

Acute Psychiatric, Cognitive, and Use-Related Effects of High-Potency Cannabis in Young Adults without Psychotic Disorders: A Systematic Review of Randomized Controlled Trials

Psikotik Bozukluğu Olmayan Genç Yetişkinlerde Yüksek Potansiyelli Esrarın Akut Psikiyatrik, Bilişsel ve Kullanıma Bağlı Etkileri: Randomize Kontrollü Çalışmaların Sistematiik Bir Derlemesi

Ana López Arbeláez¹, Jhoan Vidal Utria Castro², Francisco Javier Gómez Ballesta³

¹Pontificia Universidad Javeriana Bogotá, Colombia

²Asociación de Psiquiatras de Argentina, Buenos Aires, Argentina

³Universidad Autónoma de Bucaramanga, Santander, Colombia

ABSTRACT

Cannabis potency has increased substantially in recent decades, with tetrahydrocannabinol (THC)-dominant products and high THC: cannabidiol (CBD) ratios raising concerns about their impact on mental health. To synthesize evidence from randomized controlled trials (RCTs) on the acute psychiatric, cognitive, physiological, and use-related effects of high-potency cannabis in young adults without psychotic disorders. A systematic review of 10 RCTs (total n≈391) was conducted, risk of bias assessed using RoB 2. Studies compared isolated THC or THC-dominant formulations with placebo or CBD-containing preparations. No meta-analysis was performed because of substantial clinical and methodological heterogeneity across routes of administration, THC dose, THC:CBD ratios, outcome instruments, timing of assessments, and participant characteristics. GRADE was not applied because the evidence base consisted of short-duration experimental studies with sparse study counts per outcome and heterogeneous acute outcomes, making formal certainty ratings likely to imply spurious precision. Compared with placebo, THC significantly increased psychotomimetic symptoms [Positive and Negative Syndrome Scale (PANSS) positive subscale: d=0.69; p=2.41×10⁻⁵], impaired immediate verbal memory (Hopkins verbal learning test-revised: d=0.82; p=1.31×10⁻⁶), and elevated heart rate (d=1.39; p=5.06×10⁻¹²). Approximately 52.2% of participants exhibited a PANSS response (≥3-point increase) in at least one session. Adding CBD at ratios up to 3:1 did not consistently attenuate THC effects compared with THC alone (p>0.008). However, 9 of 10 studies were judged to be at high-risk of bias, which substantially limits confidence in these findings. Experimental evidence suggests that THC-dominant cannabis can produce acute psychotomimetic effects and cognitive impairment under controlled conditions. However, because most included studies were at high-risk of bias and outcomes were heterogeneous, these findings should be interpreted as low-certainty and hypothesis-generating rather than confirmatory. The review does not establish long-term risk of psychosis, schizophrenia, or cannabis use disorder.

Keywords: Cannabis, tetrahydrocannabinol, cannabidiol, psychosis, substance-related disorders

ÖZ

Son yıllarda kenevirin etki gücü önemli ölçüde artmış; tetrahidrokannabinol (THC) ağırlıklı ürünler ve yüksek THC: kannabidiol (CBD) oranları, bunların ruh sağlığı üzerindeki etkilerine dair endişeleri beraberinde getirmiştir. Bu çalışma, psikotik bozukluğu olmayan genç yetişkinlerde yüksek etkili kenevirin akut psikiyatrik, bilişsel, fizyolojik ve kullanıma bağlı etkilerine ilişkin randomize kontrollü çalışmalardan (RKÇ) elde edilen kanıtları sentezlemeyi amaçlamıştır. Toplam 391 katılımcıyı (n≈391) kapsayan 10 RKÇ üzerinde sistematiik bir derleme yapılmış ve yanlılık riski RoB 2 aracıyla değerlendirilmiştir. Çalışmalar; izole THC veya THC ağırlıklı formülasyonları, plasebo veya CBD içeren preparatlarla karşılaştırmıştır. Uygulama yolları, THC dozu, THC:CBD oranları, sonuç ölçüm araçları, değerlendirme zamanlamaları ve katılımcı özellikleri açısından önemli klinik ve metodolojik heterojenlik bulunması nedeniyle meta-analiz yapılmamıştır. Kanıt tabanının kısa süreli deneysel çalışmalardan oluşması, her bir sonuç için çalışma sayısının azlığı ve akut sonuçların heterojenliği nedeniyle GRADE yöntemi uygulanmamıştır; zira bu koşullar altında yapılacak resmi kesinlik derecelendirmeleri, yanıltıcı bir kesinlik izlenimi yaratabilirdi. Plasebo ile karşılaştırıldığında THC; psikotomimetik semptomları anlamlı düzeyde artırmış [pozitif ve negatif sendrom ölçeği (PANSS) pozitif alt ölçeği: d=0,69; p=2,41×10⁻⁵], kısa süreli sözel belleği bozmuş (Hopkins sözel öğrenme testi-gözden geçirilmiş formu: d=0,82; p=1,31×10⁻⁶) ve kalp atım hızını yükseltmiştir (d=1,39; p=5,06×10⁻¹²). Katılımcıların yaklaşık %52,2'si, en az bir oturumda PANSS yanıtı (≥3 puanlık artış) göstermiştir. 3:1 oranına kadar

Address for Correspondence/Yazışma Adresi: Francisco Javier Gómez Ballesta, MD, Universidad Autónoma de Bucaramanga, Santander, Colombia

E-mail: franciscogomezball@gmail.com ORCID: orcid.org/0009-0003-5191-1269

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CBD eklenmesi, tek başına THC kullanımına kıyasla THC'nin etkilerini tutarlı bir şekilde hafifletmemiştir ($p>0,008$). Bununla birlikte, 10 çalışmadan 9'unun yüksek yanlılık riski taşıdığı değerlendirilmiş ve bu durum, bulgulara duyulan güveni önemli ölçüde sınırlamıştır. Deneyisel kanıtlar, THC ağırlıklı kenevirin kontrollü koşullar altında akut psikotomimetik etkilere ve bilişsel bozulmaya yol açabileceğini göstermektedir. Ancak, dahil edilen çalışmaların çoğunun yüksek yanlılık riski taşıması ve sonuçların heterojen olması nedeniyle, bu bulgular doğrulayıcı nitelikte olmaktan ziyade düşük kesinlikle ve hipotez oluşturucu nitelikte yorumlanmalıdır. Bu derleme, psikoz, şizofreni veya kenevir kullanım bozukluğu açısından uzun vadeli bir risk ortaya koymamaktadır.

