Pain Medicine, 2024, **25**, 387–399
https://doi.org/10.1093/pm/pnae004
Advance access publication 24 January 2024
Review Article

OXFORD

PSYCHOLOGY, PSYCHIATRY & BRAIN NEUROSCIENCE SECTION

Biphasic effects of cannabis and cannabinoid therapy on pain severity, anxiety, and sleep disturbance: a scoping review

Alexander Shustorovich, DO[1,*], Jamie Corroon, ND, MPH[2], Mark S. Wallace, MD[3], Michelle Sexton, ND[4]

[1]Department of Physical Medicine & Rehabilitation, JFK Johnson Rehabilitation Institute, Edison, NJ 08820, United States
[2]Department of Family Medicine, University of California, San Diego, San Diego, CA 92093, United States
[3]Department of Anesthesiology, University of California, San Diego Medical Center, San Diego, CA 92037, United States
[4]Department of Family Medicine, Centers for Integrative Health, University of California, San Diego, San Diego, CA 92093, United States

[*]*Corresponding author:* Department of Physical Medicine & Rehabilitation, JFK Johnson Rehabilitation Institute, 65 James St, Edison, NJ 08820, USA. Email: alex.shustorovich@gmail.com

Abstract

Introduction: Cannabinoids are being used by patients to help with chronic pain management and to address the 2 primary chronic pain comorbidities of anxiety and sleep disturbance. It is necessary to understand the biphasic effects of cannabinoids to improve treatment of this symptom triad.

Methods: A scoping review was conducted to identify whether biphasic effects of cannabinoids on pain severity, anxiolysis, and sleep disturbance have been reported. The search included the Embase, Biosis, and Medline databases of clinical literature published between 1970 and 2021. The inclusion criteria were (1) adults more than 18 years of age, (2) data or discussion of dose effects associated with U-shaped or linear dose responses, and (3) measurements of pain and/or anxiety and/or sleep disturbance. Data were extracted by 2 independent reviewers (with a third reviewer used as a tiebreaker) and subjected to a thematic analysis.

Results: After the database search and study eligibility assessment, 44 publications met the final criteria for review. Eighteen publications that specifically provided information on dose response were included in the final synthesis: 9 related to pain outcomes, 7 measuring anxiety, and 2 reporting sleep effects.

Conclusions: This scoping review reports on biphasic effects of cannabinoids related to pain, sleep, and anxiety. Dose–response relationships are present, but we found gaps in the current literature with regard to biphasic effects of cannabinoids in humans. There is a lack of prospective research in humans exploring this specific relationship.

Keywords: cannabis; biphasic; dose response; cannabinoids; pain; sleep; anxiety.

Introduction

Chronic pain is widely prevalent in the United States. A recent US Centers for Disease Control and Prevention (CDC) National Health Interview Survey (NHIS) data analysis identified that 20.4% of US adults had chronic pain and 8.0% of US adults had high-impact chronic pain (ie, pain that frequently causes limitation in function and activities of daily living).[1] Emotional distress and sleep disturbance are commonly associated with chronic pain, and together they are accepted as a triad of comorbidity.[2,3] In fact, comorbid depression and lower baseline function are associated with poor procedural outcomes.[4] Thus, common interventional pain medicine treatments might not always be the most appropriate for this patient population.

An adjunctive pain treatment is medical cannabis, which has been available for legal use in the United States since California passed Proposition 215 in 1996.[5] The 2 primary active compounds, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), are reported to produce anxiolytic, analgesic, sedative, and psychoactive effects upon THC's binding to endocannabinoid (CB1 and CB2) receptors and CBD's binding to other related receptors (TRPV1, GPR55, 5-HT_{1A}, and adenosine A_{2A}).[6–9] Because of its relatively benign side effect profile, cannabis has been considered a favorable remedy for chronic pain,[5] anxiety, and sleep disturbances, with pain being reported as the most common indication.[10–13] However, dosing of cannabinoids has been a challenge because of the heterogeneity of constituents among the available products, individual differences in pharmacokinetics and metabolism, differences in mode of consumption (inhaled or ingested), the role of individual tolerance, and pharmacological biphasic effects.[14,15]

Biphasic effects of cannabinoids were first suggested in 1973 and include excitatory vs depressant effects, anxiolytic vs anxiogenic effects, and hypo- vs hyperalgesia.[16] In 1995, Fride et al. reported that low doses (doses of 0.01 or 0.1 mg/kg) of anandamide (N-arachidonoylethanolamine [AEA], the first endocannabinoid to be isolated and structurally characterized) caused opposing effects in mice when compared with high doses (10 mg/kg).[17] Fride et al. noted that low vs high doses of AEA oppositely affected ambulation, catalepsy, and analgesia in mice. These biphasic effects have been seen across other

Received: 7 June 2023. **Revised:** 17 December 2023. **Accepted:** 11 January 2024

experimental paradigms and for other cannabinoids (eg, THC, CBD)[18] throughout the cannabinoid literature.[16,19,20]

It is unknown whether research explicitly describing biphasic effects of cannabinoids in humans, particularly relating to the symptom triad of pain severity, anxiety, and sleep disturbance, exists. The present review is intended to provide a comprehensive literature synthesis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines to map the available evidence and identify knowledge gaps related to biphasic effects of cannabinoids in human subjects.[21]

Methods

A scoping review (following the Joanna Briggs Institute guidelines) was conducted with a search strategy developed by a scientific librarian and included English-language studies published between 1970 and 2021 in the Embase, Biosis, and Medline databases. No review protocol was published. Medical Subject Heading (MeSH) terms are in the Supplementary Data (Appendix S1). The citations were directly uploaded to Cadima, an online client-server software application developed to facilitate review synthesis.[22] Articles included in the review met inclusion criteria for the following: (1) population—human adults more than 18 years of age; (2) concept—data or discussion of dose responses associated with U-shaped (ie, biphasic) or linear dose responses to cannabis/cannabinoids; and (3) context—use of either a validated or nonvalidated tool (eg, self-report) for assessment of outcomes on pain, anxiety, or sleep. Integral to the synthesis was a change in magnitude of the effect in either direction, based on dose. Exclusion criteria were (1) preclinical or animal studies and (2) use of synthetic enzyme modulators of endocannabinoid function. For this review, the terms *cannabis* and *cannabinoid* included all products taken in any form and mode, including semisynthetic or synthetic cannabinoids (eg, dronabinol). Observational studies that investigated self-accessed medicinal cannabis products were included.

Specifically, *biphasic* is defined as low and high doses of a drug that can have opposite effects. This consists of a rising and a falling phase, defined for purposes of this scoping review as "a dose–response phenomenon that has 2 distinct phases: the ascending limb and the descending limb in which a chemical compound induces biologically opposite effects at different doses. As dose decreases, there are not only quantitative changes in measured responses, but also qualitative changes compared with the control and high-dose level."[23] Pharmacologically, a biphasic curve contrasts to a sigmoid curve in that the response peaks as a function of dose and then flattens, before enacting an opposite dose effect at higher doses. An inverted U-shaped curve is a nonlinear relationship where effects of dose increase to a maximum and then effects decrease. Alternatively, a U-shaped curve is a nonlinear relationship where effects are maximal at extreme (low and high) doses (see Figure 1). Finding evidence for biphasic effects in humans could serve to support existing evidence that "more is not better" in dosing cannabis for therapeutic effects.[24,25] Similarly, the definition of "therapeutic" (vs recreational) dosing has lagged behind the growing popularity of medical cannabis over the past 2 decades.[24]

Relevant data were extracted and charted with Cadima software. The extraction of the data was tabular with some narrative commentary. Independent extraction was performed in duplicate, and any disagreement was discussed and resolved through consensus among 3 reviewers. The PRISMA-ScR checklist was used to guide the reporting of this scoping review. (See Supplementary Data, Appendix S2). The publications included are described in Table 1 and Table S3.

