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PERSPECTIVE

Controlling the uncontrollable? navigating naturalistic and controlled dosing in cannabis research

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Abstract

Cannabis research is advancing rapidly, yet fundamental questions persist regarding the optimal design of human studies to empirically assess the potential harms and benefits of cannabis. There exist central methodological differences between studies that rely on controlled dose paradigms, ensuring internal validity, and those that utilize naturalistic, self-administration approaches which better reflect real-world use. Controlled paradigms offer precision and regulatory alignment but fail to capture the complexity of real-world cannabis consumption. Naturalistic designs enhance ecological validity but introduce variability and pose challenges for dosing, safety, and replicability. This perspective article presents two methods: one emphasizing the scientific rigor and utility of controlled dose paradigms for regulatory outcomes (e.g., FDA), and the other advocating for naturalistic models that prioritize real-world relevance of legal market cannabis consumption which can inform policy decisions (e.g., guidelines around high THC concentrate). However, rather than representing competing alternatives, controlled laboratory and naturalistic paradigms occupy distinct positions within the evidentiary framework of cannabinoid research, each addressing scientific questions that the other cannot. An integrated methods section proposes ways to incorporate the best features of both approaches to advance cannabinoid science study design.

Keywords Naturalistic dosing · Controlled dosing · Cannabinoid dosing · CBD · THC · Hybrid designs

Introduction

In 2022, an estimated 17.7 million people in the United States (U.S.) reported daily or near-daily cannabis use, surpassing the 14.7 million who reported daily alcohol consumption (Caulkins 2024). Trending alongside this has been the rise of cannabis-related research and scientific publications. Bibliometric analyses have demonstrated significant growth and expansion in this area of research over the past two decades, which is in part driven by widespread use, funding, and policy changes (Treister-Goltzman et al. 2019; Ng and Chang 2022; Mano-Sousa et al. 2024). Yet, despite such drastic increases in cannabis use and scientific focus, researchers continue to grapple with identifying optimal methodologies to conduct rigorous studies that maximize both internal validity for causal inference and external validity for translational relevance.

Although the U.S. is amongst the few global leaders in cannabinoid research, there still exist many challenges and barriers in developing and conducting clinical cannabis studies. A key methodological concern in the field pertains to dose. In this context, controlled dosing refers to the administration of cannabis in which the potency and timing of the dose are specified by the researcher, whereas naturalistic dosing refers to *ad libitum* use based on personal preferences or typical patterns. Due to the absence of a widely accepted validated and standardized dose for cannabis, individual researchers establishing their own controlled dosing protocol can feel unsystematic and limits its translational effects. Conversely, using naturalistic *ad libitum* dosing may provide real-world relevance and keep pace with the evolving patterns of cannabis use; however, without a standard dose to reference, it lacks foundation for interpretation. Therefore, each research design inherently addresses distinct scientific questions regarding dose and

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dosing protocols and together can serve as complimentary methodologies to inform cannabinoid research.

One major barrier in establishing a dosing protocol stem from cannabis' Schedule I status, which has kept it federally illegal despite state-level legalization. Although a 2026 policy change has recently been initiated to reclassify state-licensed medical cannabis status to a Schedule III drug under the U.S. Controlled Substances Act, barriers for researchers to obtain ecologically valid cannabis may be reduced but not eliminated. Research institutions receiving federal funding must comply with federal law, preventing researchers from using dispensary products or permitting cannabis use at federally funded campuses and labs. Consequently, controlled laboratory studies depend on cannabis supplied through the National Institute on Drug Abuse (NIDA) which has historically had a limited number of DEA-approved growers and only recently has this supply expanded beyond low-potency flower to include a wider range of cannabis product type and cannabinoid content (National Center for Complementary and Integrative Health. 2023; National Institute on Drug Abuse 2025). As a result, much of the research to date has limited generalizability and underestimate real-world public health impacts (Vergara et al. 2017; Hutchison et al. 2019).