Anahtar Kelimeler: Kenevir, tetrahidrokannabinol, cannabidiol, psikoz, madde ile ilişkili bozukluklar

Introduction

The potency of cannabis available in many markets has increased markedly over recent decades, often accompanied by an increase in the $\Delta 9$ -tetrahydrocannabinol (THC) to cannabidiol (CBD) ratio, i.e., THC:CBD (that is, THC-dominant products). In the United States, forensic analyses have shown a sustained rise in the percentage of THC in plant material since the mid-1990s, along with changes in the relative presence of CBD.¹ Consistently, international studies including data from Europe have also documented substantial increases in THC and in the THC:CBD ratio in recent periods² and, specifically, seized resin has been described as showing a relevant increase in THC and in the THC:CBD ratio in national forensic series.³ This compositional shift is clinically relevant because THC, the main psychoactive agonist, can acutely induce a spectrum of transient psychiatric and cognitive effects in humans, including psychotomimetic symptoms, anxiety, and memory disturbances, with large effect sizes reported in quantitative syntheses.⁴ In adults with low or no recent exposure, controlled administration of THC via different routes [e.g., intravenous (IV) or inhaled] has shown dose-dependent cognitive impairment and increased subjective adverse effects.⁵⁻⁷

However, despite biological plausibility and the public health concern associated with “high-potency” products, key uncertainties remain regarding the specific role of the cannabinoid profile (high THC and/or high THC:CBD ratio) in mental health outcomes under experimental conditions. On the one hand, randomized trials suggest that CBD may modulate some effects of THC (e.g., paranoia or impairment of episodic memory in certain paradigms),⁸ and controlled studies evaluating THC and CBD alone and in combination have explored these effects on psychotic symptoms and memory;⁹ yet other experimental studies have not shown consistent attenuation when CBD is co-administered with inhaled THC, even with equivalent THC/CBD formulations.¹⁰ Likewise, in a design using vaporized cannabis comparing chemotypes, THC/CBD-equivalent cannabis induced less state anxiety than THC-dominant cannabis, with signals of effect modification by baseline anxiety.¹¹ On the other hand, much of the experimental evidence comes from samples with heterogeneous use patterns (including frequent users), which is critical because frequent use is associated with attenuated psychotomimetic responses to THC (possible tolerance or “blunting”), complicating extrapolation to occasional/infrequent users or those recently abstinent.⁶ Taken together, the available evidence suggests relevant acute effects, but it remains fragmented and methodologically diverse for

determine precisely whether “high potency” (THC-dominant/high THC:CBD) entails a greater burden of adverse effects than lower-potency products or placebo in young adults without psychotic disorder.

Within this framework, our hypothesis is that, in young adults without psychotic disorder, exposure to high-potency cannabis (THC-dominant; high THC and/or high THC:CBD ratio) is associated with greater adverse mental health effects reflected in increased psychotomimetic symptoms and anxiety, greater cognitive impairment (especially in memory), and greater craving or consumption-related problems, compared with lower-potency cannabis (lower THC and/or higher CBD) or placebo. We further propose that baseline vulnerability, including subclinical psychotic traits, trait anxiety, family history, prior sensitivity to cannabinoids, and selected biological factors, may modify the magnitude of these effects, contributing to the variability observed across studies. However, such vulnerability factors were expected to be reported heterogeneously across trials and were therefore treated as potential effect modifiers rather than uniformly measurable exposures.

Therefore, the aim of this systematic review was to synthesize evidence exclusively from randomized controlled trials (RCTs) in young adults without psychotic disorder who were occasional/infrequent users or recently abstinent, comparing high-potency cannabis versus lower-potency cannabis or placebo, in order to estimate the acute effect on: (1) psychotomimetic symptoms, (2) anxiety, (3) cognitive performance with an emphasis on memory, and (4) craving and outcomes related to consumption-related problems. Additionally, we explored the role of baseline vulnerability and polysubstance use as potential moderators, recognizing that these factors were not expected to be assessed systematically across all included trials.

Methodologically, this review was restricted to RCTs and used RoB 2 for outcome-level risk-of-bias assessment. Meta-analysis was prespecified only if at least two studies were sufficiently comparable in intervention profile, route of administration, comparator, participant characteristics, timing of assessment, and outcome measurement. This threshold was not met. Heterogeneity was substantial at multiple levels, including oral, IV, vaporized, and oromucosal administration; wide variation in THC dose and THC:CBD ratios; crossover and parallel designs; different user profiles (infrequent, recreational, and frequent users); and non-equivalent instruments and time windows for psychotomimetic, cognitive, anxiety, physiological, and use-related outcomes. Pooling under these conditions would have produced summary estimates with limited clinical

interpretability. Accordingly, we conducted a structured narrative synthesis and reported study-level standardized effect sizes in summary tables. GRADE was not applied because the evidence base consisted predominantly of short-duration experimental studies, with sparse study counts per comparison/outcome and heterogeneous acute or surrogate endpoints, making formal certainty ratings difficult to interpret and prone to overstating precision. Instead, interpretation was grounded in RoB 2 judgments, consistency in the direction of effect, directness to the acute experimental question, and clinical plausibility.

