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Beyond abstinence: Redefining success in cannabis use disorder treatment

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Abstract

Background: Over two decades of pharmacotherapy research has yet to yield a consistently effective medication for cannabis use disorder (CUD), in part because clinical trials have frequently prioritized abstinence as a primary or key endpoint. Abstinence, however, is difficult for many patients to attain, may not align with their treatment goals, and can obscure meaningful clinical improvements. By contrast, the alcohol and tobacco fields have advanced through adoption of validated reduction-based frameworks that capture changes in harm, functioning, and quality of life.

Argument/Analysis: This paper (1) critiques the limitations of abstinence-focused end-points in CUD trials, (2) outlines key methodological challenges, and (3) proposes a more comprehensive approach to outcome measurement. Most adult pharmacotherapy trials have been deemed negative when evaluated on abstinence, despite frequent reductions in cannabis use that are associated with improvements in psychiatric symptoms and functional outcomes. Studies evaluating non-abstinent outcomes are often difficult to interpret clinically without clearer links to mental, physical, and functional outcomes. Emerging CUD data and lessons from other substance use fields point to the need for standardized, reduction-based metrics that can more accurately detect treatment-related change.

Conclusion: Reliance on abstinence as the primary endpoint has constrained progress in CUD treatment development. Incorporating consensus-driven, reduction-based outcomes, while continuing to measure abstinence as a secondary endpoint, may better align research with patient goals, enhance interpretability of trial findings, and improve the field's ability to

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AUTHOR CONTRIBUTIONS

Tobias B. Atkin: Writing—original draft; data curation; investigation. **Frances R. Levin:** Formal analysis; supervision; project administration; funding acquisition; resources; methodology; investigation; software; validation; conceptualization; writing—review and editing. **John Mariani:** Conceptualization; supervision. **Christina A. Brezing:** Conceptualization; supervision; project administration; writing—review and editing; resources; data curation; visualization; methodology; investigation; software; validation.

identify promising interventions. Standardizing definitions for meaningful reductions is critical to advancing CUD care.

Keywords

abstinence; cannabis use disorder; clinical trials; functional outcomes; harm reduction; measurement standards; patient-centered care; reduction-based outcomes; tetrahydrocannabinol; treatment success

INTRODUCTION

According to the 2024 National Survey on Drug Use and Health (NSDUH) report, among people aged 12 years or older, the proportion who had a past-year cannabis use disorder (CUD) increased from 6.0% (or 16.7 million people) in 2021 to 7.1% (or 20.6 million people) in 2024 [1]. Past-year CUD diagnoses also increased among adults aged 26 years or older, from 4.7% to 6.1% over the same period. Daily use is rising among adolescents, older adults and pregnant people [1–3]. There is an increase in daily and near-daily cannabis users, contributing to a rising prevalence of CUD diagnoses and corresponding with a decreased perception of harm amid regulatory changes that ease access to cannabis [1, 4, 5]. CUD contributes to psychiatric, cognitive and functional burden, underscoring the need for more informative and patient-centered treatment outcomes.

At present, psychosocial interventions remain the cornerstone of evidence-based care for CUD. Randomized controlled trials and systematic reviews consistently support cognitive behavioral therapy (CBT), motivational enhancement therapy (MET) and contingency management (CM) as the most effective approaches for reducing cannabis use and CUD symptom severity [6–18]. These modalities (CBT, MET and CM) augment outcomes and show promise in both adult and adolescent samples. Across trials, combined protocols (e.g. MET + CBT ± CM) tend to yield larger effect sizes and more durable reductions in cannabis use than any single modality alone, although gains frequently attenuate over longer-term follow-up [6, 7, 10, 16, 17]. Even with optimal psychosocial treatment, however, a substantial proportion of patients do not achieve or sustain abstinence or meaningfully reduce their cannabis use (e.g. ≥50% reduction in frequency or quantity of use), highlighting the limitations of psychosocial strategies as stand-alone treatments for many individuals with CUD. Furthermore, the implementation of these intensive psychosocial treatments is often limited by provider availability and financial or time burdens [19, 20]. In addition, some individuals may disengage from treatment after achieving their personal goal of reducing use, rather than pursuing or maintaining abstinence, which may contribute to dropout in clinical trials.

In contrast to alcohol and opioid use disorders, no medication is currently approved by the US Food and Drug Administration (FDA) specifically for the treatment of CUD. Randomized trials of diverse pharmacologic agents, including cannabinoid agonists (such as dronabinol, nabilone or nabiximols), anti-epileptic medications (such as gabapentin, topiramate or valproic acid), antidepressants and other neuromodulators, have shown mixed or inconclusive effects on clinical outcomes, offering off-label strategies for symptom relief but no clear treatment guidelines [7, 21–30]. An additional limitation is that

several compounds have been evaluated in relatively small or short-duration trials without replication. For example, a randomized trial of cannabidiol demonstrated dose-dependent reductions in cannabis use but was not powered to assess abstinence efficacy or durability [31].