Results

Research librarians found 1833 citations before removal of duplicates. Once duplicate records were removed ($n = 372$),

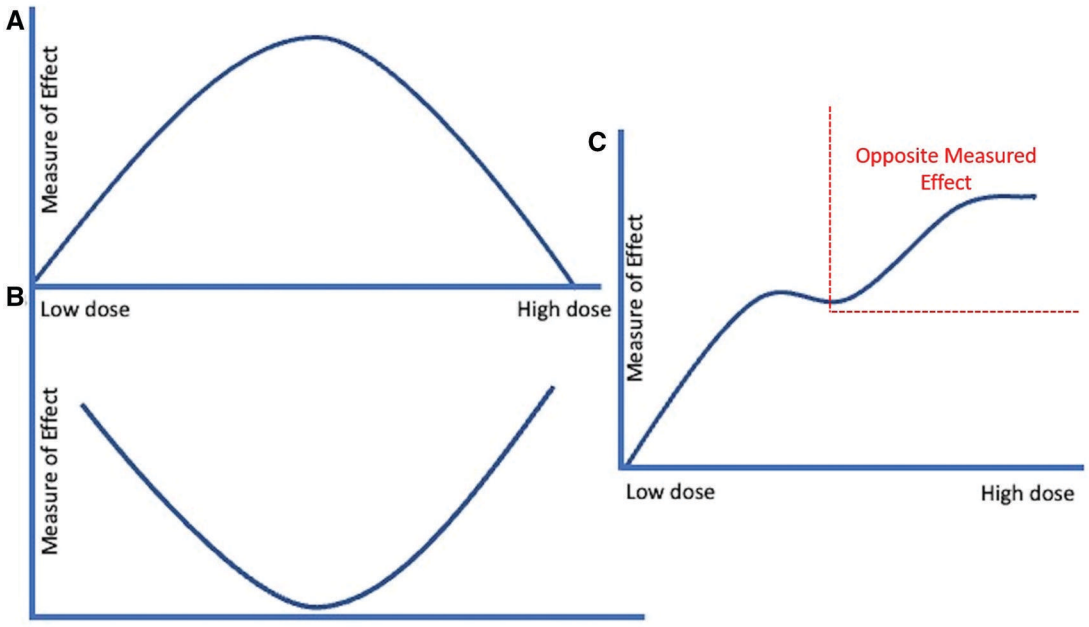

Figure 1. Dose–response curves. **(A)** Inverted U-shaped curve. A nonlinear relationship where effects of dose increase to a maximum and then effects decrease. **(B)** U-shaped curve. A nonlinear relationship where effects are maximal at extreme (low and high) doses. **(C)** Biphasic curve. Demonstrates 2 phases, an "ascending" and "descending" limb, where dose response plateaus or flattens, followed by an opposite effect at higher doses.

1461 citations remained. After exclusion of all preclinical studies and studies of synthetic endocannabinoid system modulators (eg, enzyme inhibitors), 516 studies were screened by title and abstract according to the inclusion/exclusion criteria. Forty-five publications met the eligibility criteria for full-text review. The full texts were reviewed in duplicate, and any disagreement on inclusion criteria was reconciled by a third reviewer (See Figure 2: flow diagram). Thirty papers were included in the final review, with 18 articles included in the final synthesis of results (Table 1). Twelve reported insufficient data to determine a dose–response effect and were excluded. (See Figure 2 and Table S3). Various dose–response relationships were identified, but only some qualified as potential biphasic effects on the basis of the present study's definition of "biphasic effects" (Table 2).

Studies related to pain

Fifteen studies measuring outcomes on pain were identified that met our search criteria. Nine identified a dose–response association with pain and were included in this synthesis (see Table 1). All 9 of the included studies were prospective, randomized controlled trials (RCTs) assessing the effects of THC or CBD on pain outcome measures.[26–34] Six studies included a crossover design.[26,29–33] Subjects included healthy volunteers ($n = 2$) and patients with advanced cancer and opioid-refractory pain ($n = 1$), painful diabetic neuropathy ($n = 2$), and neuropathic pain from spinal cord injury or complex regional pain syndrome ($n = 4$). Most of the studies used inhaled cannabis as the mode of administration/use. Two studies used novel forms: an oromucosal spray (ie, nabiximols) and a metered aerosol inhalation device.[28,32] One RCT focused exclusively on dronabinol (US Food and Drug Administration–approved oral formulation), whereas another focused exclusively on CBD (oral formulation) for primary pain outcomes.[27,34]

In 2007, Wallace et al. suggested evidence of biphasic effects in an RCT in healthy volunteers, where inhaled vaporized cannabis demonstrated no attenuation of capsaicin-induced hyperalgesia at any dose according to visual analog scale (VAS) scores and McGill Pain Questionnaire results.[26] There was a significant reduction in pain at the medium dose ($P = 0.011$–0.027), no effect at the lowest dose, and increased pain at the high dose ($P = 0.009$–0.002).[26]

Narang et al. administered 10 or 20 mg of dronabinol in 1 of 6 allocated sequences (single dose) to patients ($n = 30$) with chronic noncancer pain who had been on stable doses of opioid analgesics for 6 months. Effects on pain (numeric rating scale [NRS], Brief Pain Inventory [BPI]), anxiety (Hospital Anxiety and Depression Scale [HADS]), and sleep (Medical Outcomes Study Sleep Scale [MOSSS]) were assessed. This study was completed in 2 phases (phase 1: single-dose; phase 2: open-label, 4-week, multidose extension). In phase 1, total pain relief and pain intensity were significantly improved with both doses compared with placebo ($P < 0.010$). Maximum pain benefit occurred at 4 hours after administration. In phase 2, both average NRS ($P < 0.001$) and BPI ($P < 0.05$) improved significantly. There was also a significant improvement in sleep adequacy ($P < 0.05$) and in sleep disturbance and sleep problems ($P < 0.01$) according to MOSSS. Most commonly, patients experienced increased anxiety with 20 mg but not 10 mg of dronabinol compared with placebo.[27]

In 2012, Portenoy et al. administered low-dose nabiximols (THC/CBD combination oromucosal spray) to 360 patients (263 completed) with advanced cancer and opioid-refractory pain. Nabixomols was administered as an add-on therapy at low dose (2.7–10 mg/day THC/CBD), medium dose (16.2–27 mg/day THC/CBD), or high dose (29.7–43.2 mg/day THC/CBD) vs placebo. In a treatment paradigm of 1 week of titration and 4 weeks of stable dose, subjects were on a stable opioid regimen and self-administered nabiximols across the day. The 2 lower-dose groups demonstrated significant reduction in pain ($P = 0.0008$ and 0.038, respectively) and improvement of sleep disturbance (lowest dose only) compared with placebo. High doses were associated with the greatest incidence of adverse events. Adverse events did not differ significantly from placebo at the 2 lower doses.[28]

The short-term efficacy of inhaled, vaporized cannabis for diabetic painful neuropathy was assessed by Wallace et al. (2015) in 16 subjects in a crossover design. Each subject received low (1% THC: 4 mg), medium (4% THC: 16 mg), or high (7% THC: 28 mg) doses and placebo in a single session. A dose-dependent reduction in pain intensity (VAS pain reduction of 30% or greater, significance $P < 0.05$) for both spontaneous (more consistent) and evoked (via foam brush or von Frey methods) pain was observed in patients with painful diabetic neuropathy. A steep drop in pain occurred in the first 15 minutes, followed over time by a slower decrease in pain. Euphoria and somnolence were the reported adverse events experienced 100% at the high dose.[29] More recently in 2020, a secondary analysis by Wallace et al. was completed that explored the data and the association between plasma THC levels and pain response. A U-shaped response was observed, which suggested a therapeutic window of 16–31 ng/mL. Higher plasma levels of THC correlated with increased pain.[33]

In Wilsey et al., vaporized cannabis (2.9% and 6.7% THC vs placebo, administered in random order) was evaluated for analgesic efficacy in 42 participants with neuropathic pain related to disease or injury of the spinal cord. A flexible dosing protocol, with 4 initial inhalations followed by 4–8 inhalations 3 hours later, was used in the dosing sessions for effects on NRS for pain. The 2 doses did not significantly differ ($P = 0.0606$) with regard to analgesic efficacy, but there was a significant dose–response effect on pain intensity ($P < 0.0001$) and immediate responses (within 10–12 minutes) for pain and burning, cold, itching, and deep and superficial pain ($P < 0.05$).[30,31] The number needed to treat for a 30% reduction in pain was 4 patients for the lower dose and 3 patients for the higher dose.

