intra-NAc, but not intra-VTA, microinjection reduced saccharin self-administration.
Vinod 2008	Adult male CB-1R wildtype and knockout mice (Congenic strain developed from C57BL/6 J & DBA/2 J intercrosses)	SR141716A (Rimonabant) (1–5 mg/kg)	Two-bottle choice	Positive	More alcohol-preferring in B6 background wildtype mice than D2 background wildtype mice; Reduced alcohol preference in knockout mice in both B6 and D2 backgrounds; SR141716A reduced alcohol preference both in B6 and D2 mice with a stronger effect in B6 mice than D2 mice
deBruin 2011	Adult male Wistar rats	SLV330 (1–10 mg/kg)	Operant self-administration	Positive	Reduced ethanol self-administration at 10 mg/kg and cue-induced reinstatement at 3 and 10 mg/kg doses
Getachew 2011	Adult female alcohol-preferring P rats	SR141716A (Rimonabant) (0.3–2 mg/kg)	Operant self-administration	Positive	Reduced alcohol-seeking behavior and decreased alcohol self-administration during relapse and maintenance;

Table 1. continued

CB-1R Antagonists/Inverse Agonists					
Study	**Species/Strain**	**Compound (Dose)**	**Administration Method**	**Effect on Alcohol-Use Related Behaviors**	**Key Findings**
					Responding for water was low and not significantly altered by treatment.
Lallemand 2001	Young adult male Wistar rats	SR141716A (Rimonabant) (1–10 mg/kg/day)	Two-bottle choice and forced drinking	Mixed	Effects dependent on timing of administration: When given *during* chronic alcohol exposure - increased alcohol preference; When given *after* chronic alcohol exposure or to alcohol-naïve rats - decreased alcohol preference at 3–10 mg/kg/day. This effect was dose dependent. 10 mg/kg decreased the withdrawal motility at the end of chronic ethanol treatment; Had no significant effect on water consumption or body weight.
Lallemand 2004	Adult male Wistar rats	SR141716A (Rimonabant) (3–10 mg/kg/day)	Chronic alcohol vapor inhalation and subsequent 1 day one-bottle forced drinking and chronic two-bottle choice	Mixed	No effect on subsequent alcohol preference after *short* rimonabant + alcohol vapor co-exposure; However, *prolonged* rimonabant + alcohol vapor co-exposure led to increased alcohol consumption in subsequent two-bottle choice testing (after discontinuation of both treatments), suggesting compensatory adaptation from extended CB-1R antagonism; Significantly reduced water consumption during the alcoholization period; the highest dose (10 mg/kg/day) also decreased sucrose consumption.
Lallemand 2006	Adult male Wistar rats	SR147778 (0.3–10 mg/kg/day)	Chronic alcohol vapor inhalation and subsequent 1 day one-bottle forced drinking and chronic two-bottle choice	Positive	Reduced alcohol preference when administrated at the cessation of chronic ethanol intoxication
Ginsburg 2006	Adult male Lewis rats	SR141716A (Rimonabant) (0.3–5.6 mg/kg)	Operant self-administration	Neutral	Did not significantly alter responding for alcohol alone; partially antagonized Δ9-THC's effects on responding for alcohol; Did not significantly alter responding for food.
CB-1R Agonists					
Study	**Species/Strain**	**Compound (Dose)**	**Administration Method**	**Effect on Alcohol-Use Related Behaviors**	**Key Findings**
Kralik 1976	Yale-Swiss mice	Δ9-THC (10 mg/kg)	Alcohol vapor chamber passive exposure	Negative	Exacerbated severity and prolonged recovery period of alcohol withdrawal seizures
McMillan 1991	Adult rats (unspecified strain)	Δ9-THC (3–30 mg/kg)	Operant self-administration	Mixed	Acute Δ9-THC reduced alcohol intake dose-dependently; Δ9-THC (10 mg/kg) treatment reduced alcohol intake initially but alcohol intake increased during chronic Δ9-THC treatment (tolerance development), after stopping Δ9-THC, alcohol intake increased more; Acute administration dose-dependently

Table 1. continued

CB-1R Agonists					
Study	**Species/Strain**	**Compound (Dose)**	**Administration Method**	**Effect on Alcohol-Use Related Behaviors**	**Key Findings**
					decreased food pellet consumption and slightly increased water intake.
Lopez-Moreno 2004	Adult male Wistar rats	WIN 55,212-2 (0.4–10 mg/kg)	Operant self-administration	Negative	Increased alcohol relapse after alcohol deprivation across all doses highest dose caused stronger increase
Alen, 2010	Adolescent male Wistar rats	WIN 55,212-2 (2 mg/kg)	Operant self-administration	Negative	Significantly increased alcohol consumption during relapse; reduced hippocampal neurogenesis; : Increased operant responding for saccharin when combined with saccharin deprivation periods.
Alen 2008	Adult male Wistar rats	WIN 55,212-2 (2 mg/kg)	Operant self-administration	Negative	Increased alcohol relapse; effect mediated by motivational/appetitive components
Alen 2009	Adult male Wistar rats	WIN 55,212-2 (2 mg/kg)	Operant self-administration	Negative	Increased alcohol relapse
Rubio 2008	Adult male Wistar rats	WIN 55,212-2 (1 mg/kg)	Forced alcohol intake	Negative	Failed to reduce anxiety in alcohol-abstinent rats
Gallate 1999	Adult male Wistar rats	CP55,940 (10–50 μg/kg)	Operant self-administration	Negative	Significantly increased motivation for beer consumption; effect blocked by CB-1R antagonist; Increased motivation (breakpoint) for sucrose solution and near-beer to a similar extent as for beer.
Hamidullah 2021	Adolescent Sprague-Dawley rats	THC (10 mg total)	Vapor passive exposure of Δ9-THC and subsequent two-bottle choice	Negative	No effect when Δ9-THC and alcohol are in use together; increased alcohol preference on no Δ9-THC vapor -exposure days; Had no effect on food intake, but when combined with alcohol, it led to decreased water intake on days of Δ9-THC abstinence.
Malinen 2008	Adult male AA rats	WIN55,212-2 (0.5–2 mg/kg)	Operant self-administration	Negative	Low doses (0.5–1 mg/kg) increased alcohol intake when given systemically but had no effect when injected intra-accumbal or intra-VTA; highest dose had mixed effects; Had no effect on saccharin responding.
Getachew 2011	Adult female alcohol-preferring P rats	CP 55,940 (1–30 μg/kg)	Operant self-administration	Mixed	Lower doses increased alcohol-seeking during relapse; highest dose decreased alcohol-seeking responding where it was even lower than vehicle; Did not significantly alter responding for water.
Vinod 2008	Adult male CB-1R wildtype and knockout mice (Congenic strain developed from C57BL/6 J & DBA/2 J intercrosses)	CP-55,940 (10–50 μg/kg)	Two-bottle choice	Negative	Increased alcohol preference dose dependently, with stronger effect in C57BL/6 J than DBA/2 J mice