Meta-analyses and recent narrative reviews converge on the finding that, while some compounds may reduce withdrawal severity or cannabis use in specific subgroups, none has demonstrated robust, replicable efficacy on abstinence outcomes sufficient to support regulatory approval [7, 30, 32–35]. Most adult pharmacotherapy trials have been deemed negative when abstinence is used as the primary end-point, and effect sizes for reductions in use are typically modest and inconsistent across studies. As a result, contemporary guidelines and expert consensus documents characterize all medication strategies for CUD as off-label and recommend that pharmacotherapy be viewed as adjunctive rather than stand-alone treatment.

In clinical practice, pharmacologic interventions typically target co-occurring symptoms (e.g. anxiety, depression or insomnia) using standard psychiatric medications, rather than CUD itself [7, 30]. Antidepressant trials for CUD and co-occurring depression have failed to reduce cannabis use and, in some cases, have been associated with lower abstinence rates relative to placebo [28]. The treatment of co-occurring attention deficit hyperactivity disorder (ADHD) with stimulants or atomoxetine may improve attention and functioning but has not demonstrated consistent effects on cannabis consumption in controlled trials [36–38]. Off-label, symptom-targeted strategies can improve the tolerability of early abstinence attempts, reduce distress and enhance overall functioning, yet they are not evidence-based treatments for CUD and have minimal impact on cannabis use patterns in the absence of concurrent psychosocial treatment.

Taken together, the current treatment landscape is characterized by reasonably well-supported psychosocial interventions but an absence of approved medication options, despite an extensive pharmacotherapy literature. Given the significant public health burden of CUD, there is a pressing imperative to improve the measurement and treatment of CUD. These shifts are consistent with broader movements in addiction science toward dimensional models of substance use and harm reduction approaches that emphasize gradations of change rather than binary outcomes.

This article will review the current limitations of abstinence-based end-points in CUD trials and synthesize evidence from prior pharmacotherapy and psychosocial studies to highlight how methodological variability has prevented progress in treatment. It then outlines a framework for defining and operationalizing reduction-based outcomes, drawing on alcohol, nicotine and harm-reduction literature, and aligning with dimensional models of substance use. Finally, the article includes a set of standardized outcome measures to guide future CUD treatment trials and accelerate the development of effective and patient-centered interventions.

TRIALS TO DATE

Abstinence as a variable and inconsistently defined end-point

Over the past three decades, clinical trials for CUD have evaluated a wide range of psychosocial and pharmacologic interventions, often relying on abstinence as a primary end-point, despite important limitations (Figure 1). Abstinence is often included as a key outcome, alongside other measures such as frequency and quantity of use, craving, and functioning [6, 7, 9, 30, 34]. However, there is no consistent framework for how these outcomes are defined, prioritized, presented or interpreted across studies. As a result, reductions in use are often reported but treated as secondary or are difficult to compare across trials. For example, a randomized controlled trial of nabiximols looked at the primary outcome of number of days of cannabis use over an entire 12-week study period [22], while a study of quetiapine looked at changes in the number of days of use per week and categorized them as heavy, moderate or light [39]. Both medications reduced use days, but differing time frames hinder cross-study comparisons. A single lapse versus a return to heavy chronic use are not equivalent clinical outcomes, yet they are often treated similarly when abstinence is the sole end-point.

Further, the definition of abstinence in these trials is not uniformly or consistently defined. Some studies have treated abstinence as point prevalence (e.g. a single negative urine test at a visit), while others have required continuous abstinence over multiple weeks, often combining self-report with urine testing and classifying dropouts as non-abstinent [34]. Even at the level of laboratory thresholds and schedules, protocols have significant variation in defining abstinence: immunoassay cut-offs of 100 ng/ml for 11-nor-9-carboxy-Δ9-tetrahydrocannabinol (THC-COOH, the primary inactive metabolite of Δ9-tetrahydrocannabinol, or THC) have been used in behavioral trials [15], cut-offs of 50 ng/ml of THC-COOH with confirmatory quantification in pharmacotherapy trials [24] and dual qualitative/quantitative approaches with different cut-offs (e.g. qualitative 50 ng/ml and quantitative 15 ng/ml for THC-COOH) collected twice weekly [34, 36]. THC-COOH remains detectable longer in frequent users as lipophilic THC gradually releases from adipose tissue. By contrast, the biomarkers used in alcohol and tobacco research often change more quickly when use is reduced or stopped, making them easier to interpret as short-term treatment outcomes.