If, on the other hand, researchers wish to study products available on the legal market, the only option has been to employ naturalistic designs in which participants use their own legally purchased cannabis products off site to capture the use of diverse products types with varying cannabinoid concentrations. These designs sacrifice precise dose standardization and experimental control in favor of ecological validity (i.e., how well study conditions can resemble, and thus translate to, real-world environments) (Freeman et al. 2022). For these reasons, dose-controlled and naturalistic studies provide valuable evidence independently, yet the integration of these approaches can be utilized to address scientific inquires with both rigor and translational utility. How should researchers go about making the decision to use one design versus the other or to take an integrative approach? In this paper, we will inform this question by critically evaluating these two approaches to assess their respective strengths and limitations, as well as their contributions to cannabis research. Cannabis maintains a unique status in substance abuse research, given its diffuse pharmacology and its inconsistent legal status at the state and local level. Until it is possible to conduct placebo-controlled randomized laboratory experiments using legal market cannabis products, multiple complementary methodologies will remain indispensable to advancing cannabis science. Rather than representing competing alternatives, controlled laboratory and naturalistic paradigms occupy distinct positions within the evidentiary framework of cannabinoid research, each addressing scientific questions that the other cannot. Ultimately, we propose an integrative solution that addresses this methodological challenge that is singular to the field of cannabis research and offer a pathway toward advancing study design that generates evidence that is both rigorous and ecologically valid.

Controlled dose paradigms

Controlled experimental designs are fundamental in understanding dose-response relationships through the use of random assignment of cannabinoid dose, thus isolating causal pharmacological effects of cannabis, and allowing researchers to strategically develop a dosing protocol (e.g., amount, frequency, timing and intensity). Foundational research in the field of cannabis science on the behavioral, cognitive (Pope and Yurgelun-Todd 1996), psychotomimetic (D'Souza et al. 2004), reinforcing (Cooper and Haney 2008), withdrawal (Haney et al. 1999), and physiological (Heishman et al. 1990) effects of cannabinoids were first discovered through controlled dose paradigms, some of which have had notable ecological relevance. For example, a dose-controlled, residential human laboratory study utilizing THC-containing brownies, a commonly used recreational form of cannabis, at three doses (10 mg, 20 mg, and 50 mg), was instrumental in characterizing the dose-dependent pharmacokinetic and pharmacodynamic effects of edible cannabinoids (Vandrey et al. 2017).

Beyond this, there have been a number of instances in which observational studies have identified associations between patterns of cannabis use and behavior, which was later to be validated through controlled-dose laboratory studies. For example, cross-sectional surveys have linked problematic cannabis use, and more specifically, high-THC, low-CBD products with greater psychosis risk than balanced THC: CBD products (Hambrecht and Häfner 2000; Morgan and Curran 2008; Forti et al. 2009; Schubart et al. 2011), which was substantiated through rigorous methods of controlled dosing paradigms, by randomly assigning cannabinoid conditions in double-blind, placebo-controlled trials (D'Souza et al. 2004; Englund et al. 2013; Lawn et al. 2023; Ganesh et al. 2023). Further, Bhattacharyya et al. (2010) administered oral THC, CBD, or placebo, and identified distinct neural activation and opposite cognitive effects. They also showed that administering an intravenous dose of CBD before THC prevented THC-induced acute psychotic symptoms, indicating CBD may offer protective effects (Bhattacharyya et al. 2010). These findings underscore the unique value of controlled dosing paradigms, specifically regarding the timing of dose and protocol of dosing multiple cannabinoids, in causally linking specific cannabinoids with biological and psychological outcomes. In addition,

such research highlights the hypothesis-generating influence observational studies can have for controlled-dose paradigms.

Next, observational studies have consistently linked high-THC cannabis with greater driving impairment and crash risk (Asbridge et al. 2012; Hartman and Huestis 2013), however; controlled studies later established causality. One dose-controlled trial using vaporized cannabis found that products with equal parts THC and CBD impaired simulated driving as much as THC-dominant cannabis did. Interestingly, when compared to the THC-dominant cannabis, among participants dosed with a formulation of equal parts THC and CBD, it was found that CBD actually intensified the impairment on some tasks (Arkell et al. 2020). Such findings highlight pharmacokinetic complexities detectable only via controlled dosing.