Table 1. continued

CB-1R Agonists					
Study	**Species/Strain**	**Compound (Dose)**	**Administration Method**	**Effect on Alcohol-Use Related Behaviors**	**Key Findings**
Ginsburg 2006	Adult male Lewis rats	THC (1–5.6 mg/kg)	Operant self-administration	Positive	5.6 mg/kg significantly reduced responding for alcohol; Produced a similar, dose-dependent decrease in responding for food.
CBD (Cannabidiol)					
Study	**Species/Strain**	**Compound (Dose)**	**Administration Method**	**Effect on Alcohol-Use Related Behaviors**	**Key Findings**
Dirik 2025	Adult Wistar rats	CBD (30 & 60 mg/kg)	Chronic intermittent ethanol & ethanol vapor self-administration	Positive	60 mg/kg dose reduced alcohol self-administration, motivation, withdrawal signs, and stress-induced reinstatement. It reversed alcohol-induced decreases in BLA neuronal excitability and prevented neurodegeneration in the NAc shell and DMS. 30 mg/kg dose had no effect.
Viudez-Martinez 2018a	Adult male C57BL/6 J mice	CBD (20 mg/kg/day) + naltrexone	Operant self-administration	Positive	CBD,naltrexone, and their combination reduced alcohol intake at fixed ratio (FR) 1; at FR3, only their combination reduced alcohol intake; the combination also reduced seeking behavior; Had no effect on operant self-administration for water.
Viudez-Martinez 2018b	Adult male C57BL/6 J mice	CBD (30–120 mg/kg/day)	Two-bottle choice & operant self-administration	Positive	Reduced alcohol intake and preference across all doses in two-bottle choice; 30 mg/kg/day decreased self-administration, alcohol intake, and seeking behaviors
Viudez-Martinez 2020	Adult male and female C57BL/6 J mice	CBD (15–90 mg/kg)	DID	Positive	Acute CBD administration had no effects on alcohol intake; Repeated CBD (30–60 mg/kg) administration reduced intake in males only; 90 mg/kg effective in both sexes
Tringali 2023	Adolescent male Wistar rats	CBD (40 mg/kg)	IAA	Positive	Reduced alcohol intake and preference; increased corticosterone; Decreased sucrose preference but did not affect water consumption.
Gonzalez-Cuevas 2018	Male Wistar rats (age unknown)	CBD (15 mg/kg)	Operant self-administration	Positive	Reduced context-induced reinstatement; effects persisted up to 138 days; daily treatment during alcohol intoxication prevented the development of impulsivity for alcohol; Did not interfere with reinstatement of seeking for a palatable sweet solution.

Table 1. continued

CBD (Cannabidiol)					
Study	**Species/Strain**	**Compound (Dose)**	**Administration Method**	**Effect on Alcohol-Use Related Behaviors**	**Key Findings**
Maccioni 2022	Young adult male Sardinian alcohol-preferring rats & Wistar rats	CBD (6.25–100 mg/kg)	Operant self-administration	Positive	Reduced alcohol lever responses by ~45–55% in a dose fashion. Had no effect on responding for a highly palatable chocolate solution.
Gasparyan 2023	Male C57BL/6 J mice (Age is unknown)	CBD (10–40 mg/kg)	Oral gavage	Positive	40 mg/kg reduced anxiety-like behaviors during withdrawal
Melkumyan 2024	Adult male and female C57BL/6 J mice	CBD (10 mg/kg) & 3:1 CBD:THC	CIE vapor exposure	Mixed	CBD increased anxiety at 4 h withdrawal; 3:1 CBD:THC reduced anxiety at 24 h withdrawal
Other Cannabinoid Compounds					
Study	**Species/Strain**	**Compound (Dose)**	**Administration Method**	**Effect on Alcohol-Use Related Behaviors**	**Key Findings**
Zhou 2017	Adult male C57BL/6 J mice	URB597 (FAAH inhibitor) (0.125–1 mg/kg)	Two-bottle choice & IAA	Positive	Single acute administration reduced alcohol intake and preference in a dose-dependent manner. Repeated (0.5 mg/kg) administration showed similar effects. No sex differences were found; Did not affect sucrose intake but increased preference for saccharin.
Winters 2021	Adult male and female C57BL/6 J & DAGLA-/- mice	DO34 (DAGL inhibitor) (50 mg/kg)	Two-bottle choice & CIE vapor exposure	Positive	Both genetic and pharmacological inhibition of DAGL significantly decreased alcohol consumption and preference in continuous access model; pharmacological inhibition reduced alcohol consumption and preference aversion-resistant and CIE models; reduced reinstatement; No effect on sucrose preference.
Navarrete 2018	Adult male C57BL/6 J mice	AM630 (CB2 antagonist) & JWH133 (CB2 agonist) (1 mg/kg)	Oral self-administration	Positive	CB2 antagonist increased, CB2 agonist decreased alcohol consumption and reinforced responses
Cippitelli 2007	Male adolescent Wistar rats	AM404 (anandamide transport inhibitor) (0.4–10 mg/kg)	Operant self-administration	Positive	Dose-dependent decrease in alcohol self-administration; Did not modify operant responding for saccharin or alter food intake in food-deprived rats.

Studies are categorized by cannabinoid type and mechanism of action, detailing species/strain, specific compound, dosage, administration methods, observed effects on alcohol-use related outcomes, and key findings.

AA, Alko Alcohol; *CIE*, Chronic Intermittent Alcohol, *DAGL*, Diacylglycerol Lipase; *DID*, Drinking in the Dark, *FAAH*, Fatty Acid Amide Hydrolase, *IAA*, Intermittent Access to Alcohol. *LED*, Lowest Effective Dose; *msP*, Marchigian Sardinian Alcohol-Preferring; *NAc*, Nucleus Accumbens; *P*, Alcohol-Preferring; *PR*, Progressive Ratio; *sP*, Sardinian Alcohol-Preferring; *VTA*, Ventral Tegmental Area.

bottle choice paradigm [49]. At high doses (5.6 mg/kg), Δ9-THC significantly reduced responding for both food and alcohol [47], likely reflecting non-specific behavioral suppression rather than selective effects on alcohol reinforcement (Table 1).

Cannabidiol (CBD). Nine preclinical studies administrating CBD consistently demonstrated reductions in alcohol intake across various paradigms (Table 1). Our meta-analysis, which incorporated 20 experiments from seven studies, showed a significant overall effect of CBD on reducing alcohol intake (SMD = -0.70, 95% CI [−1.07, −0.34] (Fig. 4). Examination of the dose-response relationship (Supplementary Figure S3), including data from 11 unique doses, suggested a potential non-linear pattern ($p = 0.085$), following an inverted U-shaped curve with optimal efficacy at intermediate doses.

Dose-dependent reductions in alcohol intake, preference, and operant responding were observed at CBD doses ranging from 30-120 mg/kg [75–77], with specificity for alcohol versus water reinforcement as evidenced by reduced breaking points (i.e., the maximum reinforcement threshold at which effort expenditure is discontinued due to diminished reward valuation) specifically for alcohol.

CBD (15 mg/kg) significantly reduced context-induced reinstatement (the return of drug-seeking behavior triggered by environmental cues), with effects persisting up to 138 days post-treatment [48]. In addition, important data showed sex and dose related differences with male mice responding to moderate CBD doses (30-60 mg/kg), while females required higher doses (90 mg/kg) to achieve comparable reductions in binge-like drinking [76].

Other cannabinoid compounds. Several studies targeting alternative components of the endocannabinoid system yielded promising results. URB597, a FAAH inhibitor that increases the endogenous cannabinoid anandamide, reduced alcohol intake and preference by 40-60% through CB-1 R-dependent mechanisms [81]. DO34, a DAGL inhibitor reducing 2-arachidonoylglycerol synthesis, decreased intake in chronic alcohol use models and attenuated reinstatement [80].

CB-2R modulation produced bidirectional effects, with antagonism (AM630) increasing and agonism (JWH133) decreasing alcohol intake and reinforced responses [65]. The anandamide transport inhibitor AM404 (0.4-10 mg/kg) dose-dependently reduced alcohol self-administration in rats by up to 60% while preserving responding for natural rewards like saccharin responses [35]. Notably, this effect appeared independent of classical cannabinoid receptors, as CB-1R, CB-2R, and vanilloid receptor antagonists failed to block AM404's actions, suggesting a novel mechanism for selectively targeting alcohol reinforcement.

Human studies

Human studies (n = 19) employed varied methodological approaches including controlled laboratory administration paradigms in individuals without AUD and therapeutic trials in persons who drink heavily or individuals with AUD. Experimental designs ranged from acute placebo-controlled crossover administration studies to longitudinal interventions lasting up to 12 weeks. Interventions investigated included CB-1R inverse agonists (rimonabant, n = 2), Δ9-THC through various administration routes (n = 10), CBD at multiple dosages (n = 8), and limited exploration of minor cannabinoids like cannabinol (CBN) (n = 1) (Table 2).