Using a novel metered inhaled aerosol system, a crossover RCT was reported by Almog et al., in which THC was administered in 3 arms over 3 consecutive visits (placebo, 0.5 mg THC, and 1 mg THC) to 25 patients with chronic neuropathic pain or complex regional pain syndrome. Subjects were allowed to continue with stable doses of other pain medications, including opioids. Both the 0.5-mg and 1-mg doses were associated with a decline in pain intensity at 15 minutes after inhalation and onward. A larger statistically significant reduction in VAS was appreciated with the 1.0-mg dose of THC compared with placebo and the 0.5-mg dose ($P = 0.0058$ and $P = 0.0015$, respectively). Although a dose response was appreciated, no high dose was implemented for comparison (1.0 mg was the maximum dose administered). Adverse events were mild, requiring no intervention.[32]

Table 1. Scoping review literature with direct dose responses.

Author, year	Population/size	Drug / dose / length of intervention	Design	Objective	Outcome measures	Dose response	Outcomes
Pain							
Wallace et al., 2007	Healthy volunteers, $n = 15$	Cannabis (NIDA) THC potency of 2%, 4%, 8%, placebo (CBD/CBN ≤ 0.25%).	Randomized, double-blinded, placebo-controlled, crossover trial	To determine whether inhaled cannabis would reduce experimental pain and hyperalgesia (intradermal capsaicin)	Spontaneous and elicited pain: thermal sensation, thermal pain, touch, and mechanical pain (VAS) and affective pain (McGill Pain Questionnaire)	Low dose did not differ from placebo at any time point (5 min/40 min) Significant (40-min time point) reduction in pain sensation at medium dose ($P = 0.011$–0.027). High dose increased pain perception ($P = 0.009$–0.002).	Acknowledged biphasic effects: Higher serum levels of THC and 11-OHTHC were negatively associated with subjective pain at both early and late time points. Did not attenuate hyperalgesia at any dose.
Narang et al., 2008	Patients with chronic noncancer pain on stable opioid doses; $n = 30$	Dronabinol (THC) 10 or 20 mg in 1 of 6 allocated sequences.	Phase 1: A double-blinded, randomized, placebo-controlled, single-dose study; followed by Phase 2: Open-label, 4-week, multidose extension study: 5–20 mg TID with stepwise dosage schedule.	To examine the analgesic effects of cannabinoids among patients with chronic noncancer pain who report moderate-severe pain while taking stable doses of opioids	Single dose at 8 hours: pain (NRS, BPI); anxiety (HADS); sleep (MOSSS); pain intensity, anxiety, depression irritability (Sum of Pain Intensity Difference); Global Satisfaction rating.	Phase 1: Pain (total relief and intensity) significantly improved both doses vs placebo ($P<0.010$). Phase 2: Significant decreases in average pain scores ($P<0.001$); BPI ($P < 0.05$) and MOSSS ($P < 0.01$); increase in sleep adequacy ($P < 0.05$). Most common adverse event was increased anxiety with 20-mg dose compared with placebo (but not with 10 mg).	Phase II: 20 mg had increased occurrence of drowsiness and sleepiness; sleep disturbances due to pain significantly decreased and sleep adequacy increased during prolonged use of dronabinol. No information was provided about doses used in Phase 2 by the subjects.
Portenoy et al., 2012	Patients with advanced cancer and opioid-refractory pain; $n = 360$	THC 2.7 mg / CBD 2.5 mg (nabiximols). Sprays/day: low: 1–4; medium: 6–10; high 11–16.	Randomized, double-blind, placebo-controlled, graded-dose study	Evaluate the analgesic efficacy and safety of nabiximols in 3 dose ranges in patients with advanced cancer and opioid-refractory pain.	BPI-sf, EORTC; QLQ-C30 V3; PAC-QoL; MADRS: At baseline 2 weeks post 5-week titration. PGIC at the study termination visit.	The 30% pain reduction responder rate was not significant for nabiximols vs placebo (overall $P = 0.59$). All-groups analysis showed the effect was significant in the 2 lower-dose groups ($P = 0.008$ and 0.038, respectively); combined low and medium groups estimated median difference between treatment groups of 10.5% in favor of nabiximols.	Low-dose nabiximols was associated with the most significant reduction in pain and improvement of sleep quality. High dose was associated with the most adverse events.

(continued)

Table 1. (continued)

Author, year	Population/size	Drug / dose / length of intervention	Design	Objective	Outcome measures	Dose response	Outcomes
Wallace et al., 2015	Adults with painful diabetic neuropathy; $n = 16$	Inhaled cannabis (NIDA) THC (1%, 4%, 7%) in 400 mg of plant material (4, 16, or 28 mg THC per dosing session) vs placebo	Randomized, double-blinded, placebo-controlled crossover study; within-subjects design	To assess the short-term efficacy and tolerability of inhaled cannabis in patients with PDN. Four distinct sessions, separated by 2 weeks.	Pain intensity: spontaneous, evoked (VAS), and at 5, 15, 30, 45, and 60 minutes and every 30 minutes for an additional 3 hours. Cognitive testing: TMT.	There is a dose-dependent reduction in pain intensity for both spontaneous and evoked pain; decreases in spontaneous pain for the high-dose cannabis were significantly greater placebo after 30, 45, and 60 min. High dose had significant greater effect on von Frey pain after 15, 45, and 60 min.	Although dose-dependent effect, more adverse events in the higher dose. Comparison of the proportions of participants who achieved at least 30% reduction in spontaneous pain scores did not show statistically significant results.
Wilsey et al., 2016	Adults with neuropathic pain; $n = 42$	Smoked cannabis THC 2.9% or 6.7% compared with placebo cannabis (NIDA) on three 8-hour experimental sessions with 3-day washout.	Randomized, double-blind, placebo-controlled, crossover design	To assess the analgesic efficacy of vaporized cannabis in patients with neuropathic pain related to injury or disease of the spinal cord.	Pain intensity: NRS; and PGIC; NPS	A significant stairstep effect (Tukey test) where the most pain occurred with placebo, significantly less pain was measured at the 2.9% THC dose, and at the 6.7% THC, significantly less pain was experienced compared with the lower dose and placebo.	A significant dose–response effect was realized for these 3 treatment doses according to the Cochran-Armitage trend test ($P < 0.0001$).
Wilsey et al., 2016	Patients with spinal cord injury and neuropathic pain; $n = 42$	THC: 2.9% and 6.7% vaporized cannabis (NIDA)	Randomized, placebo-controlled crossover trial	Analyze THC pharmacokinetics to optimize analgesic effects of cannabis in patients with spinal cord injury.	Pain (NPS) and blood samples taken at 240 and 420 minutes after second dose	6.7% THC cannabis provided more relief as indicated by a greater negative percent change from baseline for all tested parameters compared with 2.9% THC ($P = 0.0395$)	Both burning and itching were reduced significantly more from baseline with the higher active THC dose than with the lower one ($P = 0.0174$).
Almog et al., 2019	Patients with chronic neuropathic pain or complex regional pain syndrome; $n = 25$	THC: 0.5 or 1 mg compared with placebo. Single inhalation on 3 separate visits: aerosolized cannabis containing 22%THC, <0.2% CBD/CBN	Randomized, double-blinded, placebo-controlled, crossover trial (3 arms)	To test the pharmacokinetics, analgesic effect, cognitive performance, and safety effects of THC in patients with chronic pain (medical device).	Pain intensity: VAS at 5, 15, 30, 60, 90, and 120 min.	Reduction of pain VAS score was statistically significantly larger in the 1.0-mg dose than in the placebo and the 0.5-mg dose; 120 minutes most significant change.	The study demonstrated a dose-dependent pharmacokinetic profile, as well as a reduction in pain intensity in response to the inhalation of small doses. No high dose assessed.