Further, a controlled dosing protocol is essential for medication development and regulatory approval by agencies such as the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA), which require placebo-controlled randomized trials to determine efficacy and safety. Cannabis-based medications including Epidiolex© (Devinsky et al. 2017; Thiele et al. 2018) and Sativex© (Blake et al. 2006; Nurmikko et al. 2007; Vermersch 2011) gained approval through such trials. Informatively, CBD's clinical use for seizures like Dravet Syndrome began with anecdotal and observational evidence (Hussain et al. 2015; Tzadok et al. 2016; Devinsky et al. 2016); however, preclinical studies and placebo-controlled trials were required to confirm safety, tolerability, and dose-response efficacy. Although naturalistic, observational study designs gathered invaluable anecdotal reports on CBD's therapeutic effect, to verify such evidence studies require control of dose exposure, fidelity, accuracy, and adherence. Without this rigor, regulatory approval and clinical integration of cannabis-based medications would not be possible.

Controlled dosing designs also address key confounds in cannabis research by employing standardized protocols and random assignment, which minimize selection effects and maximize internal validity (Shadish et al. 2002). This rigor ensures precise dosing, reduces expectancy and co-use confounds (Subbaraman and Kerr 2015; Ito et al. 2021; Chen et al. 2025b), and allows reliable replication. As a result, controlled laboratory studies provide causal inferences, valid dose–response effects, and data that can be synthesized across trials to build cumulative knowledge in cannabis science.

Beyond methodological rigor, studies with controlled dosing also offer other practical and ethical benefits that may take precedence over external validity, depending on the stage of scientific development. Compared to naturalistic, *ad libitum* administrations, standardized dosing conducted in laboratory settings under researcher supervision allows for safety monitoring, so potential adverse reactions are noticed and managed quickly and effectively. This enhances participant safety, especially among vulnerable populations (e.g., older adults, individuals with existing psychiatric symptoms) who might be at greater risk for cannabis-related adverse effects (Lev-Ran et al. 2013; Han et al. 2023). Moreover, controlled dosing may promote greater compliance and less adverse events due to relatively consistent cannabinoid exposure across participants over the course of the study, which is often not feasible in naturalistic settings. Although often informed by naturalistic, observational data, controlled dose research remains the gold standard for generating dose-response data essential to regulatory approval. These data also guide clinical practice, providing healthcare providers with evidence-based recommendations amid rising patient interest in medical cannabis (Ziemianski et al. 2015). Standardized dosing and random assignment are required to establish causality, support approval of cannabis-based medications, and inform public health policies and safety guidelines.

Naturalistic, self-administration designs

The evolution of legal market cannabis has outpaced researchers' ability to holistically test its effects in federally funded, dose-controlled trials, leaving notable knowledge gaps on the public health impact of legal market use (Vergara et al. 2017; Sevigny et al. 2023; Rezkalla and Kloner 2024). Naturalistic observational research has helped fill this gap, providing critical insights into the rapidly evolving market while simultaneously informing dose-controlled study designs (Englund et al. 2023). In self-administration studies, participants use either their own product or a randomly assigned dispensary product as they typically would, therefore featuring doses that are more representative of real-world THC exposure (which is often higher than that observed in fixed-dose designs) and associated effects (Cooper and Haney 2009; Bidwell et al. 2020). For example, in the previously referenced controlled-dose study testing for driving impairment following THC and CBD inhalation, participants used a THC cannabis flower dose of 13.75 mg, which was significantly lower than what has been reported in *ad libitum* cannabis studies (51.25 mg) (Arkell et al. 2020; Bidwell et al. 2022). Although controlled laboratory studies can examine a wide range of THC doses, including relatively high exposures, standardized dosing protocols and regulatory constraints may result in the use of more conservative dosing regimens when compared to naturalistic use. Thus, doses used and cannabinoid blood levels seen in controlled studies may not always reflect typical

exposure patterns in naturalistic settings, which can limit generalizability of findings.