Methods

Study Design

We conducted a systematic review of the literature focused on RCTs that assessed, in young adults without psychotic disorder, the acute effects of exposure to/administration of high-potency cannabis (THC-dominant; high THC and/or a high THC:CBD ratio) on psychiatric, cognitive, physiological, and use-related outcomes, compared with lower-potency cannabis or placebo. The review protocol was registered prospectively under registration number 1343813. Results were synthesized without meta-analysis because prespecified clinical and methodological heterogeneity precluded meaningful quantitative pooling.

Eligibility Criteria

Types of Studies

We included RCTs comparing high-potency cannabis with lower-potency cannabis and/or placebo. We excluded non-randomized studies, observational studies, case series, qualitative studies, animal studies, and reviews.

Types of Participants

We included young adults (e.g., ≥ 18 years, with mean/median within the young-adult range as defined by each study) without a baseline diagnosis of psychosis, schizophrenia, or schizophrenia-spectrum disorders. Broad age ranges (including studies starting at age 16) were accepted when samples represented non-psychotic populations and the aim was to evaluate acute/subacute effects of THC/CBD.

We included infrequent/occasional users and frequent non-dependent recreational users, provided the trial controlled exposure through prior abstinence (e.g., 12-24 h or as specified), toxicology screening, and/or restrictions close to the session (alcohol/tobacco/cafeine or other substances).

Baseline vulnerability variables and relevant comorbidities were recorded and extracted when available (e.g., family history of psychosis, subclinical symptoms, baseline anxiety, endocannabinoid/COMT genotypes).

Types of Interventions/Exposures

Exposure was defined as controlled administration of THC ($\Delta 9$ -THC) and/or cannabis preparations (vaporized cannabis/

extracts, oral/oromucosal formulations, or IV), with explicit reporting of dose/concentration and, when applicable, CBD content and the CBD:THC ratio.

- **Higher potency:** THC without CBD or with a high THC:CBD ratio (e.g., CBD:THC 0:1 or 1:1), higher THC dose (dose-response), or extracts/cannabis with high THC (mg or %).

- **Comparators:** Lower potency (lower THC and/or relatively higher CBD; e.g., CBD:THC 2:1-3:1+) and/or placebo/vehicle (hemp/capsules/spray/IV vehicle).

Inhaled/vaporized, oral, oromucosal, and IV routes were accepted when protocols were standardized and described washout in crossover designs.

Types of Outcomes

Primary outcomes

- Acute psychotomimetic/psychotic symptoms [e.g., Positive and Negative Syndrome Scale (PANSS) positive subscale, Psychotomimetic States Inventory (PSI), Social Problem-Solving Scale (SSPS), community assessment of psychic experiences].
- Acute anxiety [e.g., visual analogue scale (VAS) for anxiety or other scales].
- Cognition, especially verbal memory [e.g., Hopkins verbal learning test-revised (HVLT-R), Rey auditory verbal learning test (RAVLT)] and/or attentional performance.

Secondary outcomes

- Craving, cue salience, and endophenotypes related to problematic use (e.g., metacognitions questionnaire, dot-probe, satiety/wanting).
- Subjective effects [e.g., high, drug liking, Addiction Research Center Inventory (ARCI)], adverse events.
- Neurophysiological measures associated with psychotomimetic states (e.g., electroencephalography/auditory steady-state response, "neural noise").

Exclusion Criteria

Studies were excluded when they: (i) included baseline psychosis/schizophrenia or absence of psychosis could not be ensured; (ii) did not report dose/ratio and did not allow inference of relative potency; (iii) were not randomized; (iv) evaluated non-relevant outcomes (pharmacokinetics only, without clinical correlates); or (v) were animal/*in vitro* studies.

Search Methods for Study Identification

Electronic Searches

Systematic searches were conducted in PubMed/MEDLINE, Embase, and LILACS from database inception to 10 February 2026. Search strategies combined controlled vocabulary (e.g., MeSH/Emtree/DeCS) and free-text terms for cannabis/marijuana, $\Delta 9$ -THC, CBD, potency (high THC and/or THC:CBD ratio), and psychotomimetic, anxiety, cognition, and use-related outcomes. The full search strategies for all databases, including

PubMed/MEDLINE, are provided in Supplementary Tables 1-3. No language restrictions were applied.

Other Sources

Reference lists of included studies and contextual articles were reviewed to identify additional trials. Conference abstracts and gray literature were not searched because such records often provide incomplete or unverifiable methodological and outcome information, with higher risks of duplication and reporting bias, which could compromise RoB 2 assessment and comparability across studies. Instead, we prioritized fully reported sources (peer-reviewed articles) and, when applicable, consulted trial registries to corroborate the existence of unpublished studies.

Data Collection and Analysis

Study Selection

At least two reviewers independently screened titles and abstracts and then independently assessed the full texts of potentially eligible studies against prespecified inclusion and exclusion criteria. Discrepancies were resolved by consensus and, when needed, by consultation with a third reviewer. The process was documented in a PRISMA flow diagram.

Data Extraction and Management

Two reviewers independently extracted data using a piloted form. Discrepancies were resolved by consensus and, when needed, by consultation with a third reviewer. We collected:

- **Study characteristics:** Country, setting, design (parallel/crossover), randomization method, blinding, sample size, attrition, follow-up.
- **Participants:** Age, sex, eligibility criteria, use pattern (occasional/infrequent/recently abstinent), baseline vulnerability (e.g., family history of psychosis, schizotypal traits, baseline anxiety, trauma history, subclinical symptoms) when reported, and concomitant substance use (tobacco, alcohol, others).
- **Intervention/exposure:** %THC, mg THC, %CBD or mg CBD, THC:CBD ratio, route, dose, duration, standardization, and co-interventions.
- **Outcomes:** Instruments used, time points, required statistics (means/standard deviations, change scores, proportions), adverse events, and operational definitions.
- **Statistical results:** Effect estimates, p-values, and, when reported or calculable from available summary data, standardized effect sizes (Cohen's d or Hedges' g) with 95% confidence intervals (CIs) for primary outcomes; information on correction for multiple comparisons/family-wise error was also extracted when available.