(continued)

Table 1. (continued)

Author, year	Population/size	Drug / dose / length of intervention	Design	Objective	Outcome measures	Dose response	Outcomes
Wallace et al., 2020	Adults with pain: diabetic neuropathy; $n = 16$	Inhaled cannabis (NIDA) THC (1%, 4%, 7%) in 400 mg plant material (4, 16, or 28 mg THC per single dosing session) vs placebo	A randomized, double-blinded, placebo-controlled crossover design	A secondary analysis of data from Wallace et al. (2015) to examine the association between THC plasma levels and pain response.	Pain intensity: VAS Serum THC quantification	A negative linear relationship of plasma THC with pain reduction up to a point, where rising THC levels then result in a positive linear relationship. U-shaped response.	As THC plasma levels increased, pain reduces (16–31 ng/mL as a therapeutic window), and as THC plasma levels increase, pain increases.
Arout et al., 2021	Healthy non–cannabis-using volunteers; $n = 17$	CBD: 0, 200, 400, and 800 mg oral (Insys Therapeutics)	Double-blind, placebo-controlled, within-subject outpatient clinical laboratory study	Determine the analgesic effects, abuse liability, safety, and tolerability of acute CBD: 4 experimental sessions	Experimental pain threshold and pain tolerance via cold pressor test; measured at baseline and at 60, 120, 180, 240, 300, and 360 minutes after CBD administration	CBD did not elicit consistent dose-dependent analgesia. Low dose (200 mg) increased pain threshold. High dose (400 and 800 mg) decreased pain threshold, both relative to placebo.	All doses of CBD increased ratings of painfulness compared with placebo ($P < 0.01$).
Anxiety							
Liguori, 2003	Adult users of cannabis; $n = 7$	Smoked marijuana cigarettes (0.003%, 2%, or 3.5% THC) (NIDA)	Randomized, double-blind, placebo-controlled, within- subject design	To compare behavioral and subjective effects of cannabis inhalation (6–7 hours after waking) after partial sleep deprivation or after a typical night of sleep.	ESS, SSS, MSLT; procedures; VAS for feelings of: Anxious, clear-headed, confused, energetic, high, impaired, relaxed, sluggish, and stoned	A significant dose/time interaction ($P < 0.01$) on ratings of anxious was due to higher ratings at 2 min after smoking with 3.5% THC ($P < 0.001$) compared with 2% THC or placebo.	3.5% THC dose, but not the 2.5% THC dose, significantly impaired equilibrium and increased body sway outcomes but not brake latency.
Hunault et al., 2014	Adult males experienced with recreational cannabis use; $n = 24$	Cannabis joints THC: 0.003%, 9.75%, and 23.12% (29 mg, 49 mg, and 69 mg) vs placebo; smoked 2–9 per month	Randomized, double-blind, placebo-controlled, crossover study	To establish acute subjective effects after smoking joints containing tobacco. Four separate sessions with 8-hour observation	VAS for bodily symptoms: sedation/anxiety; mood symptoms: alertness, contentment, and calmness; and for drug effect	Increased anxious feelings. Also increased feeling high, dizziness, dry-mouthed feeling, palpitations, impaired concentration, and memory.	Dose-dependent effects significant at higher doses: THC significantly decreased alertness, contentment, and calmness.
Linares et al., 2019	Healthy adult males, 18–35 years; $n = 57$	Placebo and CBD (purified: 150, 300, and 600 mg)	Randomized, double-blind, controlled trial; public speaking test	Assess whether the anxiolytic effect of CBD in humans follows the same pattern of an inverted U-shaped dose–effect curve observed in many animal studies.	Spielberger State-Trait Anxiety Inventory; Visual Analog Mood Scale performed immediately after 4-min speech and at 30 min afterward.	Low and high dose of CBD had no effect on SPST. Inverted U-shaped response on Visual Analog Mood Scale.	No effect at low or high dose. Only intermediate dose had a significant effect on anxiety.

(continued)

Table 1. (continued)

Author, year	Population/size	Drug / dose / length of intervention	Design	Objective	Outcome measures	Dose response	Outcomes
Childs et al., 2017	Healthy volunteers; $n = 42$	THC: 0, 7.5, or 12.5 mg (Marinol capsule)	Randomized, double-blind trial	Assess the influence of delta-9-THC on emotional responses to an acute psychosocial stressor (TSST) compared with a non-stressful task.	VAS subjective distress score; PASA; pre/post testing; STAI; DEQ; ARCI; POMS, blood pressure, heart rate; salivary cortisol.	Dose–response increases anxiety before the task. Self-reported reductions in stress and anxiety with the 7.5-mg dose. Small but significant increase in anxiety with the higher dose of THC (12.5 mg).	Increase in subjective distress was significant before (12.5 mg) and after the test (7.5 and 12.5 mg) compared with placebo. 12.5 mg but not 7.5 mg increased anxiety compared with placebo.
Casarett et al., 2019 *	Medical cannabis users; $n = 2431$	Ad libitum use of self-accessed medical cannabis products (inhaled only) with various dose/ratios of THC and CBD	Retrospective cohort study using self-report (Strainprint mobile app)	To determine the relative contributions of THC and CBD to patients' self-ratings of efficacy for common palliative care symptoms.	11-point NRS symptom severity for 6 symptoms (neuropathic pain, insomnia, anxiety symptoms, depressive symptoms); post-traumatic stress disorder (PTSD)–related flashbacks and anorexia.	Several symptoms were very sensitive to increasing THC:CBD ratios: neuropathic pain (OR 3.58); insomnia (OR 2.39). Response for anxiety was not significant (OR 1.13) but had an inverted U-shaped response curve.	Up to a 1:1 ratio of THC:CBD was associated with a positive response for anxiety symptoms, then decreasing response.
Wildes et al., 2020	Adults with chronic pain using prescribed opioids; $n = 150$	THC or CBD: 0 to >30% potency, estimated by the participant	Cross-sectional survey	To understand how/whether reported cannabis use changed/moderated relationship between negative affect and cognition over the past 30 days.	Social support: PROMIS 4a; Anxiety: GAD7; Depression: PHQ-8.	Higher percentages of THC and CBD were positively related to depression and anxiety.	30-day cannabis use whereby more and higher concentrations of cannabis use (CBD and THC) were related to significantly higher burdens of depression, anxiety, and cognitive impairment.
Steeger et al., 2021	Adult, health cannabis users; $n = 300$	Self-accessed cannabis products, oral or inhaled: Flower (reported in % THC/CBD) edibles (reported in mg of THC/CBD) and concentrate (% THC/CBD)	Prospective, self-report, observational	To understand whether self-reported cannabinoid potency contributes to variance in cannabis/health metrics over and above frequency of use.	BDI; BAI; MDS; HRQL, SF-12	No significance based on potency found. Past month frequency of use significant for concentrate on depression and anxiety scores BDI*; BAI*** And for all product forms for frequency: BDI *; BAI** ($^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.005$).	No significance based on potency was found. Higher flower and concentrate frequency were positively associated with all 3/2 (respectively) measures of problematic cannabis use.

(continued)

Table 1. (continued)

Author, year	Population/size	Drug / dose / length of intervention	Design	Objective	Outcome measures	Dose response	Outcomes
Sleep							
McClure, et al., 2012	Adults with cannabis use dependence disorder; $n = 20$	Ad libitum ingestion of cannabis 3% THC (0.8 g per joint) for 2 days followed by 3 days of abstinence	Observational study	To measure cannabis smoking topography characteristics during periods of ad libitum use: withdrawal, craving during abstinence, and cognitive task performance.	MWC; MCQ; PSQI; cognitive performance tasks; sleep continuity/architecture (polysomnography)	Puff volume negatively correlated with sleep efficiency and positively correlated with sleep latency. Puff volume and puff duration were positively correlated with total time awake after sleep onset. Puff duration positively correlated with subjective reports of sleep latency and negatively correlated with sleep quality and mood on morning awakening.	Years of frequent use was associated with sleep disturbance on PSG and increased latency during abstinence.
Carley et al., 2018	Adults with moderate-severe obstructive sleep apnea; $n = 73$	THC 2.5 or 10 mg (dronabinol), 1 hour before bedtime, daily for up to for 42 days.	Fully blinded parallel groups, placebo-controlled randomized trial	To investigate dronabinol as a treatment for obstructive sleep apnea	Apnea–hypopnea index, ESS, wakefulness test (MWT), adverse events, treatment adherence	Dronabinol dose-dependently reduced apnea–hypopnea index 2.5 mg: ($P = 0.02$) and 10 mg: ($P = 0.003$). 10 mg/day significantly reduced ESS score by ($P < 0.0001$) compared with placebo.	MWT sleep latencies, gross sleep architecture, overnight oxygenation parameters unchanged in all groups.

