

Association of Cannabinoid Administration With Experimental Pain in Healthy Adults

A Systematic Review and Meta-analysis

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IMPORTANCE Cannabinoid drugs are widely used as analgesics, but experimental pain studies have produced mixed findings. The analgesic properties of cannabinoids remain unclear.

OBJECTIVE To conduct a systematic review and meta-analysis of the association between cannabinoid drug administration and experimental pain outcomes in studies of healthy adults.

DESIGN, SETTING, AND PARTICIPANTS A systematic search of PubMed, EMBASE, MEDLINE, PsycINFO, and CINAHL was conducted from the inception of each database to September 30, 2017. Studies were eligible for inclusion if they met criteria, including healthy participants and an experimentally controlled administration of any cannabinoid preparation in a quantified dose. Studies that used participants with chronic pain were excluded. Data extracted included study characteristics, cannabinoid types and doses, sex composition, and outcomes. Study quality was assessed using a validity measure previously established in published reviews. Random-effects meta-analyses were used to pool data and generate summary estimates.

MAIN OUTCOMES AND MEASURES Experimental pain threshold, pain tolerance, pain intensity, pain unpleasantness, and mechanical hyperalgesia.

RESULTS Eighteen placebo-controlled studies (with 442 participants) were identified. Of the 442 participants, 233 (52.7%) were male and 209 (47.3%) were female. For sample ages, 13 (72%) of the 18 studies reported a mean sample age (26.65 years), 4 (22%) reported a range, and 1 (6%) reported a median value. The search yielded sufficient data to analyze 18 pain threshold comparisons, 22 pain intensity comparisons, 9 pain unpleasantness comparisons, 13 pain tolerance comparisons, and 9 mechanical hyperalgesia comparisons. Cannabinoid administration was associated with small increases in pain threshold (Hedges $g = 0.186$; 95% CI, 0.054-0.318; $P = .006$), small to medium increases in pain tolerance (Hedges $g = 0.225$; 95% CI, 0.015-0.436; $P = .04$), and a small to medium reduction in the unpleasantness of ongoing experimental pain (Hedges $g = 0.288$; 95% CI, 0.104-0.472; $P = .002$). Cannabinoid administration was not reliably associated with a decrease in experimental pain intensity (Hedges $g = 0.017$; 95% CI, -0.120 to 0.154 ; $P = .81$) or mechanical hyperalgesia (Hedges $g = 0.093$; 95% CI, -0.059 to 0.244 ; $P = .23$). The mean quality rating across studies was good.

CONCLUSIONS AND RELEVANCE Cannabinoid drugs may prevent the onset of pain by producing small increases in pain thresholds but may not reduce the intensity of experimental pain already being experienced; instead, cannabinoids may make experimental pain feel less unpleasant and more tolerable, suggesting an influence on affective processes. Cannabis-induced improvements in pain-related negative affect may underlie the widely held belief that cannabis relieves pain.

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Cannabinoids (the collective term for all of the drugs examined in this study, including plant-based cannabis, which can contain multiple compounds) have long been considered effective for reducing pain¹ and are frequently proposed as treatment options in pain management.² Cannabinoid analgesia is of increasing clinical interest, and research on this topic has grown exponentially in recent years.^{3,4} Despite substantial legal changes surrounding medical cannabis, consensus is emerging that better quality research is needed to understand the analgesic efficacy of cannabinoids.⁵⁻⁹ Recent reviewers have even concluded that no high-quality evidence exists to support the effectiveness of cannabinoids in treating any chronic pain condition.^{5,6} Yet, cannabis is an approved pharmacotherapy for chronic pain in US states where medical use is permitted.¹⁰ Pain is also the most common clinical indication for medical cannabis use.¹¹⁻¹³ Patients have reliably endorsed the belief that cannabis is helpful in alleviating pain.¹⁴ However, the analgesic properties of cannabinoids remain poorly understood.

Systematic reviews have concluded that cannabinoids confer modest reductions in self-reported pain ratings among certain clinical pain samples.^{2,6,15,16} Numerous confounding factors covary with pain in clinical populations, making the evaluation of analgesia difficult.¹⁷ Laboratory pain assessments of healthy adults may be better suited for investigating the analgesic properties of drugs.¹⁷⁻¹⁹ Experimental pain studies of cannabinoid analgesia in healthy human participants have produced mixed results,²⁰ with some even reporting cannabis-induced increases in pain sensitivity.²¹⁻²³ To our knowledge, the varied findings from the literature have never been quantitatively synthesized. This systematic review aimed to use meta-analysis to evaluate the evidence for cannabinoid analgesia in healthy adult participants in experimental pain studies.

Methods

This systematic review adhered to the guidelines recommended by the Cochrane Collaboration,²⁴ the Centre for Reviews and Dissemination,²⁵ and the PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) 2015 statement.²⁶⁻²⁹ All review stages were conducted by 2 independent raters (M.J.D., D.M.), and discrepancies were resolved by consensus or by consulting a third reviewer. A protocol was established and preregistered on PROSPERO (CRD42017073762). Data were collected from August 24, 2017, to November 30, 2017.