For one, tolerance, metabolism, and self-titration make use highly variable across individuals, which has created notable challenges in defining a standardized dose for cannabis. Unlike alcohol, for which the Widmark formula provides a standardized (albeit imperfect given known variability in metabolism and tolerance) approach to dosing based on sex and body weight (Widmark 1922), no reliable dosing formula yet exists for cannabis. Importantly, this limitation affects both controlled and naturalistic study designs. Naturalistic approaches do not eliminate this variability; rather, they allow researchers to characterize how users adaptively self-titrate dose through adjustments in frequency, inhalation patterns, and product selection to achieve desired effects (Heishman et al. 1989; McClure et al. 2012; van der Pol et al. 2014; Leung et al. 2021), which can later inform and guide dose-controlled study designs. There is evidence to suggest that certain patterns of smoking puff topography (e.g., increased puff inhalation volume) may be associated with increased blood THC levels, subjective effects, and dependence severity (Azorlosa et al. 1995; Korf et al. 2007; McClure et al. 2012; van der Pol et al. 2014). Frequent cannabis users may also develop a tolerance and prefer to use larger amounts of higher potency products to achieve desired effects (Leung et al. 2021; Borodovsky et al. 2025).

In addition, cannabinoid concentrations reported on legal-market product labels are often inaccurate or inconsistent (Giordano et al. 2025), which can further complicate dose estimation in naturalistic studies but highlights the importance of studying cannabis exposure as it actually occurs in real-world settings. Although regulations for state-licensed independent laboratory testing of retail cannabis is standard across the U.S., and provides a certificate of analyses and description of the cannabinoid content of products sold (Missouri Department of Health and Senior Services 2023; Colorado Department of Revenue 2024; Oregon Health Authority (OHA) 2025), labeled THC concentrations can vary by +/- 15%. Together, these factors make it such that even when controlled administration studies include moderate to high THC doses, standardized dosing protocols may not reflect the dynamic self-titration strategies among people who use cannabis employ in real-world settings. Further, rigid dosing protocols also run the risk of deterring participation in populations already familiar with cannabis by failing to accommodate for individuals' preferences.

Naturalistic study designs therefore offer advantages for ecological validity by capturing real-world behaviors and preferences across product form (flower, edible, concentrate) (Inman and Cservenka 2024; Han et al. 2025), mode of administration (e.g., joint vs. bong) (Gunn et al. 2020; Swan et al. 2021; Cloutier et al. 2022; Chen et al. 2025a), strain (Belendiuk et al. 2015; Gilbert and DiVerdi 2018; Okey et al. 2022), and cannabinoid content (Boehnke et al. 2019; Shi et al. 2019). Until recently, practices such as dabbing THC concentrates could not be examined in dose-controlled studies. Even now this research remains extremely rare due to strict regulatory barriers, lack of access to commercially relevant high-THC products, and potential ethical concerns around administering potent forms of cannabis in controlled settings. Indeed, self-administration studies show that concentrates, particularly dabs, produce greater THC exposure and intoxication (Bidwell et al. 2020; Chen et al. 2025a) and are linked to higher cannabis use disorder (CUD) symptoms and cannabis-related consequences (Bidwell et al. 2018; Gunn et al. 2020). These findings carry major public health relevance by reflecting how high-potency products are actually used in legal markets. Even so, variability in cannabis product composition, self-selection, tolerance, and uncontrolled environmental factors all limit causal inference when conducting naturalistic observational studies. Thus, naturalistic designs cannot simply substitute the rigor and reproducibility by controlled laboratory studies, rather, this highlights the potential benefits of integrating study designs that incorporate legally available cannabis products within a controlled laboratory setting to enhance translational relevance while still maintaining a rigorous approach. Thus, these key gaps in the literature remain.

Further, naturalistic designs are uniquely poised to investigate individuals' experiences using cannabis in their daily lives over time. Longitudinal naturalistic studies have documented therapeutic benefits of cannabis for chronic pain (Cuttler et al. 2022; Melendez et al. 2024), insomnia (Kuhathasan et al. 2021; Nacasch et al. 2022), and anxiety and depression (Cuttler et al. 2018; Ross et al. 2018; Minhas and Lunn 2023), reflecting effects that may be overlooked in controlled paradigms. Social context also shapes subjective effects, affective experiences, and risks, with implications for both medical and recreational users (Spinella et al. 2019; Okey et al. 2022; Denson et al. 2023; Chang et al. 2024). It is also unclear whether cannabis tolerance varies across familiar versus unfamiliar environments, as shown with opioids (Siegel 1984; Gerevich et al. 2005). Thus, relying solely on controlled doses and settings may distort conclusions about cannabis's therapeutic benefits and risks despite its widespread use in daily life.