Abbreviations: ARCI = Addiction Research Center Inventory; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; BPI-sf = Brief Pain Inventory, short form; CBD = cannabidiol; CBN= cannabinol; DEQ = Drug Effects Questionnaire; EORTC = European Organization for Research and Treatment of Cancer; ESS = Epworth Sleepiness Scale; GAD7 = General Anxiety Disorder Scale; HADS = Hospital Anxiety and Depression Scale; HRQL, SF-12 = Health-related quality of Life; MADRS = Montgomery-Asberg Depression Rating Scale; MCQ = Marijuana Craving Questionnaire; MDS = Marijuana Dependence Scale; MOSSS = Medical Outcomes Study Sleep Scale; MSLT = Multiple Sleep Latency Test; MWC = Marijuana Withdrawal Checklist; MWT = Maintenance Wakefulness Test; NIDA = National Institute on Drug Abuse; NPS = Neuropathic Pain Scale; NRS = numeric rating scale; OHTHC = Hydroxyl delta-9 Tetrahydrocannabinol; PAC-QoL = The Patient Assessment of Constipation Quality of Life; PASA = Primary Appraisal, Secondary Appraisal rating scale; PDN = Painful Diabetic Neuropathy; PGIC = Patient Global Impression of Change; PHQ8 = Patient Health Questionnaire; POMS = Profile of Mood States; PROMIS = Patient-reported outcomes measurement Information Systems: 4a: Emotional support; PSQI = Pittsburgh Sleep Quality Index; PTSD = post-traumatic stress disorder; QLQ-C30 V3 = Quality of Life Questionnaire-Core30 (version 3); SPST = Simulation Public Speaking Test; SSS = Stanford Sleepiness Scale; STAI = State Trait Anxiety Inventory; THC = delta-9 tetrahydrocannabinol; TMT = Trail-making test; TSST = Trier Social Stress Test; VAS = visual analog scale.

* Indicates that more than just 1 of our selected outcomes (pain, anxiety, sleep) was measured.

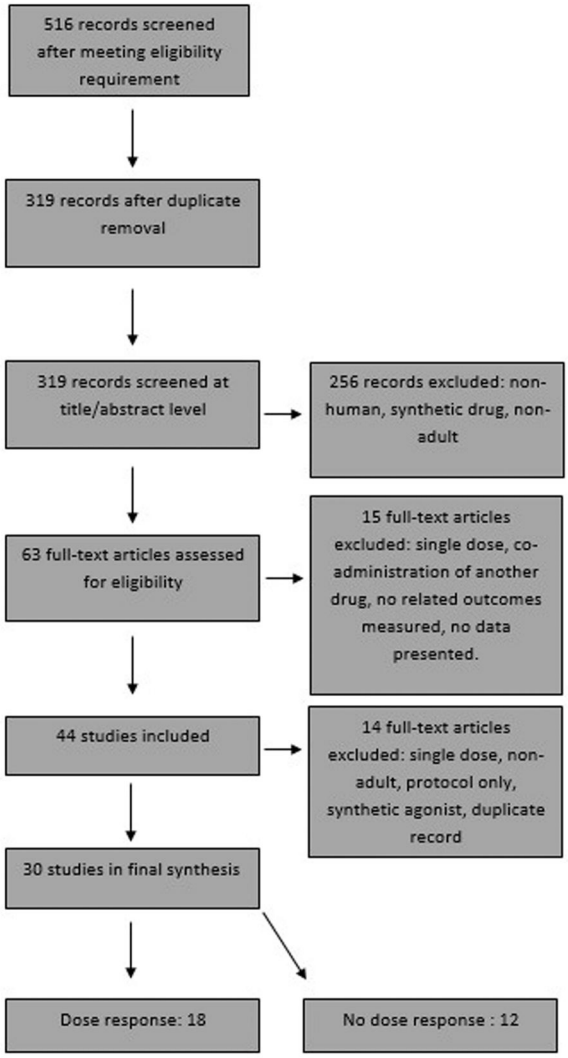

Figure 2. Study flow diagram. Visual demonstration of systematic screening and selection of database searches according to inclusion/exclusion criteria.

One trial by Arout et al. used various doses of CBD exclusively in healthy non–cannabis-using volunteers. Experimental pain was induced with the cold pressor test at varying time points and doses. There was no consistent dose-dependent analgesia, but low-dose CBD (200 mg) increased pain threshold, whereas higher doses (400 and 800 mg) decreased pain threshold, relative to placebo.[34]

Studies related to anxiety/sleep

Thirteen studies that specifically measured cannabis/cannabinoid effects on anxiety and 2 studies that measured effects on sleep disturbances were identified (Table 1 and Table S3). Of these, 7 studies that identified a dose–response association with anxiety and 2 with sleep parameters are included in the present synthesis.[35–43] Five of the anxiety studies were prospective, and 2 were retrospective.[35–41] Of the 5 prospective studies, 4 were RCTs, of which 2 used inhaled cannabis (smoked THC or CBD of various of concentrations); 1 RCT administered oral doses of CBD; and 1 administered semisynthetic THC (dronabinol).[35–38] Two retrospective cohort studies of cannabis use and 1 prospective observational study of cannabis were identified.[39–41] Notably, none of the included studies enrolled a cohort with a formal diagnosis of anxiety or any anxiety disorder, and 1 study group was subjects with chronic pain using prescribed opioids.[40] Subjects were otherwise healthy volunteers or experienced cannabis users. Sleep studies included adults with cannabis use disorder and adults with moderate to severe obstructive sleep apnea.[42,43]

In Hunault et al. (2014), inhaled cannabis acutely and significantly increased anxiety at higher compared with lower doses of THC relative to placebo. Subjective effects were measured in 24 experienced cannabis users in a crossover model on 4 separate test days (comparing 29, 49, and 65 mg THC [0.003%, 9.75%, and 23% THC], administered with tobacco) vs placebo. Actual milligram doses are difficult to ascertain because of the potential loss of THC via side-stream smoke and other factors.[36] Side effects were measured on the VAS, with dizziness, impaired memory, and sedation increased with all doses. The most pronounced effects were

Table 2. Potential for biphasic effects.

First author, year	Diagnosis	Response	Potential for biphasic effect	Effect
Pain				
Wallace, 2007	Healthy	U-shaped	Yes	Pain
Narang, 2008	Chronic noncancer pain	Dose	No	Anxiety
Portenoy, 2012	Cancer	Biphasic	Yes	Pain
Wallace, 2015	Diabetic neuropathy	U-shaped	Yes	Pain
Wilsey, 2016	Neuropathic	Dose	Yes	Pain
Almog, 2019	Neuropathic, nociplastic	Dose	No	Pain
Wallace, 2020	Diabetic neuropathy	U-shaped	Yes	Pain
Arout, 2021	Healthy	None	No	Pain
Anxiety				
Liguori, 2003	Healthy	Dose	No	Anxiety
Hunault, 2014	Healthy	Dose	No	Anxiety
Linares, 2019	Healthy	U-shaped	Yes	Anxiety
Childs, 2017	Healthy	Dose	Yes	Anxiety
Casarett, 2019	Various	Dose	Yes	Anxiety
Wildes, 2020	Chronic pain	Dose	No	Anxiety
Steeger, 2021	Healthy	None	No	N/A
Sleep				
McClure, 2012	Cannabis use disorder	Dose	No	Sleep
Carley, 2018	Apnea	Dose	No	Sleep

in the first 2 hours after smoking with the highest THC dose. Nicotine might have influenced the outcomes.