Eligibility Criteria

Studies published in peer-reviewed publications were eligible for inclusion in this systematic review if they included the following: (1) healthy human samples, (2) an experimentally controlled administration of any cannabinoid preparation in a quantified dose, (3) a comparative no-cannabinoid or placebo-controlled condition, and (4) an experimental pain stimulus and any established pain reactivity assessment. Stud-

Key Points

Question What is the association between acute cannabinoid administration and experimental pain reactivity in healthy adults?

Findings This systematic review and meta-analysis of 18 studies including 442 adults found that cannabinoid drugs were associated with modest increases in experimental pain threshold and tolerance, no reduction in the intensity of ongoing experimental pain, reduced perceived unpleasantness of painful stimuli, and no reduction of mechanical hyperalgesia.

Meaning Cannabinoid analgesia may be largely driven by an affective rather than a sensory component. These findings have implications for understanding the analgesic properties of cannabinoids.

ies that used participants with chronic pain were excluded because of the potential confounding factors associated with these populations, including altered sensory processing.¹⁷⁻¹⁹

Search Procedure and Study Selection

Reviewers searched PubMed, EMBASE, MEDLINE, PsycINFO, and CINAHL from the inception of each database to September 30, 2017 (eAppendix 1 in the [Supplement](#)). Reference lists of eligible studies were manually screened. Titles and abstracts were screened for eligibility after removing duplicate results. Full-text articles were screened further using inclusion and exclusion criteria. Both raters agreed on the final list of studies.

Pain Outcomes

Experimental assessments of pain threshold, pain tolerance, pain intensity, pain unpleasantness, and mechanical hyperalgesia were identified as established pain reactivity outcomes.^{17,30,31} Pain threshold is typically defined as the lowest stimulus intensity perceived as being painful.³²⁻³⁴ Tolerance is the maximum intensity that can be withstood in a given situation.³²⁻³⁴ Ongoing pain intensity is measured using scales that assess sensory dimensions of pain, whereas unpleasantness is rated using scales that assess affective dimensions of pain.³⁴ Mechanical hyperalgesia is generally defined as increased pain sensitivity to mechanical stimulation.^{17,30,34} As an index of central sensitization,³⁵ mechanical hyperalgesia reflects enhanced excitability of spinal dorsal horn neurons.^{36,37}

Methodological Quality

Study quality and validity was assessed using a 12-item scale (eAppendix 2 in the [Supplement](#)), which was developed using PEDro (Physiotherapy Evidence Database) guidelines,³⁸ PRISMA-P 2015 recommendations,²⁶ and Cochrane Collaboration criteria.³⁹ This scale was adapted from similar systematic reviews of experimental analgesia.^{40,41} Certainty in evidence was evaluated using the GRADE criteria (rating range: very low to high certainty) to rate confidence in summary estimates.⁴² (The GRADE approach considers issues of internal validity, inconsistency, indirectness, imprecision, and other considerations [eg, publication bias] for each outcome.)

Data Extraction

Statistical information (eg, means, SDs) for each pain outcome was recorded to calculate effect sizes.⁴³ Additional data were recorded for moderation analyses, including cannabinoid type, cannabinoid dose level, and sex composition.

The following decisions were made when calculating effect sizes using available data. First, when studies tested a pain outcome (eg, tolerance) using multiple pain-induction methods (eg, heat, pressure), a mean pooled effect size was computed for the overall meta-analysis. Second, multiple cannabinoid types (eg, dronabinol, cannabis) and/or doses (eg, high, low) examined within a single study were treated as individual comparisons. Third, when serial postadministration pain measurements were taken, the largest single time point contrast (ie, peak effect) between the active or placebo conditions was identified and the corresponding statistics were extracted. Fourth, in studies that administered additional agents (eg, opioids), data were extracted from cannabinoid-only conditions. Fifth, if studies divided participants into subgroups without reporting overall sample statistics, the means and SDs were combined to restore the original sample values; if studies recruited and examined subsamples (eg, males, females) independently, the effect sizes for each group were input as separate comparisons.⁴⁴ Sixth, for data presented graphically (eg, charts), a validated data-extraction software (WebPlotDigitizer, version 4; Ankit Rohatgi) was used if the corresponding authors were unable to provide statistics.⁴⁵ Seventh, when variability statistics were not reported, conservative estimates were back-computed using 2-sided *P* values and sample sizes and subsequently used in effect-size calculations.⁴³ If statistical significance was indicated as less than a specific *P* value (eg, $P < .05$), a rounded *P* value (eg, $P = .05$) was used in these estimates. When statistical significance was indicated but a specific *P* value was not reported, a conservative $P = .05$ was used. For null comparisons reported in 2 studies^{46,47} as having $P > .05$, conservative variability estimates were derived using sample sizes and $P = .99$. Eighth, for 2 studies^{48,49} that provided data in the form of median, minimum, and maximum values, SDs were estimated using published quantitative methods.⁵⁰ Finally, effect sizes for matched groups were computed assuming a conservative correlation of 0.7.^{43,44}

Statistical Analysis

Effect-size calculations and meta-analytic statistics were performed using Comprehensive Meta-Analysis, version 3 (Biostat). Given the methodological variability in how experimental pain outcomes are measured,^{40,41,51} Hedges *g* was calculated to produce effect sizes in standard-score units. Random-effects meta-analyses of Hedges *g* values provided summary estimates for each pain outcome. Interpretation of Hedges *g* is similar to that of Cohen *d*, with 0.20 corresponding to small size, 0.50 corresponding to medium size, and 0.80 corresponding to large size.⁵² Positive Hedges *g* values indicated analgesic effects, whereas negative values represented hyperalgesic responses.