These inconsistencies matter in CUD because both qualitative and quantitative urine measures have important, distinct limitations. Qualitative ‘positive/negative’ urine tests can remain positive for THC-COOH for prolonged periods after cessation among chronic frequent users of cannabis, such that it may take ‘a month or longer’ to obtain a negative test, even during abstinence [34]. Quantitative assays offer more information than binary results, but concentrations are not straightforward to interpret, and quantitative trajectories can reflect residual excretion rather than new use [34]. In practice, even when weekly urine testing for THC metabolites is paired with timeline follow-back (TLFB) self-report, the misclassification of abstinence versus non-abstinence remains plausible [14, 34].

Reduction signals in psychosocial and pharmacologic trials

Early psychosocial trials established that reductions in cannabis use and related problems are achievable even when sustained abstinence is uncommon [6, 10, 12]. In a foundational randomized trial, Stephens and colleagues compared relapse prevention with a social support condition and observed substantial reductions in the number of days of use and cannabis-related problems over the follow-up in both groups, without clear differences in abstinence outcomes [12]. Similarly, Copeland *et al.* demonstrated that brief CBT interventions reduced cannabis use frequency relative to minimal intervention, while abstinence rates remained low across treatment arms [10].

Subsequent trials introduced CM approaches designed to make abstinence more achievable by pairing this approach with tangible reinforcement. Voucher-based CM added to MET or coping-skills training increased abstinence during the active treatment period (typically 14 weeks) when abstinence was defined as repeated negative urine cannabinoid tests [15, 17]. Carroll and colleagues extended these findings in young adults, showing improved abstinence during treatment when CM was combined with CBT [14, 16]. Abstinence effects often diminished after reinforcement contingencies ended and reduced use frequency persisted longer over follow-up [16, 17]. In adolescent samples, CM has also produced positive abstinence outcomes during treatment in highly structured contexts [11], though similar attenuation after treatment is common. The Cochrane review conducted by Gates *et al.* found evidence supporting these evidence-based behavioral modalities for reducing cannabis use but noted substantial heterogeneity in abstinence definitions and limited evidence for long-term abstinence [6].

Pharmacotherapy trials for CUD have evaluated anticonvulsants, antidepressants, cannabinoid agonists and medications targeting withdrawal or comorbid symptoms [30]. Across these studies, a common pattern emerges: medications may improve withdrawal, retention or use patterns without producing clear advantages in binary abstinence outcomes [30]. Trials of cannabinoid agonists illustrate this clearly. In outpatient studies of dronabinol combined with psychosocial treatment, dronabinol reduced withdrawal symptoms and improved retention but did not increase abstinence relative to placebo when abstinence was defined by urine cannabinoid testing [21, 40]. A pilot outpatient trial of nabilone showed reductions in self-reported cannabis use over time in both active and placebo groups, without significant between-group differences in abstinence or urine outcomes [24].

Not all cannabinoid agonist trials were negative when outcomes extended beyond binary urine-verified abstinence. In a randomized trial conducted during cannabis withdrawal, nabiximols increased the number of days without cannabis use during treatment, compared with placebo, when days of non-use across the entire trial over 12 weeks were used as the primary outcome [22]. This measure reflects intermittent days without use rather than sustained abstinence, which is typically defined as a continuous period of non-use (e.g. 2–3 weeks or the longest duration of abstinence). In contrast, a larger multi-site outpatient nabiximols trial used reduction in days of illicit cannabis use as its primary outcome and found significant benefit on this measure, while abstinence outcomes reported secondarily did not differ between groups [22].

In a proof-of-concept randomized trial, gabapentin reduced cannabis use and withdrawal severity and improved executive function deficits, relative to placebo [25]. A randomized controlled trial of quetiapine for cannabis dependence was in fact positive when the primary outcome was defined as a reduction in days of use [39]. In contrast, antidepressant strategies have generally not improved cannabis outcomes. In a randomized trial of venlafaxine extended-release in adults with co-occurring cannabis dependence and depression, depressive symptoms improved, but abstinence rates were lower in the venlafaxine group than in the placebo group [28]. These findings suggest that improvement in comorbid psychopathology does not reliably translate into abstinence and highlight the importance of matching end-points to theoretical mechanisms of action.

Adolescent trials have yielded the most consistent abstinence signals in the pharmacotherapy literature. In a randomized controlled trial, adolescents receiving *N*-acetylcysteine combined with CM had greater odds of submitting negative urine cannabinoid tests during treatment compared with placebo [41]. However, a subsequent adult trial of *N*-acetylcysteine did not replicate these abstinence effects [29]. Differences between adolescent and adult findings likely reflect not only developmental factors but also differences in treatment context. Adolescent trials typically include greater external structure, parental involvement and reinforcement tied directly to abstinence, which may amplify abstinence outcomes independent of medication effects [40].