When data were insufficient, we attempted to obtain information by contacting authors or reviewing trial records/protocols. Intention-to-treat analyses were prioritized when available; when not, the study's analytic approach was documented.

Critical Appraisal/Risk of Bias Assessment

Risk of bias was independently assessed by at least two reviewers using RoB 2 for each outcome and measurement time point, considering five domains: (1) randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) outcome measurement, and (5) selection of the reported result. For crossover RCTs, design-relevant biases (e.g., carryover effects) were additionally considered in line with the applicable RoB 2 structure. Discrepancies were resolved by consensus and, when needed, by consultation with a third reviewer. An overall judgment per outcome was assigned: low-risk, some concerns, or high-risk.

Bias Control

Handling Missing Data

Attrition and its balance between arms were described quantitatively. The potential impact of missing data was evaluated within RoB 2 (missing data domain). When possible, results were extracted using the most conservative method available (e.g., intention-to-treat). A differentiated qualitative synthesis was planned when missing data were substantial or imbalanced.

Assessment of Reporting Bias

Reporting bias was explored by comparing methods/protocols (when available in registries) with published results, and by identifying expected outcomes that were not reported. No asymmetry tests (e.g., funnel plots) were performed due to the absence of meta-analysis and/or the limited number of studies per outcome.

Quantitative and Qualitative Synthesis Plan

Given substantial clinical and methodological heterogeneity, no meta-analysis was conducted. Heterogeneity was driven by differences in the operational definition of high potency (absolute THC dose, THC:CBD ratio, or both), route of administration (oral, IV, vaporized, or oromucosal), trial design (parallel or crossover), participant profiles (infrequent, recreational, or frequent users), outcome instruments, and timing of post-exposure assessments. In addition, several outcomes were reported in ways that were not directly combinable across studies. A structured narrative synthesis was therefore performed, with tables summarizing study characteristics, direction of effects, and study-level standardized effect sizes when available or calculable. GRADE was not applied because the evidence base was composed mainly of short-duration experimental studies with heterogeneous acute or surrogate outcomes and too few directly comparable studies per outcome to support meaningful outcome-level certainty ratings. Instead, interpretive confidence was based on RoB 2 judgments, consistency of findings, directness to the experimental question, and clinical plausibility.

Results

Study Characteristics

Across 10 experimental trials, participants included healthy volunteers, infrequent cannabis users, recreational users, and frequent users. Interventions involved oral, IV, vaporized, and oromucosal cannabinoid preparations. Study characteristics are summarized in Table 1.

Effects of THC-Dominant Preparations versus Placebo or Lower-Potency Comparators

Across studies comparing THC-dominant preparations with placebo or lower-potency comparators, the most consistent findings were increases in subjective intoxication and

psychotomimetic/dissociative phenomena, with additional effects on selected cognitive and physiological outcomes. Standardized effect sizes (Cohen's *d* or Hedges' *g*), with 95% CIs when available or calculable, are summarized in Table 2. Mohammad Aghaei et al.¹² reported that oral dronabinol increased subjective "high" and markedly elevated CADSS and PSI scores, with no relevant changes in RAVLT but an increase in heart rate. Similarly, Ranganathan et al.¹³ found that IV Δ^9 -THC strongly increased subjective "high" and impaired RAVLT performance when administered before encoding, but not after encoding. Cortes-Briones et al.¹⁴ also observed acute increases in PANSS positive, negative, general psychopathology, and total scores, together with reduced gamma synchrony [40 Hz inter-trial coherence (ITC)] and an inverse association between ITC and PANSS under active conditions.

Table 1. Characteristics of included randomized controlled trials

Study	Design/population	Intervention/exposure	Comparator	Route	Main outcome domains
Mohammad Aghaei et al. ¹²	Randomized, placebo-controlled, crossover; healthy participants; prior cannabis exposure; no CUD	Oral THC (dronabinol) 10 mg	Placebo	Oral	Subjective high, dissociation/psychotomimetic symptoms, verbal memory, heart rate
Ranganathan et al. ¹³	Randomized experimental trial; healthy participants	IV Δ^9 -THC pre-encoding or post-encoding	Baseline/placebo condition	IV	Verbal memory encoding/retrieval, subjective high
Cortes-Briones et al. ¹⁴	Randomized experimental trial; healthy participants	Active THC condition	Placebo/inactive condition	IV	PANSS domains, gamma-band neural oscillations, psychotomimetic effects
Sainz-Cort et al. ¹⁵	Naturalistic randomized crossover; cannabis social-club members	Vaporized THC extract; THC+CBD (2:1); CBD extract	Placebo (hemp) and across-condition comparisons	Vaporized	Psychotomimetic symptoms, subjective high, sedation
Schoedel et al. ¹⁶	Randomized, double-blind, placebo-controlled, crossover; recreational users	Nabiximols and dronabinol at different doses	Placebo	Oromucosal/oral	Drug liking, subjective high, abuse liability, cognition, adverse events, PK
Ganesh et al. ¹⁷	Randomized crossover experimental trial; healthy volunteers with prior exposure	IV THC alone; IV CBD alone; IV CBD+THC (1:1, 2:1, 3:1)	THC alone and placebo	IV	PANSS positive, VAS high, anxiety, neural noise
Oliver et al. ¹⁸	Randomized, double-blind, crossover; healthy infrequent users	Vaporized cannabis with fixed THC and variable CBD (0:1, 1:1, 2:1, 3:1)	Baseline and THC-only comparator	Vaporized	Attentional bias, cue salience/preference, PK
Englund et al. ¹⁹	Randomized, double-blind, crossover; healthy infrequent users	Vaporized cannabis with CBD:THC ratios 0:1, 1:1, 2:1, 3:1	Baseline and THC-only comparator	Vaporized	Verbal memory, PANSS positive, psychosis-like experiences, heart rate, PK
Woelfl et al. ²⁰	Randomized, double-blind, placebo-controlled experimental trial; healthy volunteers	CBD and THC in pretreatment/co-administration design	Comparator arms including placebo	Oral/experimental administration	Emotion, cognition, attention
Hindocha et al. ²¹	Randomized experimental trial; young cannabis users with genotyping	THC and THC+CBD preparations	Relevant active comparator condition	Inhaled/experimental administration	Addiction endophenotypes, wanting, attentional bias, genotype interactions