Heterogeneity was assessed using the Cochran *Q* test. Higgins I^2 was used to evaluate the proportion of variation across studies, with scores of 25% corresponding to low,

50% corresponding to moderate, and 75% corresponding to high heterogeneity.^{53,54} The Kendall τ statistic provided an SD estimate for different population effect sizes.⁴⁴ Funnel plots and Egger bias tests were used to assess publication bias.⁵⁵

Moderator Analyses

When significant heterogeneity was indicated, moderation analyses were conducted to test the influence of several factors on cannabinoid analgesia. Mixed-effects analyses were used to test categorical moderators, whereas meta-regression analysis was used for continuous moderators. Primary moderators were cannabinoid type and dose level (high vs low), given that analgesic effects may differ as a function of varying pharmacologic properties. Sex composition was also explored as a potential moderator, given the evidence that cannabinoid analgesia may be more robust in males.⁴⁷

Results

Study Inclusion

The searches yielded 1831 total results (eFigure 1 in the Supplement). One additional study was identified by manually examining references.⁵⁶ After duplicate removal, 1281 records were reviewed and 1255 were excluded. In total, 26 full-text articles were assessed for eligibility, of which 18 studies (69%) satisfied the inclusion criteria and were retained for analysis.

Study Characteristics

Study characteristics are presented in the Table. The 18 studies examined 442 participants in total. Of the 442 participants, 233 (52.7%) were male and 209 (47.3%) were female. For sample ages, 13 studies (72%) reported a mean sample (26.65), 4 (22%) reported a range,^{22,59,62,64} and 1 (6%) reported a median value.⁵⁸ All studies included a placebo-controlled condition, and 16 (89%) used a crossover (within-participant) design. To avoid carryover effects, all but 1 crossover study⁶⁵ used a mean (range) washout period of 9.13 (2-48) days between active and placebo administrations. (For the single study that did not use a washout period, carryover effects were avoided by testing transdermal patches containing either the active or the placebo preparation simultaneously on different forearms.) All studies examined healthy participants, and 10 studies (56%) described verifying this health status with comprehensive medical and psychiatric evaluations.^{46-49,56-60,66} Studies were conducted in the United States, Austria, Switzerland, Germany, Canada, and the United Kingdom. Publication years ranged from 1974 to 2016.

Plant-based cannabis was administered in 6 studies (33%).^{22,46,47,57,60,66} Four studies (22%) administered dronabinol, a synthetic form of Δ^9 -tetrahydrocannabinol (THC).^{46,61,62,64} Four studies (22%) administered synthetic Δ^9 -THC capsules that were not specified by name.^{23,56,59,67} One study (6%) administered a cannabis extract that was standardized at 20 mg of Δ^9 -THC but contained cannabidiol (CBD) in