Many CUD trials collected detailed longitudinal data beyond abstinence, including frequency and quantity of use, withdrawal, craving, functioning and quality of life. Analyses of these data indicate that reductions in cannabis use are clinically meaningful. Brezing *et al.* showed that both abstinence and reduced frequency of cannabis use were associated with improvements in quality of life among treatment-seeking individuals with CUD [42]. Levin *et al.* demonstrated that non-abstinent outcomes capture meaningful treatment effects and often align more closely with patients' stated goals, which frequently include moderation rather than abstinence [40]. Building on this work, McClure *et al.* aggregated data from seven CUD treatment trials to derive empirically grounded reduction metrics associated with improved functioning, drawing parallels with reduction-based end-points adopted in alcohol treatment research [43].

Patient goals and motivation shape outcome interpretation

Growing evidence in the CUD literature indicates that patient motivation and treatment goals strongly influence outcomes and determine whether abstinence-based end-points are realistic or informative [34, 40]. Reviews of CUD trials show that many treatment-seeking individuals, particularly in adult outpatient settings, pursue moderation rather than abstinence, and that outcomes often align more closely with these goals than with uniform abstinence criteria [40, 42]. Secondary analyses further demonstrate that motivation and readiness to change moderate treatment response. This is consistent with the stages of change framework, in which readiness to change shapes both treatment engagement and achievable outcomes. For example, Gray and colleagues found that baseline motivation differentiated abstinence outcomes in adolescent *N*-acetylcysteine trials, with treatment effects varying across motivational subgroups [44]. Taken together, these findings show

that abstinence functions differently across heterogeneous samples and that failing to assess motivation prospectively may hide meaningful treatment effects [8, 34]. Future trials should therefore assess motivation and treatment goals explicitly and incorporate these constructs into analytic strategies to better identify which interventions work optimally for which patients. The importance of motivation also underscores the value of re-analyzing existing trial data sets, many of which include rich longitudinal data that have not been fully leveraged. Secondary analyses stratified by motivation, severity and treatment goals may reveal clinically meaningful changes and inform treatment [34, 42, 43].

Emerging observational data also suggest that non-traditional data sources may identify treatment signals not yet tested in randomized trials. In a large electronic health record-based cohort study, Wang *et al.* found that treatment with semaglutide was associated with a reduced likelihood of incident and recurrent CUD among individuals treated for obesity or Type 2 diabetes [45]. While such findings do not substitute for randomized clinical trials, they highlight the potential role of real-world data and claims-based analyses in identifying candidate interventions.

DEFINING REDUCTION IN USE

Why reduction-based outcomes matter

Defining what constitutes a meaningful ‘reduction’ in CUD is central to advancing treatment research yet remains one of the least resolved challenges in the field. Clinically, changes in use often occur along a trajectory rather than as a binary shift from use to abstinence (Figure 2). Frequency can be operationalized across multiple levels, including days of use, number of use occasions per day and time spent using within a day. For example, clinically meaningful reduction may include a ≥50% decrease in the number of days of use, a shift from daily to intermittent use (e.g. ≥25 to ≤10 days/month) or reductions in within-day use (e.g. from 10+ to 3–5 use episodes), particularly when accompanied by improvements in functioning. Although many trials collect detailed longitudinal data on cannabis use, there is no shared framework for how reduction should be measured, interpreted or compared across studies. As a result, potentially important treatment effects, particularly in pharmacotherapy trials, are often difficult to detect or contextualize. Reviews of outcome assessment emphasize wide variability in end-points and analytic approaches, limiting synthesis and comparisons across studies [34].

A critical but underdeveloped aspect of defining reduction in cannabis use is its relationship with downstream medical risk, which provides a necessary anchor for determining whether reductions are clinically meaningful. While reductions in frequency or quantity are often reported, their clinical significance depends on their relationship with health outcomes. Emerging evidence suggests that cannabis use may affect multiple physiological systems, including cardiovascular, respiratory, gastrointestinal and reproductive domains. For example, cannabis exposure has been associated with acute cardiovascular effects (e.g. tachycardia, blood pressure changes) and potential longer-term vascular dysfunction, while chronic inhalation is linked to bronchitic symptoms, and cannabis hyperemesis syndrome represents a well-characterized complication of heavy use [46]. In the reproductive domain, cannabinoids may adversely affect both male and female fertility,

including spermatogenesis, ovulation and implantation [47]. However, most studies do not systematically quantify dose, frequency or severity of use in relation to these outcomes, limiting the ability to determine what degree of reduction confers meaningful benefit. Establishing these dose–response relationships will be essential for defining clinically meaningful CUD reduction thresholds [48].