In summary, naturalistic at-home use, EMA, and dispensary-partnered studies capture product choice, frequency, dosing, and contextual influences largely absent from laboratory-based designs. Ecological momentary assessment (EMA) is especially valuable for capturing real-time patterns of use, context, and consequences. Such approaches may generate more generalizable data to better inform

public health and policy (Haug et al. 2017; Stith et al. 2023), however there remain fundamental limitations on the inferences and interpretations drawn from such designs. Also, naturalistic designs are more susceptible to confounding from expectancy effects (Chen et al. 2025b), self-selection bias (Skrzynski et al. 2026), and imprecision in estimating cannabinoid dose, particularly given variability in legal-market labelling (Giordano et al. 2025). Additionally, because exposure is not experimentally controlled, naturalistic studies are not appropriately suited for establishing dose-response relationships and causal interpretability the way dose-controlled laboratory paradigms are, ulimately emphasizing the importance of integrating both approaches.

Bridging the divide: designing smarter, integrated methods for cannabis research

Controlled and naturalistic dosing paradigms are designed to achieve complementary goals in understanding the effects of cannabis and cannabinoid use, and both methods have evident strengths. However, when these studies are conducted in isolation each have notable limitations. Growing methodological literature has emphasized that these two approaches should be triangulated to offer more robust and translational findings (Munafò and Davey Smith 2018; Freeman et al. 2022; Englund et al. 2022). It is proposed that controlled and naturalistic dosing approaches be integrated to better capture the full spectrum of cannabis effects and adequately advance cannabis research. Importantly, the choice between controlled, naturalistic, or hybrid dosing approaches should be guided by the specific research questions being asked. Studies designed to establish causal pharmacological mechanisms or support medication development typically require tightly controlled dosing protocols, whereas studies examining real-world patterns of use, population-level exposure, or policy-relevant outcomes may benefit from naturalistic designs. Hybrid approaches are particularly useful when research questions span both domains: for example, when translating laboratory dose-response findings into real-world effectiveness or when using observational data for inform experimental dose selection. Below, we present several strategies for integrating these two methodologies that leverage the complementary strengths of both and provide researchers with a framework for moving the field forward.

Controlled-dose studies with naturalistic follow-up (or vice versa)

Integrating controlled and naturalistic designs can balance internal and external validity. One approach is to conduct a controlled-dose study followed by a naturalistic follow-up, akin to the progression from efficacy (e.g., effect under controlled conditions) to effectiveness (e.g., effect in real-word settings) trials in clinical research (Abu-Sawwa et al. 2022; Georgieva et al. 2023; Schenberg 2025). Although uncommon in cannabis research, this two-phase model has demonstrated value. A well-known example is Epidiolex (cannabidiol) for epilepsy: while RCTs identified adverse effects such as diarrhea and elevated liver enzymes (Devinsky et al. 2017, 2018), follow-up studies using medical record data revealed different real-world outcomes, including discontinuation due to lack of effectiveness or seizure worsening, and the interaction with clobazam dosing (Georgieva et al. 2023). Such findings illustrate that controlled trials alone may produce "extrapolator's fallacy," assuming efficacy observed in RCTs will generalize across diverse populations and contexts (Singal et al. 2014; Schenberg 2025). A two-phase design allows controlled studies to establish safety, dosing, and proof of concept, while naturalistic follow-ups capture tolerability and effectiveness in broader use.

Alternatively, naturalistic studies can precede controlled dosing trials. Observational data on product type, potency, patterns of use, reasons for use, and self-reported outcomes can guide which products NIDA sources for research and help refine hypotheses for controlled dose testing. This bottom-up approach systematically translates real-world data into more rigorous protocols, enabling researchers to evaluate causal relationships between cannabis use and reported benefits or risks.

Controlled-dose paradigms are the gold standard and are required for the approval of cannabis-based medicines. However, when considering the development of such therapeutics, a combination of controlled and naturalistic approaches can help to establish both causal efficacy and dosing parameters, in addition to real-world safety and effectiveness. On the other hand, collecting naturalistic observational data on patterns and dosing of cannabinoids for a specified condition can then later be used to inform a controlled experimental design. Researchers can prioritize dose fidelity and accuracy in their controlled study while focusing on broader product inclusion and dose variability in the naturalistic design in order to maximize translational relevance.