Table. Characteristics of Studies Included in the Systematic Review

Source	Design	No. (% Male)	Age, y (mean)	Cannabinoid Type	Dose Evaluated	Administration Method	Main Outcomes (Pain Stimulus)
Cooper et al, ⁴⁶ 2013	C	30 (50)	27 (mean)	Plant-based cannabis; dronabinol	Low dose: 800 mg of 1.98% THC cannabis; high dose: 800 mg of 3.56% THC cannabis; low dose: 10 mg of dronabinol; high dose: 20 mg dronabinol	Cigarettes (cannabis); capsule (dronabinol)	Intensity (CP); threshold (CP); tolerance (CP); unpleasantness (CP)
Cooper and Haney, ⁴⁷ 2016	C	42 (50)	28 (mean)	Plant-based cannabis	800 mg of 3.56%-5.60% THC cannabis	Cigarettes	Intensity (CP); threshold (CP); tolerance (CP); unpleasantness (CP)
Greenwald and Stitzer, ⁵⁷ 2000	C	5 (100)	20.6 (mean)	Plant-based cannabis	750-990 mg of 3.55% THC cannabis	Cigarettes	Threshold (HP)
Hill et al, ²² 1974	B	26 (100); 20 ^A /6 ^{PC}	21-30 (range)	Plant-based cannabis	1 g of 1.4% THC cannabis	Spirometer crucible	Threshold (EP); tolerance (EP)
Kalliomäki et al, ⁴⁹ 2012	C	30 (100)	29.3 (mean)	Nabilone	High dose: 2-3 mg of nabilone; low dose: 1 mg of nabilone	Capsule	Intensity (IC); threshold (TC + HP); mechanical hyperalgesia area (TC + BSP)
Kalliomäki et al, ⁴⁸ 2013 ^a	C	19 (100)	28.1 (mean)	AZD1940	Low dose: 400 µg of AZD1940	Capsule	Intensity (IC); threshold (TC + HP); mechanical hyperalgesia area (TC + BSP)
	C	22 (100)	28.1 (mean)	AZD1940	High dose: 800 µg of AZD1940		
Kraft et al, ⁵⁸ 2008	C	17 (0)	23.45 (median)	THC-standardized cannabis extract	20 mg of THC	Capsule	Intensity (IC); threshold (HP; EP; UV + HP; UV + EP); tolerance (HP; EP; UV + HP; UV + EP); neurogenic flare area (IC); mechanical hyperalgesia area (IC + PP)
Lee et al, ⁵⁹ 2013	C	12 (100)	24-34 (range)	THC	15 mg of THC	Capsule	Intensity (TC; TC + PP); unpleasantness (TC; TC + PP)
Libman and Stern, ⁵⁶ 1985 ^a	B	60 (0); 30 ^A /30 ^{PC}	21 (mean)	THC	Low dose: 10 mg of THC	Capsule	Threshold (PP); tolerance (PP)
	B	18 (0); 9 ^A /9 ^{PC}	21 (mean)	THC	High dose: 20 mg of THC		
Milstein et al, ⁶⁰ 1975	C	31 (52)	32.75 (mean)	Plant-based cannabis	600 mg of 1.3% THC cannabis	Inhalation device	Tolerance (PP)
Naef et al, ⁶¹ 2003	C	12 (50)	25 (mean)	Dronabinol	20 mg of THC	Capsule	Intensity (CP); threshold (HP; EP); tolerance (HP; PP)
Naef et al, ⁶² 2004	C	8 (50)	26-50 (range)	Dronabinol	0.053 mg/kg body weight of THC aerosol	Aerosol inhalation	Intensity (CP)
Redmond et al, ⁶³ 2008	C	17 (41)	22.85 (mean)	Nabilone	Low dose: 0.5 mg of nabilone; high dose: 1 mg of nabilone	Capsule	Intensity (CP)
Roberts et al, ⁶⁴ 2006	C	13 (54)	18-49 (range)	Dronabinol	5 mg of THC	Capsule	Intensity (HP); unpleasantness (HP)
Rukwied et al, ⁶⁵ 2003	C	20 (50)	29 (mean)	HU210	50 µL of HU210 solution	Transdermal patch	Intensity (TC); threshold (HP; TC + HP); mechanical hyperalgesia area (TC + PP; TC + BSP)
Wallace et al, ⁶⁶ 2007	C	15 (73)	28.9 (mean)	Plant-based cannabis	Low dose: 800 mg of 2% THC cannabis; medium dose: 800 mg of 4% THC cannabis; high dose: 800 mg of 8% THC cannabis	Cigarettes	Intensity (IC; PP); threshold (HP; CP; PP; IC + HP; IC + CP; IC + PP); neurogenic flare area (IC); mechanical hyperalgesia area (IC + PP; IC + BSP)
Walter et al, ²³ 2015	C	30 (50)	27.4 (mean)	THC	20 mg of THC	Capsule	Tolerance (EP)
Walter et al, ⁶⁷ 2016	C	15 (47)	26.6 (mean)	THC	20 mg of THC	Capsule	Pain intensity (GP); pain unpleasantness (GP)

Abbreviations: superscript A, active condition; B, between-participants design; BSP, brush-stroke pain; C, crossover within-participants design; CP, cold pain; EP, electric pain; GP, gas pain; HP, heat pain; IC, intradermal capsaicin; superscript PC, placebo-controlled condition; PP, pressure pain;

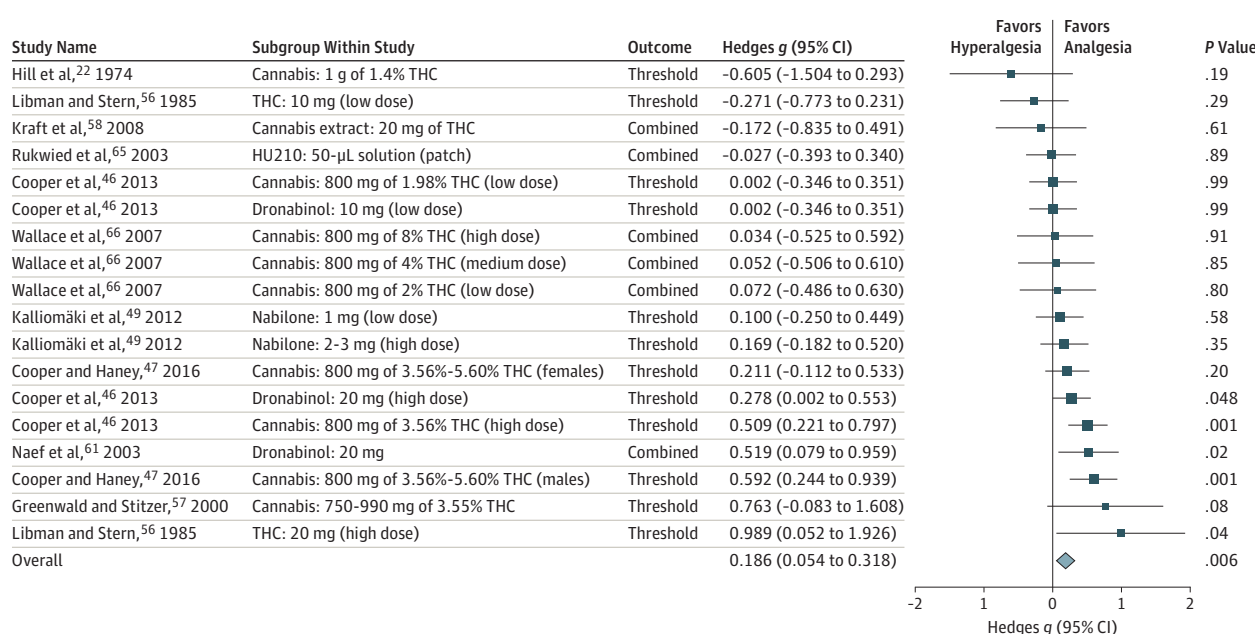
TC, topical capsaicin; THC, Δ⁹-tetrahydrocannabinol.