Other substance use fields demonstrate how progress can follow from clearer agreement about outcomes. In alcohol use disorder (AUD), large epidemiologic and clinical trial data sets have demonstrated that reductions in heavy drinking, clearly and consistently defined by agreed upon definitions of what quantifies a drink as well as defining a heavy drinking day, were associated with improvements in blood pressure, liver enzymes, cardiovascular risk, sleep, mood and overall mortality [49]. Treatment development then accelerated once trials routinely incorporated agreed-upon non-abstinent end-points that captured meaningful improvement, even when abstinence was not achieved. The 2015 FDA guidance for AUD drug development explicitly recognizes outcomes beyond abstinence, including reductions in heavy drinking [50]. More recently, the FDA qualified reductions in World Health Organization (WHO) risk drinking levels as an acceptable drug development tool, reflecting a broader shift toward end-points tied to improvements in health and functioning rather than cessation alone [51]. In AUD, reduction-based end-points gained traction when heavy drinking and WHO risk drinking levels were shown to map onto improvements in health and functioning. This shift did not occur because alcohol reduction is inherently easier to measure than cannabis reduction, but because the field converged on standardized definitions for both quantity and frequency, empirically supported thresholds, and outcomes that are meaningful to clinicians and patients.

Nicotine research—leading to the development of FDA-approved treatments including nicotine-replacement therapy, bupropion and varenicline—offers a similar lesson. Early smoking cessation trials used inconsistent definitions of abstinence, leading the field to develop consensus standards for outcome measurement and reporting [52, 53]. Longitudinal cohort studies demonstrated that reductions in cigarettes per day were associated with improvements in cardiovascular risk markers, respiratory symptoms and lung function, with these benefits following a dose–response relationship [54–56]. Later studies further showed that smokers who reduced consumption substantially had lower risks of cardiovascular events, chronic obstructive pulmonary disease progression and all-cause mortality, compared with those who maintained heavy smoking, even when abstinence was not achieved [57–59]. Although nicotine is more amenable to biochemical measurement than cannabis, the broader lesson still applies: a field progresses when investigators agree on a defined set of outcomes that are practical to measure, consistently reported and meaningful in clinical settings.

Cannabis poses distinct measurement challenges that make it difficult to apply alcohol or nicotine outcome frameworks directly. As noted above, the prolonged detection of THC metabolites among frequent users limits the value of urine testing for assessing recent behavior and complicates the interpretation of quantitative results [34]. Self-reported measures, particularly TLFB assessments, are better suited to capture meaningful changes in use over time, with biological measures used selectively to support interpretation rather than define treatment success [40]. This strategy is consistent with alcohol research, where

carefully collected self-report data form the basis of validated, regulator-accepted end-points [50].

Defining the ‘quantity’ of cannabis use presents a second challenge. Unlike standard drinks or cigarettes, cannabis consumption varies widely by product type, route of administration, potency and session structure. Many patients cannot reliably estimate grams or milligrams of THC, particularly in contemporary markets dominated by high-potency products and diverse delivery systems in the absence of federal standardization of cannabis products [34, 60]. Together, these limitations make it difficult to rely on a single quantitative dose metric across trials. One response to these limitations has been to combine quantity and frequency rather than privileging either alone. In population-level measurement work, Asbridge and colleagues integrated typical quantity with recent frequency to create a quantity–frequency typology modeled on alcohol volume measures, which showed clearer gradients of cannabis-related problems and Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) scores than frequency- or quantity-only approaches [61]. Rather than abandoning quantity altogether, a more workable approach is to prioritize measures that most participants can report reliably, while supplementing them with additional detail when feasible. Emphasizing within-subject change in quantity over time allows each participant to serve as their own control and supports analyses based on mean change scores, even when between-subject comparisons of absolute dose are unreliable [34, 43]. In addition, incorporating *in vivo* assessments, such as ecological momentary assessment, may further improve the measurement of use patterns and reduce the reliance on retrospective quantity estimates [62–64].

Frequency as the core reduction end-point

Within this context, frequency of use stands out as the most practical and scalable reduction end-point. Frequency can be measured in several ways, including number of days of use, number of use occasions per day and time spent using within a day. Frequency is easy to assess, interpretable across clinical settings, and is sensitive to change in both psychosocial and pharmacotherapy trials. Metaanalytic evidence shows that evidence-based psychosocial interventions reliably reduce the number of cannabis-use days, even when abstinence remains uncommon [6]. Frequency-based outcomes have also proven useful in medication trials. In the 12-week outpatient randomized trial of nabiximols, the primary end-point was the number of days of illicit cannabis use across the treatment period, and nabiximols demonstrated benefit on this measure despite limited effects on abstinence outcomes [22]. In addition to use days, several studies track session or episode counts per day and categorize frequency and intensity into risk levels (e.g. high/medium/low) that have been linked to changes in clinical outcomes, providing a template for thinking about within-day intensity measures or episodes per day of use [65].