Hybrid trial design

Hybrid approaches, including pragmatic trials, adaptive designs, and Bayesian methods, are increasingly used to advance drug development, assess treatment effects, accelerate data collection, and provide functional, real-world outcomes (Zhu et al. 2020; Freeman et al. 2020; Bergmans et al. 2024; Deb 2025). For example, Freeman et al. (2020)

conducted a placebo-controlled adaptive Bayesian trial of CBD for cannabis use disorder, using the first stage of the study to identify efficacious doses and limiting the second stage to only those effective doses, which was characterized by meaningful clinical outcomes such as reduction in cannabis use days and abstinence rates.

Further, as use of fixed doses rarely occurs outside of a research setting, hybrid protocols could also allow self-titration within a predefined range, preserving experimental control while accounting for external validity (e.g., real-world titration) and individual variability (e.g., tolerance). This strategy can support dose optimization (Korn et al. 2023; Guo and Yuan 2023). It has been tested with nabiximols for cannabis withdrawal and craving, where self-titration was well tolerated but produced lower doses and modest efficacy compared to fixed dosing (Trigo et al. 2016, 2018). In addition, a recent study assessing the potential protective effects of CBD prior to THC use among individuals with schizophrenia, utilized fixed doses of THC which was later noted as a limitation highlighting that participants could not self-titrate to their desired level of intoxication. Thus, it is unclear what effect the CBD would have had in a hybrid (CBD dose-controlled THC self-titrated) study design which would better reflect real-world THC use (Chesney et al. 2025).

Combined, these studies suggest that predefined ranges for participant self-titration may balance tolerability with therapeutic effectiveness. Referencing the, albeit limited, existing literature on cannabis dosing protocols and considering the researcher's study aims for testing cannabinoids (e.g., symptom reduction, subjective intoxication, medication substitution, neurocognitive effects, etc.) researchers can employ a hybrid dosing strategy to ensure clinical significance with real-world relevance.

Remote or decentralized trials

Remote and decentralized trial designs offer a promising strategy for studying dose-dependent cannabis effects in naturalistic environments while retaining elements of experimental trials, particularly when repeated measurement approaches such as EMA or biological validation are incorporated. Emerging work demonstrates the feasibility and scientific value of remote, participant-guided cannabis trials, even in federally illegal contexts. For example, Palmer et al. (2022) conducted a remote, randomized controlled trial using a behavioral intervention for nicotine vaping cessation fully delivered via telehealth, showing that naturalistic paradigms can still yield interpretable, policy-relevant outcomes (Palmer et al. 2022). The use of remote monitoring in cannabis research may pose a greater challenge in assessing reduction of use due to the lack of a simple, reliable biomarker measure. Developing such tools remains essential to support more scalable and accessible study designs, such as integrating designs like dose-controlled cannabis use in a naturalistic environment. Further, this participant-focused method can also facilitate recruitment of greater diversity in participant pools, an area in which clinical trial research continues to lack (Turner et al. 2022; Syder and Elbuluk 2023). For example, a study by Stewart et al. (2022), comparing clinic-based versus remote trials found that remote trials had increased racial, ethnic, and geographic location diversity among study participants (Stewart et al. 2022).

Another decentralized integrated trial approach is validating self-report EMA data with plasma THC and CBD levels. EMA is widely used in naturalistic studies to capture real-time subjective experiences and patterns of cannabis use. In hybrid trials, EMA reports of frequency, potency, and product type can be periodically validated through blood draws. For example, when testing products with varying cannabinoid content (e.g., THC-dominant, CBD-dominant, edibles, concentrates), researchers can match reported use and dosing with plasma levels, providing objective biological data and convergent validation. These combined data also allow assessment of acute and residual cannabinoid levels relative to reported doses (Bidwell et al. 2024).

EMA can be further strengthened through digital phenotyping, which uses smartphones and wearables to collect both passive (e.g., GPS, screen time, sleep, heart rate) and active data (EMA surveys, symptom ratings). This method characterizes patterns of use and captures dose-dependent behavioral and physiological changes in real time (Onnela 2021; Zhang et al. 2025). Through the collection and evaluation of this continuous active and passive data, in addition to cannabis use characterization, digital phenotyping can support development of dose ranges by enabling precise correlations between real-world exposure and individual-level behavioral and physiological responses (Carpenter et al. 2020). Together, these approaches are especially well suited for research questions that require capturing variability in real-world cannabinoid exposure while maintaining sufficient measurement precision to evaluate dose-response relationships across individuals and contexts.