THC: Tetrahydrocannabinol, CBD: Cannabidiol, CUD: Cannabis use disorder, IV: Intravenous, PANSS: Positive and Negative Syndrome Scale, PK: Pharmacokinetics, VAS: Visual analogue scale

Table 2. Primary acute outcomes of THC-dominant preparations versus placebo or lower-potency comparators

Study	Main comparison	Primary outcome domain	Main result	d/g	95% CI	p-value	Multiplicity correction reported?
Mohammad Aghaei et al., ¹²	Oral THC vs. placebo	Psychotomimetic symptoms/ subjective effects/ physiology	THC increased subjective high, CADSS and PSI scores, and heart rate; no relevant changes in RAVLT	d=0.43 for dose×sex signal in high; d'=0.48 in women	NR	p=0.05 for dose×sex interaction; CADSS p=0.0001; PSI p<0.0001; heart rate p<0.0001	Unclear
Ranganathan et al., ¹³	IV THC vs. baseline/ placebo	Cognition/ subjective effects	THC impaired verbal memory when given pre-encoding, but not post-encoding; THC also increased subjective high	NR	NR	Significant in original trial	Unclear
Cortes-Briones et al., ¹⁴	THC vs. comparator	Psychotomimetic symptoms/ neurophysiology	THC increased PANSS positive, negative, general and total scores, reduced gamma synchrony, and showed an inverse ITC-PANSS association	NR	NR	Significant in original trial	Yes
Sainz-Cort et al., ¹⁵	Vaporized THC vs. placebo	Psychotomimetic symptoms/ subjective effects	THC produced the largest increases in feeling high, sedation, and PSI scores, including cognitive disorganization and paranoia	NR	NR	Significant in original trial	Unclear
Schoedel et al., ¹⁶	Nabiximols or dronabinol vs. placebo	Subjective effects/abuse liability/adverse events	Dose-dependent increases in drug liking/high; higher peak THC exposure with dronabinol; more adverse events at higher doses	NR	NR	PK differences p<0.001 at comparable doses	Unclear
Ganesh et al., ¹⁷	IV THC-containing conditions vs. placebo/ lower-potency comparators	Psychotomimetic symptoms/ subjective high	PANSS positive and VAS high showed significant overall THC effects across phases	NR	NR	PANSS positive global p<0.00001; VAS high global p<0.00001	Yes
Englund et al., ¹⁹	THC alone (0:1) vs. baseline	Cognition/ psychotomimetic symptoms/ physiology	THC impaired immediate and delayed verbal memory, increased PANSS positive and psychosis-like experiences, and increased heart rate	d=0.82 (HVLT-R immediate recall); d=0.69 (PANSS positive); d=1.39 (heart rate)	NR	p=1.31×10 ⁻⁶ ; p=2.41×10 ⁻⁵ ; p=5.06×10 ⁻¹²	Yes
Oliver et al., ¹⁸	THC alone (0:1) vs. baseline	Consumption-related outcomes/ attentional bias	THC produced a small increase in total cannabis attentional bias; other AB and PR outcomes were mostly non-significant	d=0.41 for total cannabis AB	95% CI 1.20 to 23.3 for mean difference, not for d	p=0.03	No for baseline contrast; yes for between-ratio contrasts

Standardized effect sizes (Cohen's d or Hedges' g) are reported when available from the original article or calculable from published summary statistics. When 95% confidence intervals (CI) correspond to raw mean differences or model-based estimates rather than standardized effect sizes, this is indicated in the table. Multiplicity correction/family-wise error is reported only when explicitly stated by the original study. THC: Tetrahydrocannabinol, CBD: Cannabidiol, PANSS: Positive and Negative Syndrome Scale, PSI: Psychotomimetic States Inventory, CADSS: Clinician-Administered Dissociative States Scale, HVLT-R: Hopkins verbal learning test-revised, RAVLT: Rey auditory verbal learning test, VAS: Visual analog scale, ARCI: Addiction Research Center Inventory, ITC: Inter-trial coherence, PK: Pharmacokinetics, NR: Not reported/not reliably calculable from published data, AB: Attentional bias, IV: Intravenous

In cannabis social-club users, Sainz-Cort et al.¹⁵ showed that vaporized THC produced the largest increases in VAS “feeling high,” sedation (ARCI), and PSI scores, including cognitive disorganization and paranoia, compared with placebo. In frequent users, Schoedel et al.¹⁶ reported dose-dependent increases in “drug liking” and “high” with nabiximols and dronabinol, along with higher peak THC exposure with dronabinol and more adverse events at higher doses. Likewise, Ganesh et al.¹⁷ found significant overall effects on PANSS positive scores and VAS “high” under IV THC-containing conditions.