To improve interpretability, frequency should be reported in standardized formats. Clinically meaningful reduction may include a percent decrease in use days, a shift from daily to intermittent use or fewer use occasions per day. Common options include days of use over a fixed window (e.g. past 28 or 7 days), percent change from baseline and categorical shifts that reflect intuitive clinical transitions, such as movement from daily to intermittent use.

A person who moves from near-continuous use throughout the day to use confined to the evening may experience a substantial improvement, even if the number of use days does not change. To capture this kind of change, frequency may also be assessed as the number of occasions per day or as use within defined time windows, such as morning, afternoon, evening and night. Success may reasonably be indexed as percent reduction, movement between predefined risk categories or the attainment of a clinically meaningful threshold, depending on the study question. Analyses of non-abstinent outcomes suggest that such category shifts can reveal treatment effects that would otherwise be obscured [40]. These approaches also align with patient goals, which frequently emphasize cutting down rather than quitting entirely, particularly among adults seeking outpatient treatment.

Linking reductions to functioning and health

Beyond global functioning, reductions in cannabis use have been associated with improvement in specific, patient-salient symptom domains. Reductions in use should ideally be interpreted alongside changes in sleep, mood, anxiety, social functioning and overall quality of life. A seven-trial analysis showed that reduced cannabis frequency improved sleep and cannabis-related problems, with global improvement reported [43]. Observational and secondary analyses similarly indicate that reductions in cannabis use, particularly reductions in frequency of use, are associated with improvements in anxiety and depressive symptoms as well as sleep quality, independent of complete cessation [42, 66, 67]. Together, these findings indicate that reductions in cannabis use are linked to patient-salient improvements in functioning and symptoms.

Reduction is best understood as part of a broader trajectory of change rather than as an end-point that competes with abstinence. Harm-reduction approaches across substance use disorders emphasize engagement, retention and incremental improvement as pathways toward longer-term goals, including abstinence for individuals who ultimately pursue it. In CUD, where motivation and treatment goals vary widely, reduction-based outcomes allow trials to capture meaningful progress among individuals who are not ready for complete cessation, while still allowing an examination of movement toward abstinence over time [40]. Newer assessment approaches, including more frequent *in vivo* measures, such as with ecological momentary assessment, may help capture clinically meaningful changes in patterns of use that are not reflected in days-of-use metrics alone [64]. For example, a shift from near-continuous use throughout the day to use limited to the evening hours may represent a substantial functional improvement, even if the number of days of use does not change [40, 43]. This type of within-day pattern change is conceptually similar to nicotine research, where time to first cigarette is used as a marker of dependence severity, independent of total consumption [68]. Clear, standardized reduction outcomes, especially frequency- and pattern-based measures tied to functional improvement, help align CUD trials with patient-centered change and reveal promising interventions.

CONCLUSION: A MATRIX OF OUTCOMES FOR CANNABIS USE DISORDER TRIALS

A standardized outcome matrix

We propose that the next phase of CUD trial design shifts toward a practical, consensus-driven matrix of outcomes that can be implemented across intervention types and trial settings (Figure 3; Table 1). The purpose of this matrix is not to declare one end-point as 'best' in all circumstances, but to ensure that every CUD trial measures change using a shared set of outcomes that are defined and reported in a consistent way, allowing results to be compared and synthesized. In this framework, frequency of use should be treated as a core outcome, while quantity, route, context and functional measures serve as supporting variables that help interpret change. Abstinence remains an important element of the matrix, but abstinence does not need to occupy the highest position in the outcome hierarchy for every study (Table 1).

We propose a tiered outcome framework in which frequency of use serves as the core domain, interpreted alongside supporting modifiers (e.g. context, quantity, route) and changes in functioning and health.

Core and supporting domains

At the center of this matrix, we propose that frequency of use serves as a core outcome that all trials collect and report in a standardized fashion. Frequency is feasible to assess, sensitive to change and interpretable across treatment modalities, and it has a growing empirical base linking reductions in use to functional improvement, including pooled trial analyses and outcome-development work by Budney, McRae-Clark and colleagues [43, 65].

Future trials can build on this foundation by extending frequency beyond a single 'days of use' metric to capture more granular dimensions of use. Days of use reflects overall exposure, but can miss clinically meaningful change when patterns of use shift within a day. For example, an individual who moves from near-continuous use throughout the day to use limited to evening hours may experience substantial functional improvement even if the total number of use days does not change. This type of change is readily recognized by clinicians and is analogous to nicotine research in which time to first cigarette serves as a marker of dependence severity, independent of total consumption. Incorporating granular measures of use allows trials to capture reductions in severity without requiring the precise quantification of dose.