A 2003 double-blind, randomized, within-subject study design by Liguori et al. used an overnight sleep study in recreational cannabis users ($n = 31$) to test cannabis use and impairment after partial sleep deprivation. Subjective effects were measured after sleep deprivation, comparing inhaled cannabis at THC concentrations of 2% and 3.5% smoked 6 hours after waking from either a typical night of sleep or partial sleep deprivation. Drug effects measured on VAS at 2 minutes after smoking revealed that ratings of "anxious" were increased significantly at 3.5% THC compared with 2% THC and placebo ($P < 0.0001$).[35]

In Childs et al., dose-related effects of dronabinol in healthy volunteers were explored, compared with placebo, in the experimental setting of a psychosocial stress task (Trier social stress test) compared with a nonstressor. Subjective distress was measured by 3 items on a 100-mm line. The 12.5-mg dose significantly increased VAS ratings of subjective distress compared with 7.5 mg or placebo ($P < 0.01$; $P < 0.001$). Low dose was found to mitigate the negative emotional effects of a psychosocial stressor in young people.[38]

CBD was administered to 57 healthy male volunteers in a 2019 trial by Linares et al. investigating anxiolytic effects in the experimental setting of simulated public speaking. The Visual Analog Mood Scale measured anxiety and showed lower induced anxiety levels in the 300-mg dose group than in the placebo group ($P = 0.042$). Overall, the Visual Analog Mood Scale results revealed a U-shaped response curve effect on subjective effects of anxiety. At the time the speech was performed, anxiety was worse at the low and high doses than at the middle dose, which indicates a potential therapeutic window.[37]

Three studies provided data on self-reported cannabis use: a 2019 retrospective cohort study by Casarett et al., a 2020 cross-sectional survey by Wildes et al., and a 2021 prospective observational study by Steeger et al.[39–41] A retrospective survey approach queried 2431 medical cannabis users to compare relative contributions of THC and CBD for effects on palliative care symptoms (THC/THC + CBD). Data from a cannabis use tracking app (Strainprint) were used. Adults with persistent pain (by self-report) provided information on cannabis constituents, use, and symptoms. A THC:CBD ratio >1 was associated with reduced effectiveness for anxiousness. Palliative care symptoms, affect, and health metrics related to potency or frequency of use were measured.[39] In general, for subjects who endorsed chronic pain, higher concentrations of both THC and CBD (by percentage weight) or higher frequency of use (not based on potency) correlated with increased anxiety and depression.[40,41]

A 2012 observational study by McClure et al. and a 2018 RCT by Carley et al. on cannabis effects on sleep were identified.[42,43] The observational study was in adults with cannabis use disorder who used ad libitum smoked cannabis (3% THC) for 2 days followed by 3 days of abstinence. Dose-dependent effects were reported on sleep with the Pittsburg Sleep Quality Index. Sleep efficiency, or time asleep, was negatively correlated with greater puff volume after withdrawal, reinforcing that sleep disturbance was associated with withdrawal.[42] The RCT tested dronabinol in subjects with moderate to severe sleep apnea at doses of 2.5 or 10 mg for up to 6 weeks, with the primary outcome being the apnea–hypopnea index. Dronabinol significantly and dose-dependently reduced the Epworth Sleepiness Scale scores and significantly improved apnea–hypopnea index as well as total time spent in non–rapid-eye-movement sleep.[43]

Discussion

The results of this scoping review demonstrate a small number of available studies that report dose-dependent responses of THC on pain, anxiety, and sleep-related measures. CBD alone did not elicit consistent dose-dependent analgesia, and the literature is weak for any effect on anxiety. Among the studies selected for synthesis, dose responses were present for THC on pain severity and anxiety but not sleep.

When the triad components are reviewed individually, the pain domain has the strongest evidentiary support for a potential biphasic effect of THC (Table 2). One study specifically commented on the biphasic response to escalating doses of THC.[33] This was a secondary analysis of data observing effects of THC for painful diabetic neuropathy (original study also part of the present synthesis).[29] A negative linear relationship of plasma THC with pain reduction was observed up to a point, until rising THC levels began to demonstrate a positive linear relationship.[33] CBD alone did not elicit consistent dose-dependent analgesia and conversely was shown to exacerbate experimental pain on some measures.[34] Similarly, an inverted U-shaped response was observed for anxiolysis, with the medium dose of CBD being effective (300 mg). However, that study was small ($n = 12$), was conducted in healthy subjects, and used only 3 doses with wide interdose variability (100 mg, 300 mg, and 900 mg).[37] Still unsubstantiated is whether CBD at any dose could be effective for chronic pain, anxiety, or sleep. For subjects from the included studies who endorsed chronic pain, higher dosages of both THC and CBD or higher frequency of use correlated with increased anxiety and depression.[40,41]

Across all domains of the symptom triad, higher ratios of THC:CBD are associated with increased pain, anxiety, and sleep disturbance.[26,27,36–43,28–35] It is important to note that even semisynthetic THC (dronabinol) in patients with chronic noncancer pain demonstrated a similar dose response, with 20 mg (high dose) eliciting anxiety. Total pain relief and pain intensity were significantly improved with all doses compared with placebo ($P < 0.010$), and both average NRS ($P < 0.001$) and BPI ($P < 0.05$) scores improved in the longer-term phase 2 study by Narang et al. There was also a significant improvement in sleep adequacy ($P < 0.05$) based on improved MOSSS. Patients experienced deleterious effects more frequently with the higher dose.[27]

Soon after THC was isolated in 1964, human dose studies on intoxication commenced.[44,45] A study in healthy volunteers found that subjective intoxication varied with the dose of THC. CBD was reported early in the human literature to have "blocking" effects on THC intoxication when they were given together.[46] However, mixed results on any countereffects of CBD on THC add to confusion about dosing and cannabinoid ratios.[47,48] THC 5 mg is a standard oral dose unit defined by the US National Institutes of Health (NIH).[49] There is no standard potency for inhaled cannabis (measured by percentage THC of total weight of the plant or extract). The NIH recognizes that "the same quantity of THC may have different effects based on route of administration, other product constituents, an individual's genetic make-up and

metabolic factors, prior exposure to cannabis, and other factors."[50]

In a classic review of endocannabinoid system function in 2006, Pacher wrote, "Many of the psychological effects of cannabis and THC are biphasic and bidirectional, depending on mode of administration, dose, personality, time frame, degree of tolerance, and various other environmental and individual factors."[19] Accordingly, studies have noted beneficial effects with low or medium doses of cannabinoids and adverse effects with high doses, including increased anxiety, hyperalgesia, and somnolence.[26,36,51–53] It is important to note that the heterogeneity of study designs and their respective data makes it difficult to generalize these findings to patients with pain, as well as to the general population.

Sleep efficiency was negatively correlated with inhalation volume after withdrawal, reinforcing the association of sleep disturbance with cannabis withdrawal. However, this sheds little light on any biphasic effects of inhaled cannabis on sleep outside of the withdrawal paradigm.[42] Doses of dronabinol up to 10 mg could benefit sleep without interrupting rapid-eye-movement sleep,[43] but this has not yet been demonstrated in patients with pain who present with sleep disturbance. Similarly, it is unclear whether specific doses are associated with dose–response effects on sleep architecture or rapid-eye-movement sleep. Nonetheless, this might suggest an underlying biphasic phenomenon. There is a need for prospective dose-ranging studies on the effects of cannabis or THC for sleep efficiency.

Among the studies included in the present synthesis, heterogeneity of the study populations, methods, exposures, and measurements of effect is evident and represents a limitation of the review. Across the studies, study populations included healthy volunteers, patients with chronic pain, and patients with neuropathic and cancer-related pain.[26–34] One could argue that this mixed cohort generally represents patients presenting to pain departments with co-occurring anxiety and sleep disturbances.