Other considerations

Incorporating hybrid trial and integrated designs, researchers are better positioned to combine the causal inference afforded by controlled dosing with the real-world relevance afforded by naturalistic designs. In pursuing innovative study designs and approaches for cannabis and cannabinoid research, there are several factors to consider in the development and execution of these trials. For instance, when

Table 1 Comparison of key strengths and limitations of controlled vs. naturalistic designs and the key elements of the proposed integrated designs

Study Design	Description	Strengths	Limitations
Dose-controlled	Dose-controlled design in which participants receive **fixed doses** of cannabis products to evaluate its efficacy and dose-response effects	• Higher internal validity • Enables examination of causal effects and dose-response relationship • Clearer assessment of underlying pharmacokinetic and pharmacodynamic mechanisms • Necessary for medication development and approval from regulatory agencies	• Low external validity and generalizability • Not reflective of medicinal or recreational cannabis products or potency • Difficult to account for tolerance or individual variability of use
Naturalistic	Observation of participants who use cannabis in their natural environments **without experimental control** over dosage, product type, or usage patterns, to assess real-world effects and behaviors	• Higher external validity (e.g., reflects real-world cannabis use including products, dosing, exposure, and frequency) • Can examine broad and diverse range of cannabis product and methods • Ability to study cannabis self-titration and tolerance	• Low internal validity • Difficult to replicate • Greater confounding factors (e.g., self-selection and expectancy bias • Inconsistent or inaccurately reported dosing
Study Design	Description	Key elements	
Integrated Designs	Integration of dose-controlled and naturalistic use study **designs for optimizing** cannabis research clinical trials	• Controlled-dose study followed by naturalistic study (or vice versa) • Self-titration of cannabis use within predefined dose range • Bring-your-own cannabis product for use evaluated in a laboratory setting • Fully remote or decentralized clinical trials • Ecological momentary assessment and digital phenotyping for advancing observation of naturalistic use	

conducting a naturalistic trial that is specifically evaluating multiple cannabis products, it is of critical importance to allow for random assignment to product type (e.g., flower, concentrates, edibles). Allowing participants to choose their own cannabis product can exacerbate the problems of expectancy bias and selection effects (Boden et al. 2013; Anthenien et al. 2021). When random assignment is not possible due to regulatory (e.g., IRB) requirements, there is some evidence that quasi-random assignment, such as when participants are randomly assigned to a product and then can either accept or reject assignment, yields relatively unbiased results (Skrzynski et al. 2026). Accuracy and reliability in reporting cannabis product types, routes of administration, and cannabinoid content (THC and CBD) is essential across all study designs. When utilizing legal-market products in hybrid research designs, researchers should prioritize obtaining and reporting independent third-party laboratory testing data on cannabinoid content and product consistency within and across packages, batches, and lots. While such testing does not fully characterize individual exposure or dose, it provides important information for interpreting study findings and contextualizing product use (National Academies of Sciences, Engineering, and Medicine et al. 2017; Colorado Department of Revenue 2024). Equally important is standardization in assessment of cannabis use patterns and reporting of self-titrated doses and dose ranges to support research, clinical, and policy applications (Freeman and Lorenzetti 2020; Volkow and Weiss 2020). Given the wide variability of medical and recreational products, defining a "standard" dose remains challenging (Oldfield et al. 2021; Spindle et al. 2022; Stith et al. 2023). Standardized assessment and reporting are also critical for harmonizing data across studies and enabling meta-analyses.

Conclusion

As recreational and medical cannabis markets expand rapidly, research must keep pace. Conducting cannabis clinical trials presents significant methodological and logistical challenges, but innovative designs can leverage the complementary strengths of internal and external validity, providing critical evidence on cannabis's risks and benefits for public health Table 1.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Not applicable.

Ethical considerations There were no human participants in this article and informed consent was not required.

Competing interests The authors declare no competing interests.

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