CB-1R antagonists/inverse agonists. Two placebo-controlled clinical trials administered rimonabant (20 mg/day) to individuals who consume alcohol but found limited efficacy despite promising preclinical results. A 14-day double-blind, placebo-controlled design included persons with heavy alcohol use (n = 39), which were monitored via daily call-ins to report alcohol consumption and subsequently underwent a laboratory alcohol self-administration paradigm. Despite confirmed medication adherence through blood rimonabant levels, no significant differences were observed in alcohol consumption compared to placebo ($p = 0.17$), with similar rates of drinking days (5.7% vs. 6.0%) and drinks per drinking day (3.2 vs. 3.6) [44]. Similarly, a 12-week double-blind, placebo-controlled study among individuals recently completing alcohol detoxification (n = 258) found no significant differences between rimonabant and placebo in relapse to any drinking (41.5% vs. 47.7%) or heavy drinking episodes (27.7% vs. 35.6%, $p = 0.13$) [71]. Although safety was generally acceptable, the rimonabant group showed slightly higher rates of depression-related events compared to placebo (3.8% vs. 1.6%).

Δ9-THC. Ten human studies investigating Δ9-THC-alcohol interactions employed various methodological approaches, from controlled laboratory administration to naturalistic designs.

Experimental laboratory studies examining the interaction between cannabis and alcohol showed inconsistent findings regarding blood alcohol concentration. In one study [59] involving 15 healthy male volunteers consuming standardized alcohol doses (0.7 g/kg), cannabis smoking significantly reduced peak BAC by approximately 30% and delayed time to peak by 55 min. However, subsequent controlled investigations have produced mixed results. One study found no significant effect of oral cannabinoids on BAC [32], while others reported contradictory outcomes [33, 34] also reported contradictory findings—with Δ9-THC co-administration either elevating BAC[33] or exerting no measurable effect.

Performance assessments consistently showed additive impairments when Δ9-THC and alcohol were combined. Multiple investigations documented significant deficits in psychomotor performance, standing steadiness ($p < 0.01$), and manual dexterity ($p < 0.05$) [32, 33]. Verbal memory was particularly vulnerable to combined effects, with delayed recall showing strong impairment ($p < 0.001$) [79].

Studies of consumption patterns and subjective effects yielded mixed results. Laboratory investigations found that low-dose oral Δ9-THC (2.5 mg) reduced desire for alcohol [31], with a significant negative correlation between wanting alcohol and Δ9-THC ($r = -0.46$, $p = 0.02$) [78]. However, naturalistic studies found no evidence that Δ9-THC-dominant cannabis significantly altered alcohol consumption patterns [51] or cross-substance craving [73]. Further evidence emerged from a recent within-subject placebo-controlled randomized trial designed to assess acute cannabis effects on alcohol consumption among 138 heavy drinkers who used cannabis regularly [26]. Smoked cannabis (7.2% and 3.1% THC with trace CBD [< 0.22%]) acutely reduced alcohol self-administration relative to placebo in a dose-dependent manner: reductions of 27% ($p < 0.001$) and 19% ($p = 0.001$), respectively, as measured by percentage of total available alcohol consumed during a choice task. The 7.2% THC dose also increased latency to drinking initiation by 48% ($p = 0.005$). These behavioral effects occurred without consistent changes in craving measures, leading the authors to hypothesize that intoxication-related satiation—rather than craving suppression—may underlie the observed findings.

CBD. Eight human studies examining CBD effects on alcohol-use related outcomes revealed mixed results, with neuroimaging and psychophysiological measures showing more consistent effects than behavioral outcomes.

Recent neuroimaging evidence demonstrates CBD's impact on neural circuits underlying AUD. The ICONIC ("Investigation of the effects of Cannabidiol ON cue-InduCed alcohol craving and nucleus accumbens activation") trial first showed that 800 mg CBD significantly reduced nucleus accumbens activation to alcohol cues ($p < 0.001$) and attenuated craving in 28 adults with AUD [82]. A crossover RCT found that an acute 600 mg dose of CBD had no effect on neurometabolic markers, specifically

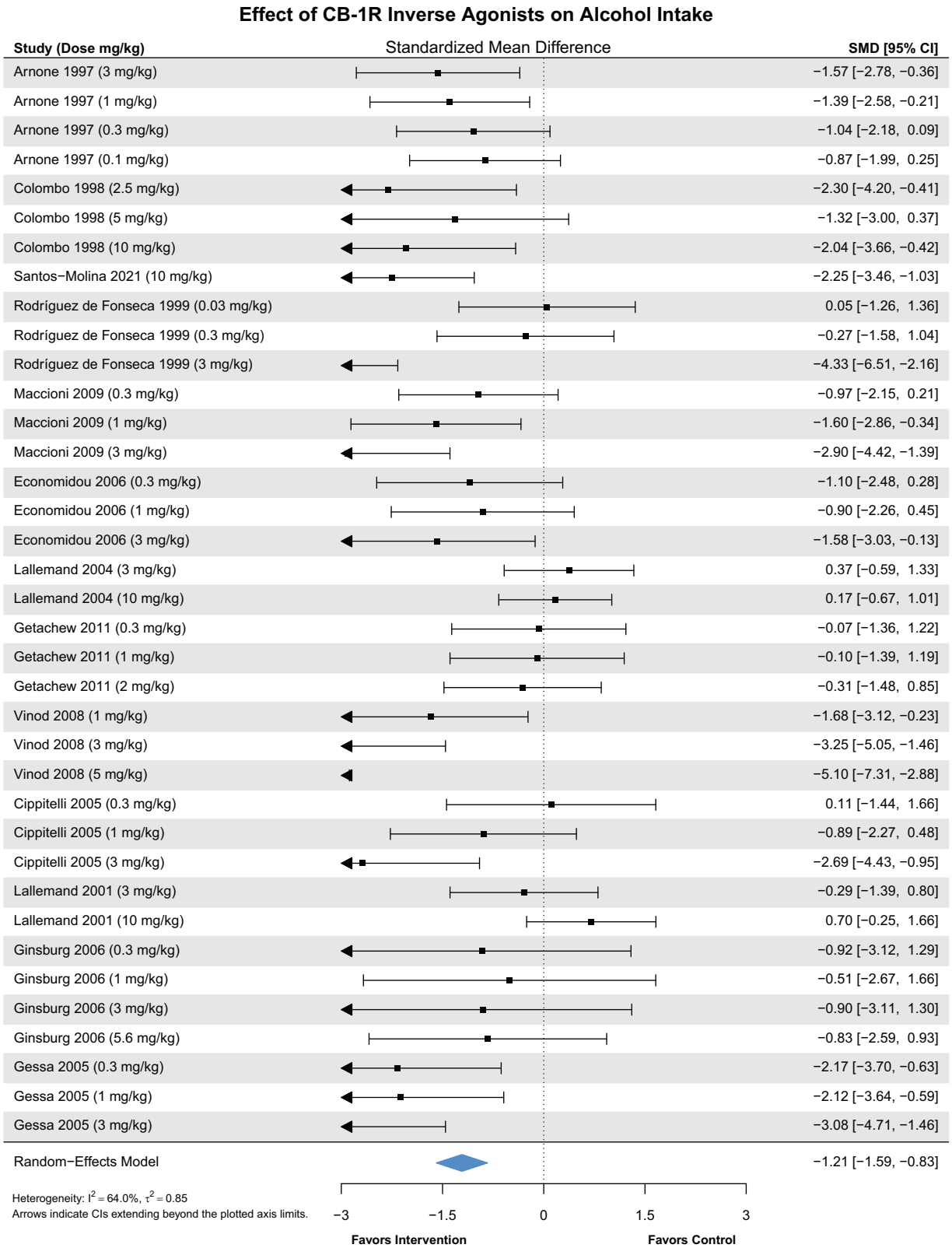

Fig. 2 Forest plot illustrating the effect of CB-1R inverse agonists, primarily SR141716A (Rimonabant), on alcohol intake in preclinical studies. It displays standardized mean differences (SMD) with 95% confidence intervals across 37 experiments. The overall pooled effect (SMD = −1.21, 95% CI [−1.59, −0.83]) shows a significant reduction in alcohol intake with CB-1R antagonist treatment compared to control conditions, with moderate heterogeneity ($I^2 = 64.0\%$).