The Modulatory Role of CBD

Evidence for a consistent modulatory effect of CBD on the acute effects of THC was limited and heterogeneous. The direction of effects, standardized effect sizes when available, and relevant statistical qualifiers are summarized in Table 3. In IV combination studies, Ganesh et al.¹⁷ found no consistent attenuation of subjective “high” across CBD:THC ratios from 1:1 to 3:1, although some specific signals were observed, including changes in neural noise/Lempel-Ziv complexity and reduced anxiety at the highest ratio in phase 2. In vaporized cannabis users, Sainz-Cort et al.¹⁵ found that THC+CBD (2:1) tended to produce lower

Table 3. Modulatory role of CBD in active-comparator trials

Study	CBD:THC ratios/design	Comparator	Outcome domain	Direction of effect	d/g	95% CI	Adjusted significance/multiplicity correction	Interpretation
Ganesh et al. ¹⁷	IV CBD+THC (1:1, 2:1, 3:1) across two phases	THC alone	PANSS positive, VAS high, anxiety, neural noise	No consistent attenuation of subjective high or PANSS positive; isolated signals for neural noise and anxiety at higher ratios	NR	NR	Yes; corrected p-values reported for some post hoc contrasts	CBD did not consistently attenuate acute THC effects; isolated domain-specific signals only
Sainz-Cort et al. ¹⁵	Vaporized THC+CBD (2:1) and CBD alone	THC alone and placebo	Psychotomimetic symptoms/subjective effects	THC+CBD tended to yield lower psychometric values than THC alone on some items; CBD alone behaved close to placebo	NR	NR	Unclear	Possible attenuation on selected items, but not a robust overall CBD effect
Oliver et al. ¹⁸	Vaporized cannabis with 0:1, 1:1, 2:1, 3:1	THC alone (0:1)	Attentional bias/cue salience	No evidence of CBD effect across ratios after correction	d=0.41 only for THC vs baseline total cannabis AB	EMM differences with 95% CIs reported for between-ratio comparisons	Yes	CBD up to 3:1 did not attenuate THC-related attentional bias outcomes
Englund et al. ¹⁹	Vaporized cannabis with 0:1, 1:1, 2:1, 3:1	THC alone (0:1)	Cognition, psychotomimetic symptoms, physiology	No significant differences across CBD:THC ratios after adjusted threshold; THC exposure similar across conditions	d reported for THC vs baseline outcomes; no ratio-specific d	Selected PK 95% CIs reported; no standardized-effect 95% CIs	Yes; adjusted threshold p>0.008	CBD up to 3:1 did not consistently attenuate THC effects under active-comparator conditions
Woelfl et al. ²⁰	CBD prior to THC/combined-arm design	Comparator arms including placebo	Emotion, cognition, attention	Changes in emotional domains and less favorable attentional/cognitive performance in the CBD/THC arm versus comparators	NR	NR	Unclear	Pretreatment paradigm suggests design-specific effects, not directly comparable with co-administration studies

Standardized effect sizes are shown when available. The column on adjusted significance/multiplicity correction reflects whether correction for multiple comparisons or an adjusted significance threshold was explicitly reported in the original study. Results from pretreatment paradigms should be interpreted separately from co-administration designs.

THC: Tetrahydrocannabinol, CBD: Cannabidiol, PANSS: Positive and Negative Syndrome Scale, VAS: Visual analog scale, AB: Attentional bias, EMM: Estimated marginal mean, PK: Pharmacokinetics, NR: Not reported/not reliably calculable from published data, CI: Confidence interval, IV: Intravenous

values than THC alone on several psychometric items, whereas CBD alone behaved similarly to placebo. In two crossover trials in healthy infrequent cannabis users, Oliver et al.¹⁸ and Englund et al.¹⁹ directly assessed whether increasing CBD content modified acute THC effects. Oliver et al.¹⁸ found that THC alone versus baseline produced a small increase in attentional bias toward cannabis, but mixed models comparing CBD:THC ratios (1:1, 2:1, and 3:1) with THC alone showed no evidence of a CBD effect after correction for multiple comparisons. Concordantly, Englund et al.¹⁹ reported that THC alone versus baseline produced robust cognitive, psychotomimetic, and physiological effects, including worse HVLT-R performance, higher PANSS positive scores, more psychosis-like experiences, and increased heart rate; however, no significant differences across CBD:THC ratios were detected after adjusted significance thresholds. Pharmacokinetic analyses showed similar THC exposure across conditions, while CBD exposure increased with dose. Finally, in a between-arms pretreatment design, Woelfl et al.²⁰ documented changes in emotional domains and an unfavorable attentional/cognitive performance profile in the CBD/THC arm versus comparators. Taken together, these findings suggest that, under the experimental conditions examined, THC accounted for most acute cognitive, psychometric, and physiological changes, whereas increasing CBD up to a 3:1 ratio did not demonstrate consistent attenuation relative to THC-only comparators.

The Role of Individual Vulnerability and Exposure Context

Some findings suggested that acute cannabinoid effects may vary according to individual vulnerability and exposure context (Table 4). Hindocha et al.²¹ reported that the effects of THC and THC+CBD on “wanting” and attentional bias depended on drug×genotype interactions involving *CNR1* and *FAAH*,

although no consistent effects were observed on overall craving. Mohammad Aghaei et al.¹² also identified a signal for a dose×sex interaction in subjective “high.” In addition, Ranganathan et al.¹³ showed that the cognitive impact of IV Δ^9 -THC depended on the timing of exposure, with impairment observed when THC was administered before encoding but not after encoding. These findings suggest that baseline vulnerability and exposure context may influence the acute effects of cannabinoids. However, the evidence was limited to a small number of trials and to heterogeneous indicators, including genotype, sex, and timing of administration, whereas other clinically relevant vulnerability factors such as family history, subclinical psychotic traits, baseline anxiety, and prior cannabinoid sensitivity were not assessed consistently across studies.