Measuring meaningful change across patterns of use

To operationalize granular measures of use, we offer one example of a simple, scalable approach that could be layered into a broader outcome matrix. In this illustrative framework, each day is divided into quadrants, such as 12:00 AM–5:59 AM, 6:00 AM–11:59 AM, 12:00 PM–5:59 PM and 6:00 PM–11:59 PM, and cannabis use is assessed within each quadrant. This information could be collected using ecological momentary assessment (EMA) or, when EMA is not feasible, structured daily diaries. The emphasis is not on a specific technology, but on the use of a standardized unit of measurement. Quadrants provide a

common language for describing within-day patterns of use and may be more sensitive to clinically meaningful change than days of use alone. Over time, similar pattern-based approaches could be evaluated for their associations with functional improvement and dependence severity and, if supported, incorporated into consensus outcome frameworks.

Quantity of use should also remain part of the matrix but should be treated explicitly as a secondary or supportive measure that is interpreted primarily within individuals over time. Asbridge and colleagues combined typical quantity and recent frequency to create a quantity–frequency typology modeled on alcohol volume measures [61]. This combined approach better characterized cannabis-related problems and ASSIST scores than frequency- or quantity-only measures. We invoke this work not to endorse a specific typology but to illustrate how combining multiple dimensions of use can improve measurement and capture meaningful gradients of harm.

Ongoing variability in cannabis products and inconsistent labeling mean that dose metrics are often noisy and difficult to compare across participants. Trials should still collect feasible quantity-related data, including basic product characteristics, when possible, but the analytic emphasis should be placed on within-person change and on linking quantity changes to other outcomes in the matrix, particularly functioning and health measures.

Health outcomes as validation anchors

Future work should validate the proposed matrix against downstream health outcomes, particularly cardiovascular outcomes, while extending to pulmonary, gastrointestinal and reproductive domains. There is emerging evidence linking cannabis use to cardiovascular outcomes, including associations with adverse cardiovascular events and arrhythmias in observational data sets [69–71]. These findings highlight a need for partnership between CUD researchers and cardiovascular researchers to clarify dose–response relationships and identify which reductions in use translate into measurable health benefit. The alcohol field offers a concrete precedent. The FDA acceptance of reductions in WHO risk drinking levels as a primary end-point created a shared framework that connected changes in use to downstream health and functioning [72]. CUD needs an analogous path by building consensus around a small set of standardized reduction measures that can be validated against outcomes that matter. Once such a matrix is in place, central questions become empirically tractable. How much cannabis constitutes harmful use? What magnitude of reduction is clinically meaningful? Several challenges remain, including the reliance on self-report, variation in what constitutes a meaningful reduction, and heterogeneity in patient goals and treatment contexts.

In summary, we propose a matrix of outcomes that includes frequency of use, granular measures of use captured through quadrants of the day and time to first cannabis use after waking, quantity interpreted as a within-person measure, abstinence as an important but harmonized outcome, and a focused set of functional and health outcomes. Progress in the field will depend on an agreement to measure and report these outcomes consistently across trials.

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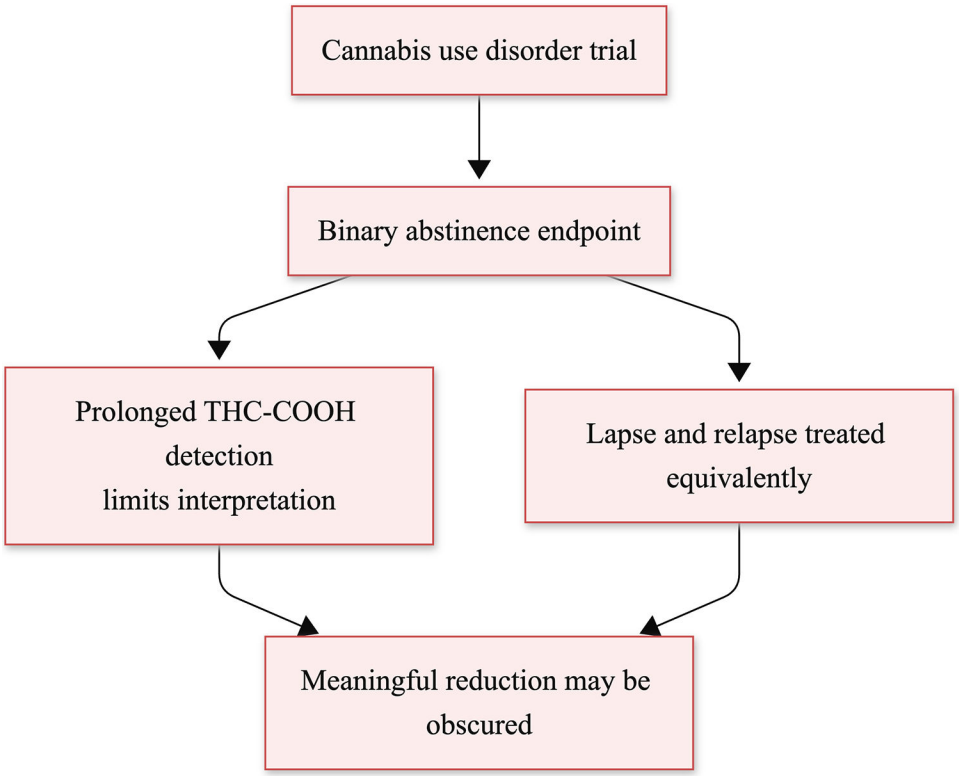