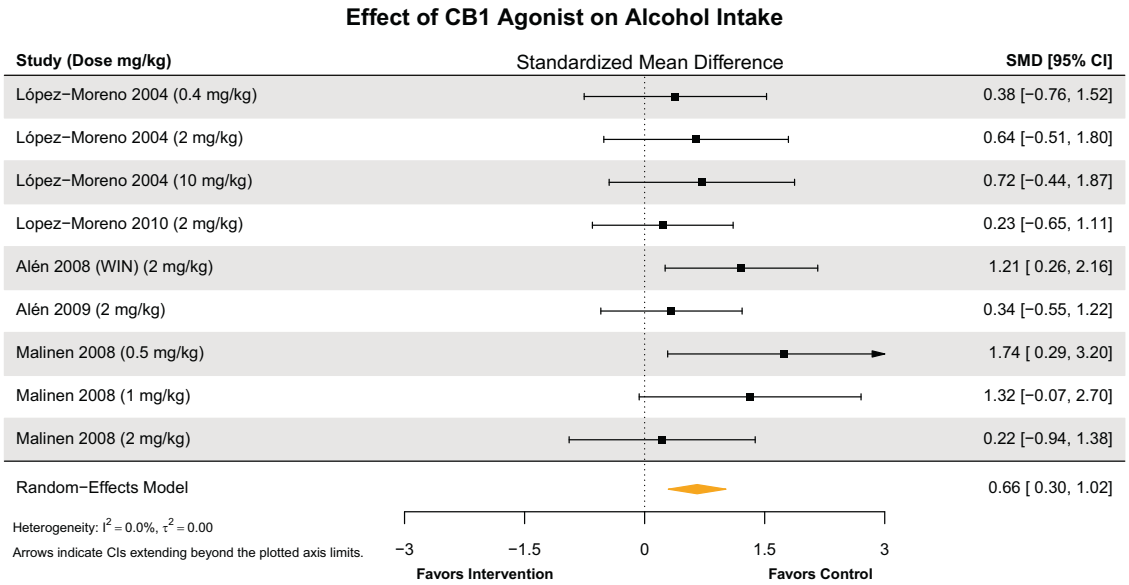

Fig. 3 Forest plot illustrating the effect of CB-1R agonists, primarily WIN 55,212-2, on alcohol intake in preclinical studies. It includes standardized mean differences (SMD) with 95% confidence intervals from 9 experiments testing various doses. The overall pooled effect (SMD = 0.66, 95% CI [0.30, 1.02]) indicates a significant increase in alcohol intake with CB-1R agonist treatment compared to control conditions, with no observed heterogeneity ($I^2 = 0.0\%$).

glutamate and glutamine (Glx) and GABA levels in the dorsal anterior cingulate cortex, or on cue-reactivity in 36 youth with AUD [85]. Another crossover trial found that 800 mg CBD for three days modulated precuneus activation in 18 individuals with AUD, though without affecting subjective craving [84]. This study also examined CBD's psychophysiological effects during alcohol cue exposure [86]. It demonstrated that CBD increased parasympathetic activity (elevated high-frequency heart rate variability) and reduced anxiety during cue exposure, while improving post-cue craving recovery without cognitive impairment [86]. These findings suggest CBD modulates both physiological and emotional responses to alcohol cues.

A preliminary clinical treatment study explored longer-term CBD administration with different formulations [87]. This 8-week RCT comparing full-spectrum CBD (containing <0.3% Δ9-THC), broad-spectrum CBD (Δ9-THC-free), and placebo in 44 individuals with moderate-severe AUD found that only full-spectrum CBD reduced craving at weeks 8 and 16 ($p < 0.001$), though drinks per drinking day remained unchanged [87]. Similarly, a 5-day naturalistic study of 120 cannabis-alcohol co-users found that CBD-dominant cannabis (23% CBD, 1% Δ9-THC) significantly reduced drinks per day (-40%), drinking days, and co-use days compared to Δ9-THC-dominant or balanced CBD/Δ9-THC strains [51]. These findings suggest CBD's therapeutic effects may be enhanced by minimal Δ9-THC content.

Earlier acute administration studies yielded inconsistent pharmacokinetic findings. While one crossover study reported that 200 mg CBD reduced blood alcohol levels (0.85 vs 0.95 g/l) without affecting psychomotor impairment in 10 healthy volunteers [38], another study in 36 heavy drinkers found no effect of 30 mg or 200 mg CBD on blood alcohol or subjective intoxication [50].

Collectively, these studies suggest CBD's therapeutic potential in AUD may be mediated through neural and autonomic modulation rather than alcohol pharmacokinetic interactions. The most consistent effects emerged with higher doses (600-800 mg) and longer administration periods. All studies reported excellent safety profiles with no serious adverse events.

Other cannabinoid compounds. Limited evidence exists for other cannabinoids, with one study examining the effects of CBN in a counterbalanced, double-dummy design with 15 healthy volunteers [32]. This methodology, which systematically varied treatment sequence while maintaining blinding through matched placebos for each active substance, found no significant effects of CBN on alcohol-use related performance measures compared to alcohol alone across multiple psychomotor assessments, including standing steadiness, reaction time, and pursuit rotor performance.

DISCUSSION

This translational systematic review and meta-analysis synthesizes preclinical and human evidence on cannabinoid system modulators for AUD, identifying mechanistic insights, translational gaps, and future pharmacotherapeutic opportunities. Preclinical data robustly demonstrates that ECS modulation, particularly through CB-1R inverse agonism and CBD, effectively reduces alcohol use behaviors in animal models. Meta-analytical findings quantified these effects, with large reductions in alcohol intake observed for CB-1R inverse agonists (SMD = −1.21), moderate increases with CB-1R agonists (SMD = 0.66), and moderate-to-large reductions for CBD (SMD = −0.70). However, human findings have yet to translate these results, emphasizing critical barriers that must be addressed to advance therapeutic development.

Preclinical evidence: Mechanistic insights

Preclinical studies provided robust evidence for the therapeutic potential of ECS modulation in AUD. Most notably, across diverse animal models, CB-1R antagonists and inverse agonists consistently reduced alcohol intake, operant responding, and relapse-like behaviors [41, 70]. The mechanisms underlying the efficacy of CB-1R antagonists/inverse agonists involve disruption of mesolimbic dopamine signaling: CB-1Rs located on GABAergic interneurons in the ventral tegmental area (VTA) normally disinhibit dopamine neurons upon endocannabinoid release, thereby facilitating reward signaling [89]. By blocking this pathway, CB-1R inverse agonists attenuate alcohol-induced dopamine release and reduce the reinforcing properties of alcohol [83, 84, 90]. Consistent with this, direct administration of CB-1R inverse agonist into the VTA reduced sign tracking in appetitive behavior [91]. Conversely, CB-1R agonists increased alcohol seeking, reinforcing