Risk of Bias Summary

The overall risk-of-bias assessment showed a predominantly unfavorable profile, with 9 of 10 studies rated at high-risk of bias and 1 of 10 rated as having some concerns (Supplementary Table 3). Overall, this indicates that the available evidence for acute outcomes, including psychosis-like psychometric measures, cognition, and physiological effects under THC-containing preparations, is substantially limited by methodological problems that may compromise internal validity, such as potential bias in the measurement of subjective outcomes, handling of missing data or attrition, deviations from protocol, and multiplicity of analyses.

Discussion

In this systematic review of 10 RCTs in populations without psychotic disorder (primarily healthy volunteers and recreational users), acute exposure to THC-dominant preparations or

Table 4. Individual vulnerability and exposure context as potential modifiers of acute cannabinoid effects

Study	Potential modifier	Comparison/context	Outcome affected	Main finding	Interpretation
Hindocha et al. ²¹	Genotype (<i>CNR1</i> / <i>FAAH</i>)	THC and THC+CBD conditions	Wanting/attentional bias/craving	Drug×genotype interactions were observed for wanting and attentional bias; no consistent effects on overall craving	Genetic variability may modify some acute cannabinoid effects
Mohammad Aghaei et al. ¹²	Sex	Oral THC vs. placebo	Subjective high	A signal for a dose×sex interaction was observed for subjective high, with stronger effects in women	Sex may influence some acute subjective THC effects
Ranganathan et al. ¹³	Timing of exposure	IV THC pre-encoding vs. post-encoding	Verbal memory	Memory impairment was observed when THC was administered before encoding, but not after encoding	The cognitive impact of THC depends on timing relative to memory processing
Sainz-Cort et al. ¹⁵	Use context/regular use pattern	Cannabis social-club users	Psychotomimetic and subjective effects	THC and THC+CBD effects were observed in a naturalistic setting among regular users	Acute effects may vary according to use context and prior exposure pattern
Schoedel et al. ¹⁶	Recreational-use history	Nabiximols and dronabinol vs. placebo	Drug liking/adverse events	Dose-dependent subjective effects were present in participants with recreational-use history	Prior exposure pattern may shape abuse-liability responses

THC: Tetrahydrocannabinol, CBD: Cannabidiol, *CNR1*: Cannabinoid receptor 1 gene, *FAAH*: Fatty acid amide hydrolase gene, IV: Intravenous

isolated THC was associated with increases in psychotomimetic/dissociative symptoms and subjective intoxication, with less consistent evidence for anxiety and cognitive impairment, particularly memory, depending on the experimental context. These results support acute experimental plausibility, but they do not establish incidence, transition risk, or persistence of psychosis, schizophrenia, or cannabis use disorder. Given that 9 of 10 studies were rated at high-risk of bias, sample sizes were generally small, and outcome definitions varied across trials, the overall body of evidence should be interpreted as low-certainty and hypothesis-generating rather than confirmatory.

Although these acute experimental findings are directionally compatible with broader public health concerns about high-potency cannabis, they should not be interpreted as direct evidence of long-term clinical risk. Experimental studies conducted over minutes to hours answer a different question from longitudinal studies of incident psychosis, schizophrenia-spectrum disorders, or cannabis use disorder. Accordingly, this review cannot determine whether high-potency cannabis increases long-term risk, nor whether acute laboratory responses translate into persistent clinical outcomes. Any extrapolation from transient psychotomimetic effects to long-term transition should therefore be considered speculative.

Our findings are consistent with previously synthesized experimental evidence on the acute psychiatric effects of THC in healthy populations. In the meta-analysis by Hindley et al.⁴ (15 studies; $n \approx 196$ –324 depending on the domain), THC versus placebo significantly increased overall psychiatric symptom severity [standardized mean difference (SMD) 1.10; 95% CI 0.92–1.28], as well as positive (SMD 0.91; 95% CI 0.68–1.14) and negative symptoms (SMD 0.78; 95% CI 0.59–0.97), all with $p < 0.0001$, and concluded that there is no consistent evidence for a modulatory role of CBD on THC's effects. In the same direction, the trials included in our synthesis show clinically relevant magnitudes for acute outcomes: for example, in a crossover design with vaporized cannabis in infrequent users, THC (0:1) versus baseline impaired immediate verbal memory (HVLT-R; $d = 0.82$) and increased positive symptoms (PANSS positive; $d = 0.69$), in addition to robust physiological changes such as increased heart rate ($d = 1.39$). These magnitudes support the biological plausibility that “high potency” (high THC/high THC:CBD ratio) increases the burden of psychotomimetic symptoms under controlled conditions, even in non-dependent users.

Although our trials are acute and do not assess incidence of psychosis, schizophrenia-spectrum disorders, or cannabis use disorder, their findings are broadly compatible with epidemiologic signals linking frequent high-potency cannabis use with psychotic outcomes. In the multicenter European Network of National Schizophrenia Networks Studying Gene-Environment Interactions study, daily cannabis use was associated with higher odds of psychotic disorder [adjusted odds ratio (OR) 3.2; 95% CI 2.2–4.1], increasing to nearly fivefold when daily use involved high-potency cannabis (adjusted OR 4.8; 95% CI 2.5–6.3). From a clinical perspective, our experimental findings may offer

biological plausibility for these epidemiologic associations, as THC-dominant exposure produced measurable acute increases in psychosis-like symptoms and cognitive impairment under controlled conditions. However, these laboratory effects were transient and should not be interpreted as direct evidence of long-term transition risk. The relationship between acute experimental responses and persistent psychiatric outcomes remains uncertain and requires longitudinal investigation.