^a Single study used different samples for each cannabinoid dose level.

the ratio of 2:1.⁵⁸ Two studies (11%) administered nabilone, a potent synthetic analogue of THC.^{49,63} One study (6%) administered HU210, another synthetic THC analogue.⁶⁵ Lastly, 1

study (6%) administered AZD1940, a recently developed synthetic cannabinoid.⁴⁸ Six studies (33%)^{46,48,49,56,63,66} evaluated multiple cannabinoid doses, providing references

Figure 1. Forest Plot of Meta-analysis for Pain Threshold



THC indicates Δ^9 -tetrahydrocannabinol.

for stratifying dose levels in moderation analyses. In 2 studies (11%) that administered multiple doses of plant-based cannabis,^{46,66} the authors considered Δ^9 -THC concentrations of 2% or lower to be low doses. Wallace et al⁶⁶ included medium (4% Δ^9 -THC) and high (8% Δ^9 -THC) conditions, which were among the highest doses of all the plant-based cannabis used in the studies examined in this review, including the high dose (3.56% Δ^9 -THC) administered by Cooper et al.⁴⁶ Therefore, medium and high conditions in Wallace et al⁶⁶ were categorized as high dose in moderation analyses, as were any cannabis doses with 3.50% Δ^9 -THC or greater. Doses of dronabinol and other synthetic Δ^9 -THC administrations were generally considered high at 15 mg or greater and low at 10 mg or lower. Nabilone doses lower than 1 mg were typically considered low, and high doses ranged from 1 to 3 mg. These observations were used to categorize low- and high-dose subgroups for mixed-effects analyses.

Independent study quality and validity ratings demonstrated good agreement across raters for total scores (intra-class correlation coefficient [ICC], 0.88), with consensus reached for 100% of discrepancies.⁶⁸ Mean quality and validity scores were high (9.8 on a 0-12 scale), with 17 studies (94%) using randomization and 16 (89%) using blinding procedures (eAppendix 2 in the Supplement).

Overall Meta-analyses

Pain Threshold

Ten studies (with 275 participants) assessed pain threshold, which provided sufficient data for 18 comparisons between cannabinoid and placebo-controlled conditions. Nine comparisons evaluated plant-based cannabis, and 9 assessed synthetic cannabinoid preparations (nabilone = 2; HU210 = 1; dron-

abinol = 3; Δ^9 -THC = 3). Meta-analysis produced an overall Hedges g of 0.186 (95% CI, 0.054- 0.318; *P* = .006), indicating a significant, yet small, association between cannabinoid administration and pain threshold (Figure 1).⁵² The mean (SD) quality or validity rating for this outcome was in the moderate to high range: 9.9 (1.66).