FIGURE 1.
Abstinence-only end-point limitations.

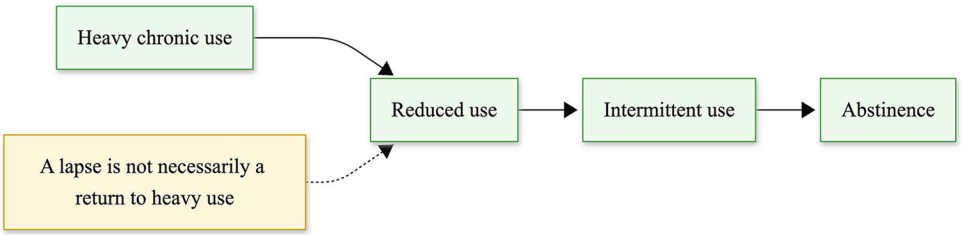

FIGURE 2.
Clinical trajectory of change.

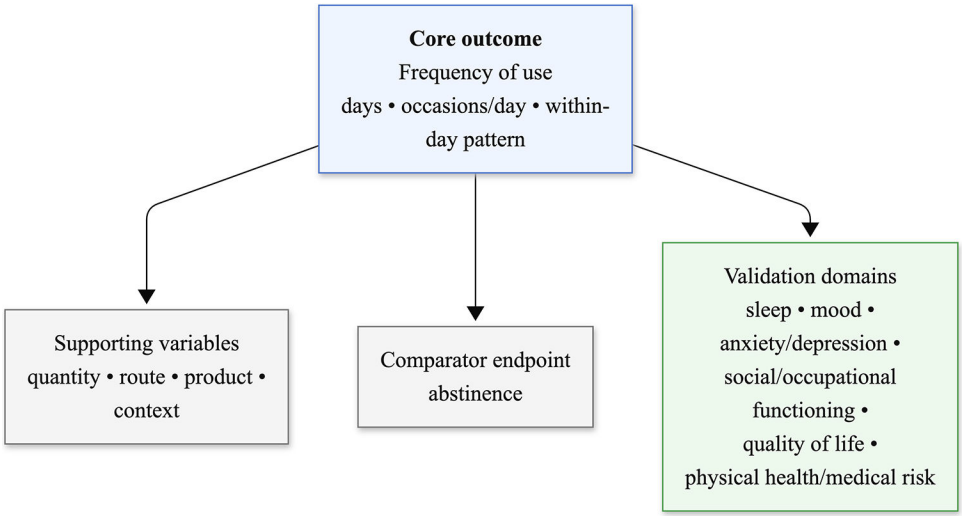

FIGURE 3.
A proposed outcome framework.

TABLE 1

Proposed outcome domains for cannabis use disorder treatment trials.

Domain	Role in matrix	Example measures	Advantages	Limitations
Frequency of use	**Core outcome**	Days of use (e.g., past 28–30 days); days of use per week; occasions per day; time-window use (morning/afternoon/evening/night)	Easy to assess; sensitive to change; interpretable across interventions; aligns with patient goals	May not capture within-day intensity without additional measures; dependent on self-report
Quantity of use	Supporting (interpretive)	Amount used per occasion; product characteristics (e.g., THC concentration); subjective estimates of dose in mg	Captures exposure and potential dose–response relationships; complements frequency	Difficult to standardize across products and routes; often imprecise and reliant on self-report
Abstinence	Core comparator	Point-prevalence abstinence; continuous abstinence; longest duration of abstinence	Clinically intuitive; historically used benchmark; facilitates comparison with prior trials	Definitions vary across studies; biologic verification complicated by prolonged THC metabolite detection
Functioning and health outcomes	Validation domain (establishes dose-response relationships)	Sleep quality; mood; anxiety/depression symptoms; social and occupational functioning; quality of life. Quantifying medical risk across cardiovascular, pulmonary, gastrointestinal, and reproductive outcomes (future research priority)	Patient-centered; reflects meaningful clinical benefit; anchors reduction to real-world outcomes	Multidimensional; may require larger samples or longer follow-up to detect change