A key finding that qualifies common hypotheses is that evidence on CBD modulation should be interpreted according to the mode and timing of administration. In recent active-comparator crossover trials using co-administration of vaporized cannabis with fixed THC and varying CBD:THC ratios within the same product, increasing CBD up to 3:1 did not consistently attenuate acute THC-induced cognitive, psychotomimetic, or physiological effects. Importantly, this interpretation is strengthened by the fact that some of these studies applied adjusted significance thresholds or correction for multiple comparisons, under which the apparent CBD-related differences were not consistently maintained. By contrast, the classic trial by Englund et al.,⁸ which used high-dose oral CBD pretreatment (600 mg) prior to IV THC (1.5 mg), reported a lower likelihood of clinically significant positive psychotic symptoms (increase ≥ 3 points) (OR = 0.22; $\chi^2 = 4.74$; $p < 0.05$), less paranoia (SSPS; $t = 2.28$; $p < 0.05$), and less episodic memory impairment (HVLT-R: $-10.6\% \pm 18.9\%$ in placebo-pretreated vs. $-0.4\% \pm 9.7\%$ with CBD; $t = 2.39$; $p < 0.05$). Therefore, findings from oral CBD pretreatment studies should not be interpreted as directly equivalent to those from co-administration studies using vaporized cannabis formulations. The discrepancy between these approaches may reflect differences in timing of administration, route, absolute CBD dose, pharmacokinetic exposure, statistical power, and the time required to reach potentially active central nervous system concentrations. In addition, some individual trials suggested isolated effects, such as reduced anxiety with higher CBD:THC ratios in a specific phase, but the lack of consistency after multiplicity correction and the overall high-risk of bias preclude concluding a generalizable protective effect of CBD under high-potency exposure conditions.

Study Limitations

The main limitation of this synthesis is low methodological certainty: 9 of 10 trials had high-risk of bias, with potential problems in subjective outcome measurement, analytic multiplicity, small sample sizes, and heterogeneous designs (oral/IV/vaporized/oromucosal routes; diverse formulations; different time windows; different instruments for psychosis, anxiety, memory, and use-related outcomes), which prevented meta-analysis and limits the precision of estimates. An additional limitation is the absence of a standardized definition of “high-potency” cannabis across the literature. Some studies operationalized potency through absolute THC dose, others through THC:CBD ratio, and others through both simultaneously; therefore, the independent effects of THC dose and cannabinoid balance could not be disentangled in this review. Generalizability to adolescents is also restricted,

outcomes were predominantly acute (minutes to hours), and they do not capture transition to persistent psychosis nor trajectories toward cannabis use disorder. Strengths include the exclusive focus on RCTs (higher internal validity for acute causal inference), an operational framework for potency based on THC and THC:CBD ratio, use of RoB 2 by outcome, and inclusion of studies with pharmacokinetics and biological moderators (genotype), enabling a more refined mechanistic interpretation than observational evidence.

In clinical practice and public health, these data support cautious preventive messaging: THC-dominant products may induce acute psychotomimetic symptoms and memory impairment even in infrequent users, and it is not prudent to assume that CBD reliably neutralizes THC's adverse effects under controlled conditions. However, because the current evidence base is methodologically fragile, these implications should be framed cautiously and not as definitive estimates of harm magnitude. In research, larger RCTs are needed with rigorous standardization of potency (mg and %), pharmacokinetic verification, clinically relevant comparators (THC gradients and wider CBD ranges), and systematic assessment of moderators (sex, baseline anxiety, subclinical psychotic traits, family history, polysubstance use). In addition, designs with subacute follow-up (days to weeks) and measurement of functional and risk outcomes (persistent symptoms, relapse, craving, self-administration patterns) are a priority to better address questions that extend beyond the laboratory.

An additional issue that warrants clarification is the role of baseline vulnerability. In this review, baseline vulnerability was considered a potential modifier of acute cannabinoid effects rather than a uniformly measured study variable. The available evidence suggests that some individual factors, such as genotype, sex, and timing-related experimental context, may influence specific outcomes; however, these signals came from a limited number of studies and were based on heterogeneous measures. Other clinically relevant vulnerability markers, including family history of psychosis, subclinical psychotic traits, baseline anxiety, trauma exposure, and prior sensitivity to cannabinoids, were not assessed systematically across the included trials. Therefore, baseline vulnerability should be interpreted as a biologically plausible but insufficiently characterized source of effect heterogeneity in the current evidence base.

Conclusion

In young adults without psychotic disorder, randomized experimental studies suggest that THC-dominant or otherwise high-potency cannabis exposures can acutely increase psychotomimetic symptoms, subjective intoxication, and, in some paradigms, memory impairment. However, the evidence should be considered low-certainty and hypothesis-generating because most included trials were at high-risk of bias, sample sizes were small, outcomes were heterogeneous, and the concept of potency was inconsistently operationalized across studies. This review does not establish long-term risk of incident psychosis, schizophrenia, or cannabis use disorder,

nor does it determine whether THC dose and THC:CBD ratio exert independent effects. Better-designed experimental and longitudinal studies are needed to connect acute laboratory effects with clinically persistent outcomes.

Footnotes

Authorship Contributions

Concept: A.L.A., J.V.U.C., F.J.G.B., Design: A.L.A., J.V.U.C., F.J.G.B., Data Collection or Processing: A.L.A., J.V.U.C., F.J.G.B., Analysis or Interpretation: A.L.A., J.V.U.C., F.J.G.B., Literature Search: A.L.A., J.V.U.C., F.J.G.B., Writing: A.L.A., J.V.U.C., F.J.G.B.

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Supplementary Tables 1-3: <https://d2v96fxpocvxx.cloudfront.net/830ebeaf-3f7e-42af-bd4b-fde69d6bc084/content-images/9d0c2f9e-86b4-4b1b-baed-566f21eb698d.pdf>

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