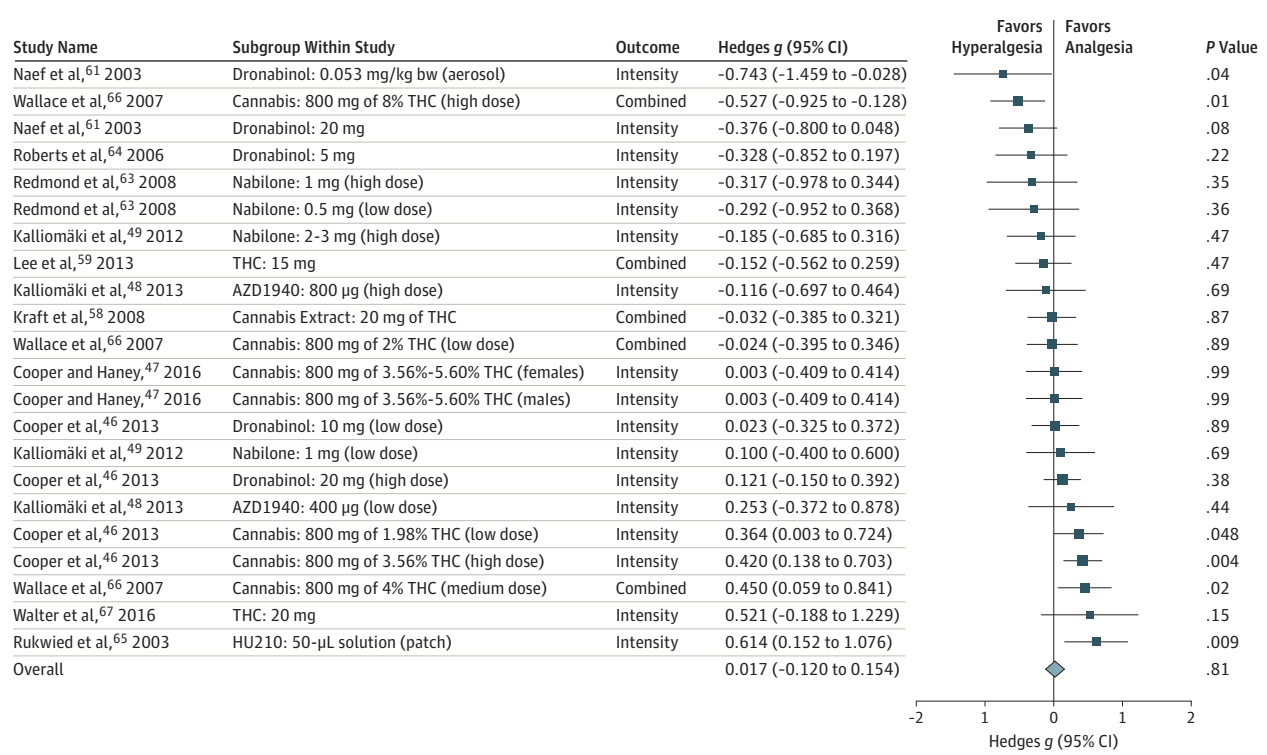
Pain Intensity

Thirteen studies (272 participants) assessed experimental pain intensity, which provided sufficient data for 22 comparisons. Seven comparisons evaluated plant-based cannabis, and 15 examined synthetic cannabinoids (nabilone = 4; HU210 = 1; AZD1940 = 2; dronabinol = 4; Δ^9 -THC = 4). Meta-analysis produced an overall Hedges g of 0.017 (95% CI, -0.120 to .154; *P* = .81), indicating that, when compared with placebo-controlled conditions, cannabinoid administration was not significantly associated with ongoing experimental pain intensity (Figure 2). The mean (SD) quality or validity rating for this outcome was in the moderate to high range: 10.2 (1.01).

Pain Unpleasantness

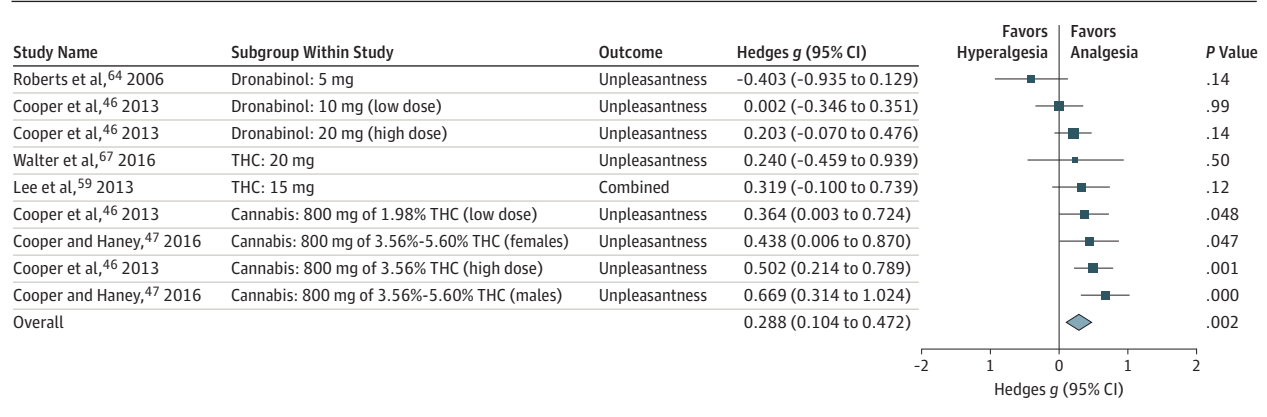
Five studies (112 participants) assessed pain unpleasantness ratings, which provided sufficient data for 9 comparisons. Four comparisons evaluated plant-based cannabis, and 5 assessed synthetic cannabinoids (dronabinol = 3; THC = 2). Meta-analysis produced an overall Hedges g of 0.288 (95% CI, 0.104-0.472; *P* = .002), indicating that cannabinoids, when compared with placebo-controlled conditions, had a significant, small- to medium-sized association with reduced unpleasantness ratings (Figure 3).⁵² The mean (SD) quality and validity rating for this outcome was in the moderate to high range: 10.2 (0.84).

Figure 2. Forest Plot of Meta-analysis for Ongoing Pain Intensity



THC indicates Δ⁹-tetrahydrocannabinol; bw, body weight.

Figure 3. Forest Plot of Meta-analysis for Ongoing Pain Unpleasantness



THC indicates Δ⁹-tetrahydrocannabinol.

Pain Tolerance

Eight studies (266 participants) assessed pain tolerance, which provided sufficient data for 13 comparisons. Six comparisons evaluated plant-based cannabis, and 7 assessed synthetic cannabinoid preparations (dronabinol = 3; Δ⁹-THC = 4). Meta-analysis produced an overall Hedges g of 0.225 (95% CI, 0.015-0.436; *P* = .04), indicating a significant, small- to medium-sized association between cannabinoid administration and pain tolerance (eFigure 2 in the Supplement).⁵² The mean (SD) quality and validity rating for this outcome was in the moderate to high range: 10.2 (0.84).