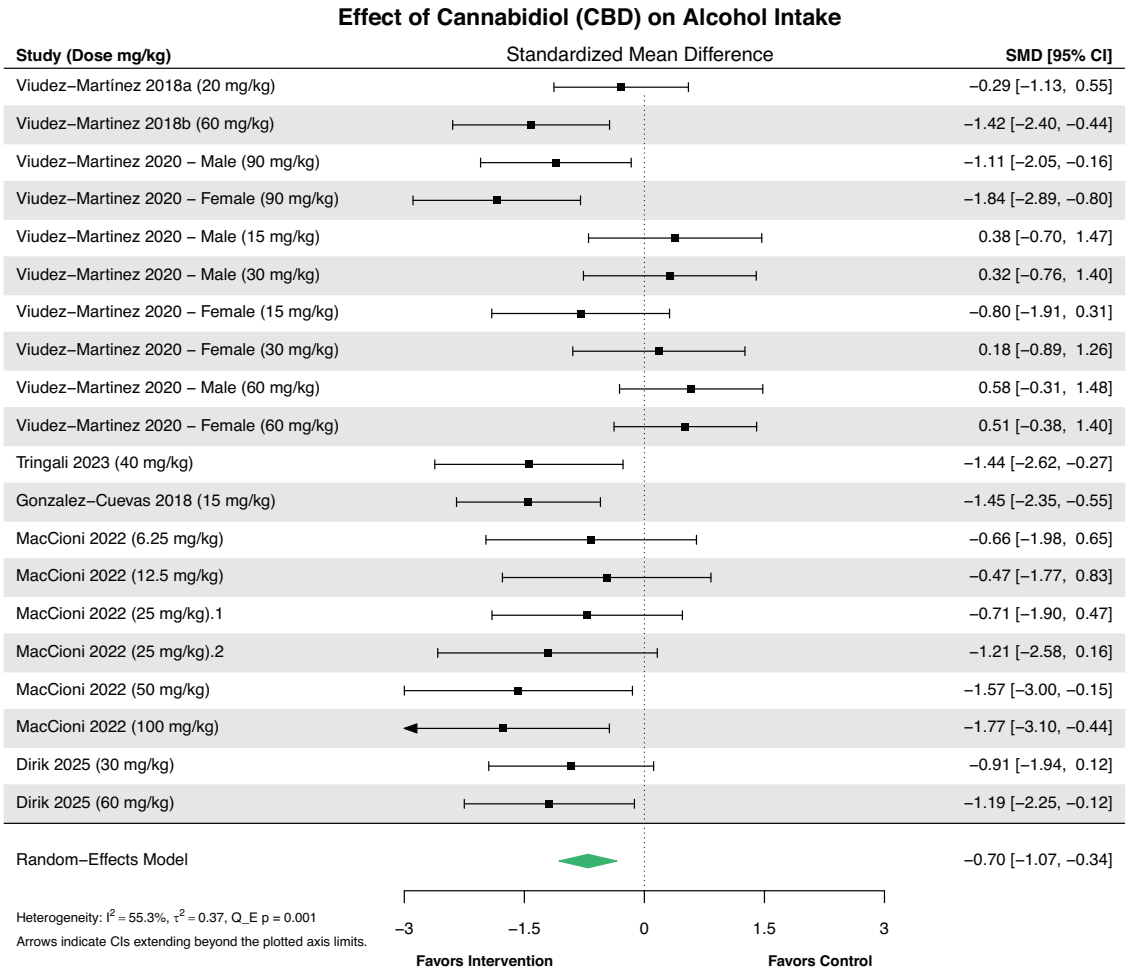

Fig. 4 Forest plot illustrating the effect of cannabidiol (CBD) on alcohol intake in preclinical studies. It presents standardized mean differences (SMD) with 95% confidence intervals from 20 experiments testing various doses across multiple studies. The overall pooled effect (SMD = −0.70, 95% CI [−1.07, −0.34]) shows a significant reduction in alcohol intake with CBD treatment compared to control conditions, with moderate heterogeneity (I^2 = 55.3%).

the role of the ECS in modulating alcohol reward [36, 41, 67, 70]. CBD demonstrated efficacy in reducing alcohol consumption and reinstatement behaviors, while attenuating withdrawal-induced anxiety and preventing reinstatement of alcohol-seeking behaviors for up to 138 days post-treatment [43, 48, 60, 76]. CBD demonstrates a pleiotropic pharmacological profile [92]. Proposed mechanisms include negative allosteric modulation of CB-1R, agonism at serotonin 5-HT1A receptors, modulation of dopaminergic and glutamatergic transmission, and activation of transient receptor potential vanilloid 1 (TRPV1) channels [93–96]. This diverse receptor profile may explain CBD's potential anxiolytic and anti-relapse properties observed in preclinical AUD models. However, sex-specific findings were underreported, with only one study noting dose-related differences between males and females [76].

Translational gaps: Bridging preclinical promise and clinical outcomes

Despite compelling preclinical evidence and strong construct validity (e.g., neurobiological rationale), successful clinical application of endocannabinoid modulators for AUD has proven challenging, revealing significant limitations in face validity (e.g. the extent to which animal models resemble the human condition), and predictive validity (e.g. their capacity to forecast clinical efficacy) [97, 98]. This translational gap arises from multiple factors. Species-specific differences in CB-1R density, regional distribution, endocannabinoid tone, and receptor signaling efficiency may alter dose-response relationships and diminish predictive validity across species [99–101]. Although animal models have been invaluable for delineating mechanisms, they cannot fully capture the psychosocial complexity of human AUD, and experimental designs often differ between preclinical and clinical paradigms. The paucity of clinical investigations further limits translational conclusions: only two placebo-controlled trials have examined rimonabant [44, 71], and CBD investigations in AUD populations remain preliminary [85, 86].

Clinical trials administrating 20 mg of rimonabant to individuals with AUD failed to demonstrate efficacy in reducing alcohol consumption, despite achieving plasma drug concentrations [44, 71]. This limited efficacy likely reflects suboptimal target engagement, as the 20 mg clinical dose achieved only partial CB-1R occupancy [102], whereas effective preclinical studies often achieved near-complete blockade. However, higher doses to improve receptor engagement are impractical, given that the current dose has been associated with serious psychiatric adverse effects, including depression and suicidality [103]. Mechanistically, these adverse effects likely stem from rimonabant's pharmacological profile as an inverse agonist, rather than a neutral antagonist. Unlike neutral antagonists that simply block receptor activation by endocannabinoids, inverse agonists suppress the constitutive (ligand-independent) activity of CB-1R [104–106]. Because tonic endocannabinoid signaling plays a critical role in regulating mood,

Table 2. Clinical studies assessing cannabinoid interventions for alcohol use disorder and related outcomes.

CB-1R Antagonists/Inverse Agonists							
Study	**Study Design**	**Sample**	**Intervention**	**Pharmacokinetic Effects**	**Performance/ Behavioral Effects**	**Subjective Effects**	**Overall Effect on Alcohol-Use Related Behaviors**
George et al. [44]	Laboratory + naturalistic; 14-day treatment trial; measured alcohol consumption; no alcohol administration	39 heavy drinkers (31 M/8 F)	Rimonabant 20 mg/day for 14 days	Rimonabant blood levels (138–350 ng/ml) confirmed adherence	No effect on laboratory drinking task or daily drinking: - Treatment effect: $F(1,37) = 1.98$, $p = 0.17$ - Drinking unchanged: 4.9 ± 0.5 drinks/day	No significant changes in: - Alcohol urge questionnaire - BAES stimulant effects - BAES sedative effects	Neutral
Soyka et al. [71]	Outpatient clinical trial; 12-week treatment; measured alcohol consumption; no alcohol administration	258 individuals with AUD who recently completed alcohol detoxification	Rimonabant 20 mg/day for 12 weeks	GGT and CDT changes non-significant vs placebo	Non-significant reduction in: - Relapse to any drinking (41.5% vs 47.7%) - Heavy drinking relapse (27.7% vs 35.6%, $p = 0.13$) - Drinking days (5.7% vs 6.0%)	No difference in alcohol craving (OCDS scores)	Neutral (slight positive trend)
THC							
Study	**Study Design**	**Sample**	**Intervention**	**Pharmacokinetic Effects**	**Performance/ Behavioral Effects**	**Subjective Effects**	**Overall Effect on Alcohol-Use Related Behaviors**
Metrik et al. [26]	Laboratory; double-blind crossover RCT; alcohol choice task; within-subjects design	138 heavy drinkers with twice-weekly cannabis use (mean age 25.6; 35% female; 76% cannabis use disorder; 43% AUD)	Smoked cannabis (7.2% THC, 3.1% THC, or 0.03% placebo) following overnight abstinence	Peak plasma THC: 167.82 ng/mL (7.2%) vs 106.31 ng/mL (3.1%); significant dose separation ($p < 0.001$)	Significant reductions in alcohol consumption: 3.1% THC: −19% ($B = -6.73$, $p = 0.001$); 7.2% THC: −27% ($B = -9.64$, $p < 0.001$); 7.2% THC increased latency to drink by 48% ($p = 0.005$)	7.2% THC reduced alcohol urge post-smoking ($p = 0.001$); No effect on ACQ-SF-R composite craving; Increased ARCI-M intoxication, heart rate, and arousal	Positive (significant reduction in alcohol consumption)
Lukas et al. [59]	Laboratory; controlled acute administration; experimental; blood sampling	15 male casual users	Smoked cannabis (0.004%, 1.26%, or 2.53% Δ9-THC) + alcohol (0.7 g/kg)	High-dose cannabis reduced peak alcohol levels by ~30% Delayed time to peak by 55 min	No specific performance measures assessed; study focused on pharmacokinetics and subjective effects	Trend toward reduced duration of subjective alcohol effects [$F(2,11) = 3.6$, $p = .066$]	Positive (reduced alcohol bioavailability)
Chesher et al. [33]	Laboratory; controlled acute administration;	12 university student volunteers	THC 10 mg/70 kg (oral) + alcohol (0.54 g/kg)	THC+alcohol led to significantly higher blood	Significant impairments in: - Standing steadiness	POMS mood ratings showed increased	Negative (increased impairment)