This scoping review has several additional limitations. Inherent to the study design, there could be a selection bias, as included studies strictly followed the proposed inclusion/exclusion criteria. The search was limited to adult human studies that reported a dose response and were indexed in the Embase, Biosis, and Medline databases. Other studies might have reported biphasic effects, but articles could have been excluded if one of the search terms was not in the title or abstract. Preclinical studies were not included in this synthesis, which was intentional for analysis of effects in humans. However, previous animal studies have described biphasic effects of cannabinoids.[15,19,54,55] Another notable limitation is the relatively small populations in the included studies, in addition to the variety of the populations studied (not necessarily in patients with pain). Except for Portenoy et al. ($n = 360$), the studies included in this synthesis had modest participant sizes.[28] Many studies use isolated cannabinoids vs the cannabis plant, which introduces potential confounding factors, as there are thousands of cannabis chemovars available to users. Short-term or single-dose studies also cannot account for tolerance to effects or for side effects than might occur with regular use.

However, despite these limitations, this review found some literature for dose responses for pain and anxiety that have the potential to be biphasic (Table 2). This scoping review highlights the limitations of cross-sectional studies and reports from self-selected populations, as well as the lack of well-characterized or standardized dosing on biphasic effects in humans. With the progressive wave of medical and recreational legalization throughout the United States, unrestricted and unfounded marketing claims, including a perceived need for high-potency cannabis for medical purposes, could harm patients.

Conclusions

Despite the fact that biphasic effects of cannabinoids have been reported in preclinical literature, this scoping review found no studies prospectively probing this concept in humans. Although dose responses have been reported for THC on anxiety and pain, the literature lacks data on opposite effects of low vs high dose. Research designed to specifically look for biphasic effects in humans for pain, anxiety, or sleep is needed. A key concept for future prospective research would be to specifically measure both increases and decreases in outcomes related to the dose. Dosing on a continuous vs dichotomous basis is needed to further define whether the biphasic concept applies to humans. As many patients could be self-referring to medical cannabis use for pain, anxiety, and sleep, there is a need to explore optimal patient outcomes in this symptom triad. Given the lack of clarity in the literature on the dose–response relationship, there are likely knowledge gaps in health care providers' understanding of cannabinoid dosing. This has implications for the safety and efficacy of cannabis in patients with chronic pain.

Acknowledgments

An abstract of this article was accepted for the annual American Academy of Pain Medicine meeting in 2023.

Supplementary material

Supplementary material is available at *Pain Medicine* online.

Funding

The authors did not receive any funding in drafting this manuscript.

Conflicts of interest: None declared.

References

1. Dahlhamer J, Lucas J, Zelaya C, et al. Prevalence of chronic pain and high-impact chronic pain among adults—United States, 2016. MMWR Morb Mortal Wkly Rep. 2018;67(36):1001-1006. https://doi.org/10.15585/mmwr.mm6736a2
2. Burgess HJ, Burns JW, Buvanendran A, et al. Associations between sleep disturbance and chronic pain intensity and function: a test of direct and indirect pathways. Clin J Pain. 2019;35(7):569-576. https://doi.org/10.1097/AJP.0000000000000711
3. Koffel E, Krebs EE, Arbisi PA, Erbes CR, Polusny MA. The unhappy triad: pain, sleep complaints, and internalizing symptoms. Clin Psychol Sci. 2016;4(1):96-106. https://doi.org/10.1177/2167702615579342
4. Cohen SP, Doshi TL, Kurihara C, et al. Multicenter study evaluating factors associated with treatment outcome for low back pain injections. Reg Anesth Pain Med. 2022;47(2):89-99. https://doi.org/10.1136/rapm-2021-103247

5. Shustorovich A, Narouze SN. History of cannabis. In: Narouze SN, ed. Cannabinoids and Pain. Springer International Publishing; 2021:3-7. https://doi.org/10.1007/978-3-030-69186-8_1
6. VanDolah HJ, Bauer BA, Mauck KF. Clinicians' guide to cannabidiol and hemp oils. Mayo Clin Proc. 2019;94(9):1840-1851. https://doi.org/10.1016/j.mayocp.2019.01.003
7. Ward SJ, McAllister SD, Kawamura R, Murase R, Neelakantan H, Walker EA. Cannabidiol inhibits paclitaxel-induced neuropathic pain through 5-HT(1A) receptors without diminishing nervous system function or chemotherapy efficacy. Br J Pharmacol. 2014;171(3):636-645. https://doi.org/10.1111/bph.12439
8. Hammell DC, Zhang LP, Ma F, et al. Transdermal cannabidiol reduces inflammation and pain-related behaviours in a rat model of arthritis. Eur J Pain. 2016;20(6):936-948. https://doi.org/10.1002/ejp.818
9. Harris HM, Sufka KJ, Gul W, ElSohly MA. Effects of delta-9-tetrahydrocannabinol and cannabidiol on cisplatin-induced neuropathy in mice. Planta Med. 2016;82(13):1169-1172. https://doi.org/10.1055/s-0042-106303
10. Sexton M, Cuttler C, Finnell JS, Mischley LK. A cross-sectional survey of medical cannabis users: patterns of use and perceived efficacy. Cannabis Cannabinoid Res. 2016;1(1):131-138. https://doi.org/10.1089/can.2016.0007
11. Lucas P, Walsh Z. Medical cannabis access, use, and substitution for prescription opioids and other substances: a survey of authorized medical cannabis patients. Int J Drug Policy. 2017;42:30-35. https://doi.org/10.1016/j.drugpo.2017.01.011
12. Lapham GT, Matson TE, Carrell DS, et al. Comparison of medical cannabis use reported on a confidential survey vs documented in the electronic health record among primary care patients. JAMA Netw Open. 2022;5(5):e2211677. https://doi.org/10.1001/jamanetworkopen.2022.11677
13. Asselin A, Lamarre OB, Chamberland R, McNeil SJ, Demers E, Zongo A. A description of self-medication with cannabis among adults with legal access to cannabis in Quebec, Canada. J Cannabis Res. 2022;4(1):26. https://doi.org/10.1186/s42238-022-00135-y
14. Spindle TR, Bonn-Miller MO, Vandrey R. Changing landscape of cannabis: novel products, formulations, and methods of administration. Curr Opin Psychol. 2019;30:98-102. https://doi.org/10.1016/j.copsyc.2019.04.002
15. Rey AA, Purrio M, Viveros MP, Lutz B. Biphasic effects of cannabinoids in anxiety responses: CB1 and GABA(B) receptors in the balance of GABAergic and glutamatergic neurotransmission. Neuropsychopharmacology. 2012;37(12):2624-2634.
16. Paton WDM, Pertwee RG. The Pharmacology of Cannabis in Man: Chemistry, Pharmacology, Metabolism, and Clinical Effects. Academic Press; 1973.
17. Fride E. Anandamides: tolerance and cross-tolerance to delta 9-tetrahydrocannabinol. Brain Res. 1995;697(1-2):83-90. https://doi.org/10.1016/0006-8993(95)00790-w
18. Sulcova E, Mechoulam R, Fride E. Biphasic effects of anandamide. Pharmacol Biochem Behav. 1998;59(2):347-352. https://doi.org/10.1016/s0091-3057(97)00422-x
19. Pacher P, Bátkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. Pharmacol Rev. 2006;58(3):389-462. https://doi.org/10.1124/pr.58.3.2
20. Ashton H, Golding J, Marsh VR, Millman JE, Thompson JW. The seed and the soil: effect of dosage, personality and starting state on the response to delta 9 tetrahydrocannabinol in man. Br J Clin Pharmacol. 1981;12(5):705-720. https://doi.org/10.1111/j.1365-2125.1981.tb01294.x
21. Tricco AC, Lillie E, Zarin W, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med. 2018;169(7):467-473. https://doi.org/10.7326/M18-0850
22. Kohl C, McIntosh EJ, Unger S, et al. Online tools supporting the conduct and reporting of systematic reviews and systematic maps: a case study on CADIMA and review of existing tools. Environ Evid. 2018;7(1):8. https://doi.org/10.1186/s13750-018-0115-5
23. Hayes DP. Nutritional hormesis. Eur J Clin Nutr. 2007;61(2):147-159. https://doi.org/10.1038/sj.ejcn.1602507
24. MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. Eur J Intern Med. 2018;49:12-19. https://doi.org/10.1016/j.ejim.2018.01.004
25. Bell AD, MacCallum C, Margolese S, et al.; External Review Panel. Clinical practice guidelines for cannabis and cannabinoid-based medicines in the management of chronic pain and co-occurring conditions. Cannabis Cannabinoid Res. 2023. https://doi.org/10.1089/can.2021.0156
26. Wallace M, Schulteis G, Atkinson JH, et al. Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers. Anesthesiology. 2007;107(5):785-796. https://doi.org/10.1097/01.anes.0000286986.92475.b7
27. Narang S, Gibson D, Wasan AD, et al. Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. J Pain. 2008;9(3):254-264. https://doi.org/10.1016/j.jpain.2007.10.018
28. Portenoy RK, Ganae-Motan ED, Allende S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain. 2012;13(5):438-449. https://doi.org/10.1016/j.jpain.2012.01.003
29. Wallace MS, Marcotte TD, Umlauf A, Gouaux B, Atkinson JH. Efficacy of inhaled cannabis on painful diabetic neuropathy. J Pain. 2015;16(7):616-627. https://doi.org/10.1016/j.jpain.2015.03.008
30. Wilsey BL, Deutsch R, Samara E, et al. A preliminary evaluation of the relationship of cannabinoid blood concentrations with the analgesic response to vaporized cannabis. J Pain Res. 2016;9:587-598. https://doi.org/10.2147/JPR.S113138
31. Wilsey B, Marcotte TD, Deutsch R, Zhao H, Prasad H, Phan A. An exploratory human laboratory experiment evaluating vaporized cannabis in the treatment of neuropathic pain from spinal cord injury and disease. J Pain. 2016;17(9):982-1000. https://doi.org/10.1016/j.jpain.2016.05.010
32. Almog S, Aharon-Peretz J, Vulfsons S, et al. The pharmacokinetics, efficacy, and safety of a novel selective-dose cannabis inhaler in patients with chronic pain: A randomized, double-blinded, placebo-controlled trial. Eur J Pain. 2020;24(8):1505-1516. https://doi.org/10.1002/ejp.1605
33. Wallace MS, Marcotte TD, Atkinson JH, Padovano HT, Bonn-Miller M. A secondary analysis from a randomized trial on the effect of plasma tetrahydrocannabinol levels on pain reduction in painful diabetic peripheral neuropathy. J Pain. 2020;21(11-12):1175-1186. https://doi.org/10.1016/j.jpain.2020.03.003
34. Arout CA, Haney M, Herrmann ES, Bedi G, Cooper ZD. A placebo-controlled investigation of the analgesic effects, abuse liability, safety and tolerability of a range of oral cannabidiol doses in healthy humans. Br J Clin Pharmacol. 2022;88(1):347-355. https://doi.org/10.1111/bcp.14973
35. Liguori A, Gatto CP, Jarrett DB, McCall WV, Brown TW. Behavioral and subjective effects of marijuana following partial sleep deprivation. Drug Alcohol Depend. 2003;70(3):233-240. https://doi.org/10.1016/s0376-8716(03)00008-5
36. Hunault CC, Böcker KBE, Stellato RK, Kenemans JL, de Vries I, Meulenbelt J. Acute subjective effects after smoking joints containing up to 69 mg Δ9-tetrahydrocannabinol in recreational users: a randomized, crossover clinical trial. Psychopharmacology (Berl). 2014;231(24):4723-4733. https://doi.org/10.1007/s00213-014-3630-2
37. Linares IM, Zuardi AW, Pereira LC, et al. Cannabidiol presents an inverted U-shaped dose-response curve in a simulated public speaking test. Braz J Psychiatry. 2019;41(1):9-14. https://doi.org/10.1590/1516-4446-2017-0015