Mechanical Hyperalgesia

Five studies (103 participants) assessed mechanical hyperalgesia, which provided sufficient data for 9 comparisons. Three comparisons evaluated plant-based cannabis, and 6 assessed synthetic cannabinoid preparations (nabilone = 2; THC = 1; AZD1940 = 2; HU210 = 1). Meta-analysis produced an overall Hedges g of 0.093 (95% CI, -0.059 to 0.244; *P* = .23), indicating no significant difference between placebo-controlled conditions and cannabinoids in the area of mechanical hyperalgesia (eFigure 3 in the Supplement). The mean (SD) quality or validity rating

for this outcome was in the moderate to high range: 10.4 (1.34).

Publication Bias

Asymmetry was not suggested in funnel plots for any of the experimental pain outcomes. Egger bias tests for pain intensity (bias = -1.89; 95% CI, -4.26 to 0.48), unpleasantness (bias = -1.62; 95% CI, -6.29 to 3.05), threshold (bias = -0.71; 95% CI, -2.76 to 1.34), tolerance (bias = -2.51; 95% CI, -5.54 to 0.51), and mechanical hyperalgesia (bias = 0.51; 95% CI, -5.82 to 6.83) produced nonsignificant results.

Moderator Analyses

Significant heterogeneity was observed across comparison effect sizes for pain threshold ($Q_{17} = 28.83$; $P = .04$; $I^2 = 41\%$; $\tau = 0.18$), intensity ($Q_{21} = 45.10$; $P = .002$; $I^2 = 53\%$; $\tau = 0.23$), unpleasantness ($Q_8 = 16.58$; $P = .04$; $I^2 = 52\%$; $\tau = 0.20$), and tolerance ($Q_{12} = 35.65$; $P < .001$; $I^2 = 66\%$; $\tau = 0.30$). I^2 values suggested low-moderate heterogeneity,^{53,54} and moderation analyses were warranted for these outcomes. Significant heterogeneity did not emerge for mechanical hyperalgesia ($Q_8 = 13.16$; $P = .11$; $I^2 = 39\%$; $\tau = 0.144$).

Cannabinoid Type

Effect sizes differed significantly as a function of cannabinoid type for both pain unpleasantness ($Q_2 = 7.98$; $P = .02$; eFigure 4 in the Supplement) and pain tolerance ($Q_2 = 20.75$; $P < .001$; eFigure 5 in the Supplement). The association of plant-based cannabis with pain unpleasantness (Hedges $g = 0.499$; $P < .001$) was significantly more robust than those of dronabinol (Hedges $g = 0.000$; $P = .99$) and other synthetic THC preparations (Hedges $g = 0.298$; $P = .10$). A significant association with pain tolerance was observed for both plant-based cannabis (Hedges $g = 0.471$; $P < .001$) and dronabinol (Hedges $g = 0.313$; $P = .002$), whereas other synthetic THC preparations were associated with a significant reduction in pain tolerance (Hedges $g = -0.378$; $P = .01$).

Dose Level

The association between cannabinoids and pain threshold differed significantly as a function of dose level ($Q_1 = 10.73$; $P = .001$; eFigure 6 in the Supplement). Higher cannabinoid doses (Hedges $g = 0.334$; $P < .001$) were associated with a significant analgesic effect, whereas lower doses were not (Hedges $g = -0.023$; $P = .77$).

Sample Sex Composition

Results from meta-regression analyses indicated that sex composition did not significantly moderate the association between cannabinoid administration and experimental pain outcomes ($P > .05$; eTable in the Supplement).

Discussion

This systematic review examined the association between cannabinoid drug administration and experimental pain outcomes using meta-analysis. Data were extracted from 18

experimental studies, which provided comparisons between cannabinoids and placebo-controlled conditions on measures of experimental pain threshold, tolerance, intensity, unpleasantness, and mechanical hyperalgesia. Pooling effect sizes revealed that cannabinoid administration was associated with small increases in pain threshold, indicating that greater amounts of stimulation were required to induce pain after cannabinoid administration. Cannabinoid administration was not associated with reduced intensity of ongoing experimental pain, suggesting that cannabinoids may not improve this sensory dimension after the pain threshold has been met. Interestingly, meta-analysis revealed small- to medium-sized reductions in the perceived unpleasantness of ongoing experimental pain after cannabinoid administration, suggesting that cannabinoids may improve an affective dimension of pain. A similar association was revealed for pain tolerance, such that participants were able to withstand greater amounts of experimental pain stimulation after cannabinoid administration. Moderation analyses indicated that the association of cannabinoid administration with both pain unpleasantness and pain tolerance was stronger for plant-based cannabis than for synthetic preparations. Cannabinoid administration was not associated with reduced mechanical hyperalgesia, which reflects central sensitization. Despite good validity scores, GRADE ratings (eAppendix 3 in the Supplement) for pain threshold, intensity, unpleasantness, and tolerance were low, primarily because of the inconsistency and indirectness domains. A moderate GRADE rating for mechanical hyperalgesia was attributable to the indirectness domain.