Table 2. continued

THC							
Study	**Study Design**	**Sample**	**Intervention**	**Pharmacokinetic Effects**	**Performance/ Behavioral Effects**	**Subjective Effects**	**Overall Effect on Alcohol-Use Related Behaviors**
	experimental; crossover design			alcohol levels (73 ± 4 vs 63 ± 3 mg/100 ml)	($F = 5.080$, $p < 0.01$) - Manual dexterity ($F = 2.551$, $p < 0.05$) - Biphasic pattern with initial impairment, partial recovery, then return of deficits	depression with Δ9-THC vs alcohol ($t = 2.0$, $p < 0.05$)	
Chesher et al. [34]	Laboratory; controlled acute administration; experimental; crossover design	15 student volunteers	THC 15 mg/70 kg (oral) + alcohol (0.54 g/kg)	No significant difference in blood alcohol levels	Significant impairments in: - Standing steadiness ($F(3,36) = 7.878$, $p < 0.01$) - Numerical reasoning ($F(3,36) = 4.570$, $p < 0.05$) - AKTG test correct responses ($F(3,36) = 5.135$, $p < 0.01$)	Not reported	Negative (increased impairment)
Bird et al. [32]	Laboratory; controlled acute administration; experimental; factorial design	161 adults with alcohol and cannabis experience	THC 215 μg/kg (oral) + alcohol (0.54 g/kg)	No significant effect on blood alcohol levels	Significant impairments in: - General performance ($F[4,580] = 12.68$, $p < 0.0125$) - Reaction speed ($F[4,580] = 6.08$, $p < 0.0125$) - Standing steadiness ($F[4,580] = 14.46$, $p < 0.0125$)	Not primary focus	Negative (additive impairment)
Ballard et al. [31]	Laboratory; controlled acute administration; experimental; crossover design	11 healthy adults with limited cannabis experience	THC 2.5 mg (oral) + alcohol (0.1 g/kg and 0.2 g/kg)	0.1 g/kg: peaked 0.02% BAC 0.2 g/kg: peaked 0.04% BAC	Significant impairments in: - Digit Span working memory ($F2,9 = 4.48$, $p = 0.045$) - DSST psychomotor performance ($F1,10 = 5.27$, $p = 0.045$)	Drug liking increased ($F2,9 = 9.88$, $p = 0.005$) THC dampened desire for more alcohol ($F[2,9] = 4.11$, $p = 0.054$)	Positive (reduced alcohol desire)

Table 2. continued

Study	Study Design	Sample	Intervention	Pharmacokinetic Effects	Performance/ Behavioral Effects	Subjective Effects	Overall Effect on Alcohol-Use Related Behaviors
THC							
Wardle et al. [78]	Laboratory; controlled acute administration; experimental; crossover design	24 healthy social drinkers	THC 7.5 mg (oral) + alcohol (0.08 g/kg M or 0.7 g/kg F)	Not reported	Not directly assessed	Significant negative correlation between wanting alcohol and Δ9-THC ($r = -0.46$, $p = 0.02$) Alcohol produced strongest "feel drug" effects (58-point increase, $t(23) = 12.069$, $p < 0.001$)	Positive (negative correlation with alcohol desire)
Wickens et al. [79]	Laboratory; controlled acute administration; experimental; crossover design	28 young adult cannabis users	Smoked cannabis (12.5% Δ9-THC, ~94 mg) + alcohol (target BrAC 80 mg/dL)	Not reported	Significant impairments in: - Verbal recall ($F(3,81) = 7.86$, $p < 0.001$, $\eta p^2 = 0.23$) - Delayed recall ($F(3,81) = 22.95$, $p < 0.001$, $\eta p^2 = 0.46$) - DSST trials attempted ($F(3,81) = 8.37$, $p < 0.001$, $\eta p^2 = 0.24$)	Combined condition effects: - Increased confusion ($F(3,81) = 6.94$, $p < 0.001$, $\eta p^2 = 0.21$) - Increased euphoria ($F(3,81) = 3.91$, $p = 0.012$, $\eta p^2 = 0.13$)	Negative (additive impairment)
Karoly et al. [51]	Naturalistic; 5-day observation; self-administration; no controlled dosing	120 cannabis and alcohol co-users	THC Group: ~24% Δ9-THC + ~1% CBD (ad libitum for 5 days)	Blood Δ9-THC levels: 6.2 ± 0.6 ng/mL Blood CBD levels: 0.5 ± 0.2 ng/mL	THC-dominant cannabis users maintained baseline alcohol consumption levels (no significant change)	Not primary focus	Neutral (no effect on alcohol consumption)
Venegas et al. [73]	Laboratory; controlled acute administration; experimental; crossover design	30 co-users	Cannabis cigarette (18–22% Δ9-THC, 0.25 g) + one standard drink	Not reported	No evidence that consuming one substance increases craving for the other substance	Alcohol increased alcohol craving by 22.7% ($t(58) = -2.48$, $p = 0.02$) Cannabis did not affect craving for either substance	Neutral (no cross-substance effects)
CBD							

Table 2. continued

CBD							
Study	**Study Design**	**Sample**	**Intervention**	**Pharmacokinetic Effects**	**Performance/ Behavioral Effects**	**Subjective Effects**	**Overall Effect on Alcohol-Use Related Behaviors**
Study	Study Design	Sample	Intervention	Pharmacokinetic Effects	Performance/ Behavioral Effects	Subjective Effects	Overall Effect on Alcohol-Use Related Behaviors
	Zimmermann et al. (2024)	Double-blind RCT; acute administration with fMRI	28 individuals with AUD	CBD 800 mg (single dose)	Mean CBD plasma: 256.76 ng/ml (CBD group) vs 0.41 ng/ml (PLC)	Reduced bilateral NAc activation during alcohol cues ($d = 1.13–1.15$); No effect on neutral cue NAc activation	Reduced craving after stress/cue exposure ($eta^2=0.15$) and during fMRI ($eta^2=0.23$); Negative correlation between CBD levels and craving
Positive (reduced NAc activation and craving)							
Kirkland et al. [85]	Double-blind, placebo-controlled, crossover RCT; acute administration with neuroimaging	36 youth with AUD	CBD 600 mg (single dose)	Not measured	No effects on ACC neurometabolites (Glx, GABA); No neural cue-reactivity changes; No psychophysiological responses (HRV, SCR)	No change in acute alcohol craving (AUQ); Alcohol cues increased craving regardless of treatment	Neutral (no effects across all measures)
Mueller et al. [87]	Double-blind, parallel-group RCT	44 individuals with moderate-severe AUD	150 mg/day of full-spectrum CBD (fsCBD), broad-spectrum CBD (bsCBD), or placebo; 8-week duration	CBD-COOH and Δ9-THC-COOH levels confirmed compliance; No pharmacokinetic data reported	No reduction in drinks per drinking day; Reduced AUDIT scores for fsCBD (week 4–16, $p = 0.017$); Reduced ICS-FC scores for fsCBD	fsCBD reduced PACS craving at weeks 8 & 16 ($p < 0.001$); bsCBD showed no craving effects; 37% correctly guessed treatment	Positive for fsCBD only (reduced craving and AUD symptoms)
Hurzeler et al. (2024)	Double-blind, placebo-controlled, crossover RCT	22 non-treatment seeking individuals with AUD	CBD 800 mg/day; 3 days	Not reported	Increased HF-HRV across cue task (elevated parasympathetic activity); No impairment on BART, CCT, TMT tasks	Reduced anxiety during cue exposure ($p < 0.027$); Improved craving recovery post-cue ($p = 0.004$); Higher baseline AUQ scores in CBD sessions	Positive (improved physiological regulation and cue recovery)
Hurzeler et al. (2025)	Same study as Hurzeler et al. (2024)	Same study as Hurzeler et al. (2024)	Same study as Hurzeler et al. (2024)	Not reported	Modulated precuneus activation to non-specific cues; No impairment in executive function	No significant change in subjective craving; No change in positive/negative affect (PANAS)	Mixed (neural changes without subjective improvements)