38. Childs E, Lutz JA, de Wit H. Dose-related effects of delta-9-THC on emotional responses to acute psychosocial stress. Drug Alcohol Depend. 2017;177:136-144. https://doi.org/10.1016/j.drugalcdep.2017.03.030
39. Casarett DJ, Beliveau JN, Arbus MS. Benefit of tetrahydrocannabinol versus cannabidiol for common palliative care symptoms. J Palliat Med. 2019;22(10):1180-1184. https://doi.org/10.1089/jpm.2018.0658
40. Wildes M, Bigand TL, Layton ME, Wilson M. Cannabis use and cognition in adults prescribed opioids for persistent pain. Pain Manag Nurs. 2020;21(1):94-99. https://doi.org/10.1016/j.pmn.2019.06.014
41. Steeger CM, Hitchcock LN, Bryan AD, Hutchison KE, Hill KG, Bidwell LC. Associations between self-reported cannabis use frequency, potency, and cannabis/health metrics. Int J Drug Policy. 2021;97:103278. https://doi.org/10.1016/j.drugpo.2021.103278
42. McClure EA, Stitzer ML, Vandrey R. Characterizing smoking topography of cannabis in heavy users. Psychopharmacology (Berl). 2012;220(2):309-318. https://doi.org/10.1007/s00213-011-2480-4
43. Carley DW, Prasad B, Reid KJ, et al. Pharmacotherapy of apnea by cannabimimetic enhancement, the PACE clinical trial: effects of dronabinol in obstructive sleep apnea. Sleep. 2018;41(1). https://doi.org/10.1093/sleep/zsx184
44. Gaoni Y, Mechoulam R. Isolation, structure, and partial synthesis of an active constituent of hashish. J Am Chem Soc. 1964;86(8):1646-1647. https://doi.org/10.1021/ja01062a046
45. Miller LL, Cornett TL. Marijuana: dose effects on pulse rate, subjective estimates of intoxication, free recall and recognition memory. Pharmacol Biochem Behav. 1978;9(5):573-577. https://doi.org/10.1016/0091-3057(78)90205-8
46. Karniol IG, Shirakawa I, Kasinski N, Pfeferman A, Carlini EA. Cannabidiol interferes with the effects of delta 9-tetrahydrocannabinol in man. Eur J Pharmacol. 1974;28(1):172-177. https://doi.org/10.1016/0014-2999(74)90129-0
47. Russo EB. Taming THC: Potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br J Pharmacol. 2011;163(7):1344-1364. https://doi.org/10.1111/j.1476-5381.2011.01238.x
48. Englund A, Oliver D, Chesney E, et al. Does cannabidiol make cannabis safer? A randomised, double-blind, cross-over trial of cannabis with four different CBD:THC ratios. Neuropsychopharmacology. 2023;48(6):869-876. https://doi.org/10.1038/s41386-022-01478-z
49. NIDA. Establishing 5mg of THC as the standard unit for research. National Institute on Drug Abuse website. Accessed May 31, 2023. https://nida.nih.gov/about-nida/noras-blog/2021/05/establishing-5mg-thc-standard-unit-research
50. Howlett K, Zarcone T. Establishment of a standard THC unit to be used in research. Accessed May 31, 2023. https://grants.nih.gov/grants/guide/notice-files/NOT-DA-21-049.html
51. Gulbransen G, Xu W, Arroll B. Cannabidiol prescription in clinical practice: an audit on the first 400 patients in New Zealand. BJGP Open. 2020;4(1). https://doi.org/10.3399/bjgpopen20X101010
52. Crippa JA, Zuardi AW, Martín-Santos R, et al. Cannabis and anxiety: a critical review of the evidence. Hum Psychopharmacol. 2009;24(7):515-523. https://doi.org/10.1002/hup.1048
53. D'Souza DC, Perry E, MacDougall L, et al. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. Neuropsychopharmacology. 2004;29(8):1558-1572. https://doi.org/10.1038/sj.npp.1300496
54. Berrendero F, Maldonado R. Involvement of the opioid system in the anxiolytic-like effects induced by delta(9)-tetrahydrocannabinol. Psychopharmacology (Berl). 2002;163(1):111-117. https://doi.org/10.1007/s00213-002-1144-9
55. Haller J, Varga B, Ledent C, Freund TF. CB1 cannabinoid receptors mediate anxiolytic effects: convergent genetic and pharmacological evidence with CB1-specific agents. Behav Pharmacol. 2004;15(4):299-304. https://doi.org/10.1097/01.fbp.0000135704.56422.40

Pain Medicine, 2024, 25, 387–399
https://doi.org/10.1093/pm/pnae004
Review Article