Strengths, Limitations, and Future Research

To our knowledge, this study is the first meta-analytic review of the association of acute cannabinoid administration with experimental pain reactivity, and it has several noteworthy strengths. Published guidelines²⁴⁻²⁸ for conducting and reporting rigorous systematic reviews were followed, and a pre-registered protocol was followed to enhance transparency. A highly sensitive search strategy was used across several electronic databases, which yielded data on multiple experimental outcomes that reflect unique aspects of the pain experience. Two independent reviewers performed all stages of the review and demonstrated good interrater reliability on a validity measure used in other analgesia reviews.^{40,41} The mean quality and validity score across studies was high, and analyses did not suggest publication bias.

Despite its notable strengths, this systematic review was limited to studies of experimental pain, which merely approximates features of clinical pain.³⁴ To produce evidence that supports the generalizability of the current findings, pain reactivity research must be conducted in clinical samples. The lack of neuropathic pain data are especially limiting, given that neuropathic pain is the primary condition for which modest empirical evidence exists that supports cannabinoid analgesia.⁶ Neuropathic pain symptoms can include spontaneous pain, altered pain thresholds, and central and peripheral sensitization.^{17,69} Our findings may lead researchers to hypothesize that cannabinoids may reduce the unpleasantness of spontaneous neuropathic pain. Null results for the mechani-

cal hyperalgesia outcome suggest that cannabinoids may not improve central sensitization in patients with neuropathic pain. The current review cannot address peripheral sensitization, given insufficient data on experimental indexes of this symptom (eg, neurogenic flare). Further efforts to translate experimental findings into clinical research are needed. Generalizability concerns notwithstanding, experimental pain models still have inferential use for assessing analgesic responses.^{30,69} Cumulative results from research on other drugs (eg, opioids) have consistently demonstrated that analgesia can be evaluated using laboratory pain assessments.³⁴ These findings support the assertion that complex pain processes may be best evaluated using experimental pain methods, such as those used in the reviewed studies, to yield insights into multiple aspects of the pain experience.³⁴

The studies examined also had important limitations. Blinding procedures used in placebo-controlled cannabinoid studies often fail because of strong psychoactive adverse effects (eg, “feeling high”). Participants, especially cannabis users, can often distinguish between active cannabis and placebo for this reason.⁷⁰ All of the reviewed studies administered psychoactive cannabinoids. In addition to confounding blinding procedures, these adverse effects may interact with widely held expectancies (eg, cannabis reduces pain) among participants to alter pain responses and possibly produce placebo analgesia. Psychotropic adverse effects also remain a salient concern among those considering cannabis-based medicines for pain.^{4,20,71} A frequently discussed topic is whether cannabinoids actually relieve pain, or simply make people in pain feel good or “high.” After all, other intoxicating substances (eg, alcohol) are also associated with analgesic outcomes.⁴¹ Both inferences likely have validity, as intoxicated mental states could alter aspects of the pain experience to provide relief. The clinical relevance of this distinction depends on the desired treatment outcome. If treatment aims to relieve pain without producing intoxication, psychoactive cannabinoids may not suffice. Pain unpleasantness is associated with functional status outcomes (eg, pain-related interference),⁷² but it remains unclear whether improvements in functionality would be offset by cannabinoid intoxication. Nonpsychoactive cannabinoids (eg, cannabidiol) should be investigated in future experimental pain or analgesia studies. Additional research is needed to determine whether expectancies for cannabinoid analgesia alter pain responses.

Study outcomes in this review were restricted to static pain measurements that offer limited mechanistic insight, and fu-

ture research should use dynamic pain assessments (eg, temporal summation) to determine whether cannabinoids affect endogenous pain facilitation and/or inhibition.⁶⁹ The available data permitted analyses of peak effects, but few studies examined how cannabinoids affect pain reactivity at multiple time points. Peak-effect analyses may be limited, given the increased possibility that these effects contain more error, which may induce bias toward finding significant results. Conversely, singular measurements may reflect either ascending or descending effects, resulting in underestimated values. More research is necessary to characterize the time course and dose response of cannabinoid analgesia using serial assessments. Cannabinoid types and doses varied across studies, and reporting of cannabis use characteristics among the samples was inconsistent. Therefore, the current review is limited in its ability to describe the analgesic efficacy of specific doses for different cannabinoid types. The dose categories described in this review may not translate into clinical practice, given that many factors can inform how doses are categorized in experiments. The long-term association of regular cannabinoid use with pain is poorly understood, and future research should investigate whether chronic use dysregulates pathophysiologic pain processes that increase the risk for chronic pain development. The influence of recreational cannabis use could not be examined because of a lack of data. Future research should examine whether the analgesic effects of cannabinoids differ as a function of cannabis use history and status, including recreational use. Nonetheless, the current results may help clarify the mixed findings reported in experimental pain studies of cannabinoid analgesia.

Conclusions

Pain is a complex phenomenon with multiple dimensions that can be affected separately.³⁴ Meta-analyses revealed that although the cannabinoids examined in this review may prevent the onset of laboratory-induced pain by increasing pain thresholds, they do not appear to reduce the intensity of experimental pain that is already being experienced. Instead, these substances make experimental pain feel less unpleasant and more tolerable, suggesting a notable influence on affective processes. The cumulative research synthesized in this review has helped characterize how cannabis and cannabinoids affect different dimensions of pain reactivity.

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