Table 2. continued

CBD							
Study	**Study Design**	**Sample**	**Intervention**	**Pharmacokinetic Effects**	**Performance/ Behavioral Effects**	**Subjective Effects**	**Overall Effect on Alcohol-Use Related Behaviors**
Consroe et al. [38]	Laboratory; controlled acute administration; experimental; crossover design	10 post-graduate student volunteers	CBD 200 mg (oral) + alcohol (1 g/kg)	CBD reduced blood alcohol levels (0.85 g/l vs 0.95 g/l) Significant reductions at 30, 60, and 120 min ($p < 0.05$)	Significant impairments in: - Finger tapping ($F = 3.34$, df=3,27, $p < 0.05$) - Cancellation test correct responses ($F = 3.4$, df=3,27, $p < 0.05$) - Error rates ($F = 3.01$, df=3,27, $p < 0.05$)	Both alcohol conditions increased: - Drunk/drugged feelings - Drowsiness - Dizziness No difference between alcohol alone vs. CBD +alcohol	Positive (reduced BAC) but Neutral (no change in impairment)
Karoly et al. [50]	Laboratory; controlled acute administration; experimental; crossover design	36 individuals with heavy alcohol drinking	30 mg or 200 mg CBD (oral) + alcohol (0.6 g/kg)	Peak blood CBD levels: - 200 mg CBD: 96.39 ng/ml - 30 mg CBD: 8.19 ng/ml CBD slowed alcohol level reductions compared to placebo	Not reported	Modest effects: - 200 mg CBD slowed reduction in stimulation - 30 mg CBD slowed reduction in sedation Effects were small magnitude with overlapping confidence intervals	Neutral (minor effects on alcohol pharmacokinetics)
Karoly et al. [51]	Naturalistic; 5-day observation; self-administration; no controlled dosing	120 cannabis and alcohol co-users	CBD Group: ~23% CBD + ~1% Δ9-THC (ad libitum for 5 days)	Blood CBD levels: 2.1 ± 0.4 ng/mL Blood Δ9-THC levels: 3.5 ± 0.9 ng/mL	Significant reductions in: - Drinks per day (−40%, 2.3 to 1.4, $\beta = 0.180$, $p = 0.031$) - Drinking days (−8%, 33% to 25%, $\beta = 0.141$, $p = 0.035$) - Co-use days (−8%, 29% to 21%, $\beta = 0.145$, $p = 0.035$)	Not primary focus	Positive (significant reduction in alcohol consumption)
Bird et al. [32]	Laboratory; controlled acute administration; experimental; factorial design	161 adults with alcohol and cannabis experience	CBD 320 μg/kg (oral) + alcohol (0.54 g/kg)	Not reported	No significant effects on any performance measure: $F[4,580] = 1.69$, $p > 0.0125$	Not primary focus	Neutral (no effect on alcohol-induced impairment)
Other Cannabinoid Compounds							
Study	**Study Design**	**Sample**	**Intervention**	**Pharmacokinetic Effects**	**Performance/ Behavioral Effects**	**Subjective Effects**	**Overall Effect on Alcohol-Use Related Behaviors**
Bird et al. [32]	Laboratory; controlled acute administration; experimental; factorial design	161 adults with alcohol and cannabis experience	CBN 320 μg/kg (oral) + alcohol (0.54 g/kg)	Not reported	No significant effects on any performance measure: $F[4,580] = 0.80$, $p > 0.0125$	Not primary focus	Neutral (no effect on alcohol-induced impairment)

Table 2. continued

Study	Study Design	Sample	Intervention	Pharmacokinetic Effects	Performance/ Behavioral Effects	Subjective Effects	Overall Effect on Alcohol-Use Related Behaviors
CBD							
Karoly et al. [51]	Naturalistic; 5-day observation; self-administration; no controlled dosing	120 cannabis and alcohol co-users	CBD + THC Group: ~10% CBD + ~9% Δ9-THC (ad libitum for 5 days)	Blood CBD levels: 1.3 ± 0.3 ng/mL Blood Δ9-THC levels: 4.8 ± 0.7 ng/mL	Maintained baseline alcohol consumption levels (no significant change)	Not primary focus	Neutral (no effect on alcohol consumption)

Studies are categorized by cannabinoid type and describe study design, sample characteristics, intervention details, pharmacokinetic interactions, behavioral and subjective effects, and overall impact on alcohol-use related behaviors.
ACC, Anterior Cingulate Cortex; *AUDIT*, Alcohol Use Disorders Identification Test; *AUD*, Alcohol Use Disorder; *AUQ*, Alcohol Urge Questionnaire, *BAC*, Blood Alcohol Concentration; *BART*, Balloon Analogue Risk Task, *bsCBD*, broad-spectrum CBD, *CCT*, Columbia Card Task, *CBD-COOH*, 7-carboxy-cannabidiol; *fsCBD*, full-spectrum CBD; *Glx*, Glutamate + Glutamine, *HF-HRV*, High-Frequency Heart Rate Variability, *ICS-FC*, Impaired Control Scale-Failed Control, *NAc*, Nucleus Accumbens, *PACS*, Penn Alcohol Craving Scale, *PANAS*, Positive and Negative Affect Scale, *PK*, Pharmacokinetic, *PLC*, Placebo, *RCT*, Randomized Controlled Trial, *SCR*, Skin Conductance Response; *Δ9-THC-COOH*, delta-9 carboxy tetrahydrocannabinol, *TMT*, Trail Making Test.

stress responses, and emotional homeostasis, pharmacological suppression of this baseline activity may precipitate anxiety and depressive symptoms [106, 107]. These safety concerns ultimately led to the discontinuation of rimonabant's development. The psychiatric adverse effects observed humans might have been anticipated through preclinical studies [108–110], emphasizing the importance of incorporating comprehensive behavioral assessments in early research. Such evaluations could improve the prediction of potential adverse effects in humans, thereby strengthening the bridge between preclinical findings and clinical applications.

An additional translational barrier involves discrepancy between dosing schedules employed in preclinical versus clinical studies. Most preclinical studies employed acute pretreatment protocols, administering compounds 15–60 min before alcohol exposure, whereas clinical trials implemented chronic daily dosing over 12–14 weeks. This temporal mismatch may contribute to translational failures through several mechanisms. First, repeated exposure can produce neuroadaptive changes in the endocannabinoid system, as evidenced by studies showing tolerance to CB-1R agonists with chronic administration [63] and compensatory increases in alcohol consumption following discontinuation of chronic CB-1R antagonism [54]. Second, acute pharmacological effects may differ qualitatively from steady-state responses. The few preclinical studies employing repeated dosing protocols often showed different effect profiles than acute administration: Zhou 2017 et al. [81] found sustained efficacy with repeated URB597, a FAAH inhibitor, administration. While Viudez-Martinez 2020 et al. reported that repeated but not acute CBD reduced alcohol intake. Future preclinical research should prioritize chronic dosing paradigms that better model clinical treatment schedules, examining both the maintenance of efficacy over time and the emergence of tolerance or sensitization.

Methodological limitations in clinical trials further contribute to the translational gap. Factors such as insufficient treatment duration (e.g., 12 weeks for rimonabant) [71], inadequate patient stratification to identify potential responders, and high placebo response rates can obscure potential treatment effects. Compounding these issues, clinical investigations have largely focused on rimonabant and, more recently, CBD. This narrow focus represents a missed opportunity to test safer and more targeted compounds that showed preclinical promise, such as neutral antagonists, FAAH and MAGL inhibitors.

Overcoming translational challenges: Methodological priorities for future research

Advancing cannabinoid-based therapeutics for AUD requires systematic methodological improvements. Preclinical studies must adopt standardized reporting of experimental variables—alcohol concentration, administration schedules, housing conditions, and demographic characteristics—to enhance cross-study comparability and translational relevance. Preclinical studies examining the effects of cannabinoid modulators on alcohol use-related behaviors have predominantly used adult male rodents (Table 1). This sex and age bias limits the generalizability of findings, particularly in understanding how cannabinoid systems influence alcohol use-related outcomes across developmental stages and in females.

Rigorous experimental design must differentiate specific therapeutic effects from non-specific behavioral suppression through appropriate controls (e.g., saccharin self-administration) while characterizing withdrawal phenotypes and circuit-level mechanisms. Understanding intervention effects on reward processing, stress reactivity, and executive control circuits provides mechanistic insights essential for clinical translation.

Clinical advancement requires integration of mechanism-based biomarkers for patient stratification. Priority endpoints include neuroimaging markers of ECS activity (CB-1R PET, fMRI cue-reactivity), peripheral endocannabinoid levels, and validated stress

response assessments. Patient stratification utilizing FAAH polymorphisms, drinking phenotypes, and comorbidity profiles may identify treatment-responsive subgroups. Critically, there is a pressing need for adequately powered, multi-site trials testing promising ECS modulators in patients with AUD to establish definitive efficacy signals. Extended psychiatric monitoring (≥ 6 months) remains crucial for detecting delayed adverse effects. These methodological refinements—emphasizing standardization, demographic diversity, mechanistic clarity, and biomarker integration— along with adequately powered, multi-site trials represent essential steps toward developing precision therapeutics that surpass current pharmacological limitations.

Although this review focuses on AUD, the translational challenges extended beyond AUD, cutting across endocannabinoid-based therapeutic development. Convergent evidence indicates that endocannabinoid signaling shapes cue reactivity, stress responsivity, and relapse risk across other substance classes, including opioids, nicotine, and psychostimulants. Additionally, the endocannabinoid system shows convergent alterations across stress-related neuropsychiatric disorders [111, 112]. Individuals with anxiety disorders, depression, and PTSD exhibit elevated baseline concentrations of both AEA and 2-AG [111], yet display blunted endocannabinoid mobilization in response to acute psychosocial stress [112]. This pattern of dysregulation becomes particularly relevant given that AUD shows high comorbidity with these stress-related disorders [113]. Consequently, endocannabinoid-directed interventions may provide dual therapeutic benefits in specific patient subgroups, simultaneously addressing alcohol use behaviors and comorbid psychiatric symptoms through restoration of endocannabinoid tone.

This comorbidity framework should guide precision medicine approaches rather than broadening treatment scope indiscriminately. Clinical trials should prospectively stratify patients based on stress-reactive versus reward-driven drinking phenotypes and comorbid anxiety or PTSD diagnoses. Outcome assessments should pair primary alcohol endpoints with endocannabinoid biomarkers and validated stress response measures. Secondary psychiatric improvements should be interpreted as mechanistically linked effects rather than independent therapeutic actions. This targeted approach further addresses the heterogeneity that has diluted treatment effects in prior trials.

Emerging pharmacotherapies: Towards safer, targeted approaches

A key next step in broadening clinical investigation is to explore the diverse pharmacotherapies suggested by preclinical research. Currently, however, a striking disparity exists between the diversity of cannabinoid pharmacotherapies examined preclinically and the limited scope of clinical investigations. While preclinical studies evaluated a broad spectrum of compounds (CBD, CB-2R agonists, neutral CB-1R antagonists, enzyme inhibitors, allosteric modulators), clinical research has focused narrowly on rimonabant and preliminary CBD studies. This translational bottleneck likely reflects multiple factors: industry hesitation after rimonabant's failure, regulatory hurdles, inadequate funding for early-phase trials, and challenges in designing appropriate proof-of-concept studies.

Peripherally restricted CB-1R antagonists (e.g., JD5037) reduced alcohol intake in preclinical models without significant CNS penetration [69]. This strategy may retain efficacy while avoiding central psychiatric side effects. Neutral CB-1R antagonists, such as AM4113 and AM6527, block receptors without suppressing constitutive activity [69]. They showed efficacy [30, 40, 66] with potentially better safety profiles. A preclinical nicotine dependence model provided a direct comparison: the neutral antagonist AM4113 matched rimonabant's efficacy in reducing nicotine self-administration and blocking cue-, priming-, and stress-induced reinstatement; critically, however, chronic AM4113 exhibited antidepressant-like effects and did not induce anxiety-like behavior, whereas rimonabant produced pro-depressant and anxiogenic effects [105]. This dissociation suggests that rimonabant's adverse effects may stem from its inverse agonism rather than simple CB-1R blockade [106].

Given its safety profile and CBD effects on multiple targets, CBD remains a candidate pharmacotherapy for AUD. Beyond its effects on the ECS, CBD exerts modulatory actions on serotonergic, dopaminergic, and glutamatergic systems [114]. The relatively high doses of CBD required for efficacy in both preclinical (30-120 mg/kg) and human studies (600-800 mg) provide insights into its mechanism of action. The high doses required suggest that these effects may not be mediated through high-affinity targets like 5-HT1A receptors, but rather through lower-affinity mechanisms such as CB-1R negative allosteric modulation, TRPV1 activation, or potentially through the combined action of multiple targets [96, 115]. Our favorable findings for CBD support its use in larger, longer-duration controlled clinical trials among people with AUD.

Preliminary human evidence also supports THC's potential to reduce alcohol consumption acutely, though the high prevalence of cannabis use disorder among responders (76%) and inconsistent craving effects warrant caution [26]. Long-term co-use patterns and risks of cannabis use escalation require evaluation before therapeutic recommendations.

By modulating endogenous cannabinoid levels, inhibitors of enzymes like FAAH and MAGL reduced alcohol intake in preclinical studies [80, 81] and may offer a safer alternative to direct CB-1R inverse agonism. Allosteric modulators (e.g., RTICBM-74 [58]) are another promising avenue; they bind to sites distinct from the orthosteric cannabinoid binding site, modulating receptor response to endogenous ligands rather than directly activating or blocking the receptor. This mechanism improves selectivity and reduces off-target effects. Additionally, CB-2R agonists showed efficacy in mice [65] with minimal psychoactivity due to the predominantly peripheral expression of CB-2R. Systematic evaluation of these diverse strategies is warranted to identify viable clinical candidates for AUD treatment.

CONCLUSION

The endocannabinoid system remains a biologically plausible and mechanistically rich target for AUD pharmacotherapy, supported by robust preclinical evidence. However, clinical translation has been hindered by adverse effects, narrow pharmacologic focus, and methodological limitations. Promising alternatives—such as CBD, THC, peripherally restricted and neutral CB1 antagonists, enzyme inhibitors, and CB2 agonists—address many of these barriers and merit systematic evaluation. Future studies should integrate biomarkers for patient stratification, employ adaptive trial designs for dose optimization, extend treatment durations to capture neuroadaptive changes, and maintain comprehensive psychiatric monitoring. Priority endpoints should include neuroimaging markers of ECS activity, peripheral endocannabinoid levels, and validated stress response assessments. Only through such methodologically rigorous, mechanism-informed approaches can we determine whether endocannabinoid modulation represents a viable therapeutic strategy for the heterogeneous population of individuals with AUD.

DATA AVAILABILITY

All data generated or analyzed during this study are included in this published article and its supplementary information files. The raw data used for meta-analyses are available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

G.P.A.C. and M.A.C-M. were responsible for the study execution, data extraction, and writing of the original manuscript. G.P.A.C. conducted the formal meta-analyses. M.C.F. developed and executed the search strategy. D.B. contributed to the conceptualization and review of the manuscript. A.K., J.K. and I.P. provided supervision and critical revision of the manuscript. J.P.D.A. was responsible for the conceptualization, supervision, funding acquisition, project administration, and writing, reviewing, and editing the final manuscript. All authors gave final approval for the version to be published and agree to be accountable for all aspects of the work.

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COMPETING INTERESTS

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