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Effects of Cannabinoid Administration for Pain: A Meta-Analysis and Meta-Regression

Julio A. Yanes, M.S.^{1,2,3,4}, Zach E. McKinnell, B.A.^{1,2,3,4}, Meredith A. Reid, Ph.D.^{1,2,3,4}, Jessica N. Busler, Ph.D.^{1,2,3,4}, Jesse S. Michel, Ph.D.¹, Melissa M. Pangelinan, Ph.D.⁵, Matthew T. Sutherland, Ph.D.⁶, Jared W. Younger, Ph.D.⁷, Raul Gonzalez, Ph.D.⁶, Jennifer L. Robinson, Ph.D.^{1,2,3,4}

¹Department of Psychology, Auburn University, Auburn, AL, USA

²Auburn University Magnetic Resonance Imaging Research Center, Auburn University, Auburn, AL, USA

³Center for Neuroscience, Auburn University, Auburn, AL, USA

⁴Alabama Advanced Imaging Consortium, AL, USA

⁵School of Kinesiology, Auburn University, Auburn, AL, USA

⁶Department of Psychology, Florida International University, Miami, FL, USA

⁷Department of Psychology, University of Alabama Birmingham, Birmingham, AL, USA

Abstract

Chronic pain states have resulted in an over-reliance on opioid pain relievers, which can carry significant risks when used long-term. As such, alternative pain treatments are increasingly desired. Although emerging research suggests that cannabinoids have therapeutic potential regarding pain, results from studies across pain populations have been inconsistent. To provide meta-analytic clarification regarding cannabis's impact on subjective pain, we identified studies that assessed drug-induced pain modulations under cannabinoid and corresponding placebo conditions. A literature search yielded 25 peer-reviewed records that underwent data extraction. Baseline and end-point data were used to compute standardized effect size estimates (*Cohen's d*) across cannabinoid administrations ($k = 39$) and placebo administrations ($k = 26$). Standardized effects were inverse-variance weighted and pooled across studies for meta-analytic comparison. Results revealed that cannabinoid administration produced a medium-to-large effect across included studies, $Cohen's d = -0.58$, 95% CI $(-0.74, -0.43)$, while placebo administration produced a small-to-medium effect, $Cohen's d = -0.39$, 95% CI $(-0.52, -0.26)$. Meta-regression revealed that cannabinoids, $\beta = -0.43$, 95% CI $(-0.62, -0.24)$, $p < 0.05$, synthetic cannabinoids, $\beta = -0.39$, 95% CI $(-0.65, -0.14)$, $p < 0.05$, and sample size, $\beta = 0.01$, 95% CI $(0.00, 0.01)$, $p < 0.05$, were associated with marked pain reduction. These outcomes suggest that cannabinoid-based pharmacotherapies may serve as effective replacement/adjunctive options regarding pain, however, additional research is warranted. Additionally, given demonstrated neurocognitive side-effects

associated with some constituent cannabinoids (i.e., THC), subsequent work may consider developing novel therapeutic agents that capitalize on cannabis's analgesic properties without producing adverse effects.

Keywords

Cannabis; Cannabinoid; Marijuana; Pain; Meta-Analysis

Chronic pain is an ever-growing concern in the United States. There is a rising economic burden – currently estimated to be between \$560 billion and \$635 billion annually – that stems from pain-related costs to patients, patient-care providers, healthcare systems, and poor treatment outcomes among clinical pain populations (e.g., chronic lower back pain, neuropathic pain, and fibromyalgia) (Henschke, Kamper, & Maher, 2015). These, and other, conditions have resulted in an over-reliance on opioid-based pharmacotherapies. Although some patients are appropriate for focused treatments involving opioids (e.g., acute pain), patients with more chronic conditions (e.g., cancer) can achieve better outcomes by managing pain through more comprehensive approaches (Chou et al., 2009). Thus, it has become increasingly important to explore additional therapeutic opportunities. In recent decades, cannabinoids – such as molecular compounds found in cannabis, including delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) – have been considered viable treatment options regarding pain (Savage et al., 2016). As recently as 2018, 30 states had enacted policies that permit cannabis use to treat various medical conditions, with 27 states citing pain-related conditions as inclusionary criteria. Despite growing access to medicinal cannabis, mixed (and on occasion, null) effects have been reported, underscoring the need to expand research efforts regarding cannabinoid-induced pain mitigation.

Recently, several reports have examined cannabinoid administration effects on subjective reports of pain (Hill, Palastro, Johnson, & Ditre, 2017). However, these accounts have produced variant, and sometimes contradictory, conclusions. In one example, Johnson and colleagues (2010) examined the impact of nabiximols (Sativex®), a standardized whole-plant cannabis extract oromucosal spray, on cancer-related pain. In that double-blind, randomized controlled trial (RCT), patients with intractable cancer pain entered a two-week administration regimen and received THC:CBD extract (2.7 mg THC and 2.5 mg CBD), THC extract (2.7 mg THC), or placebo. Patients were free to titrate their dosage as needed. Following the drug administration regimen, Johnson et al. observed significant reductions in subjective pain ratings among patients receiving THC:CBD extract compared to patients receiving placebo. THC alone was less effective. In a similar example, Portenoy and colleagues (2012) evaluated nabiximols as an add-on therapy for advanced cancer patients with opioid-refractory (unresponsive) pain. Patients were placed into low-, medium-, or high-administration conditions and pain was measured following a five-week intervention interval. At the end of treatment, Portenoy et al. found that THC:CBD extract was associated with greater pain reduction in the low-administration condition (1–4 sprays/day), but not in the medium-administration (6–10 sprays/day) or high-administration conditions (11–16 sprays/day). Taken together, these outcomes suggest that cannabinoids may represent potential pharmacological tools for pain reduction. On the other hand, several studies have

shown no difference between cannabinoids and corresponding placebo administrations. For example, Lichtman and colleagues (2018) leveraged a double-blind RCT to examine pain outcomes among cancer patients with uncontrolled pain following a two-week nabiximols administration period. Following the intervention, Lichtman et al. compared pain modulations from baseline between cannabinoid and placebo conditions, revealing no superior effects associated with THC:CBD extract. Moving forward, an important challenge facing biomedical research involves coalescing results from studies involving various pain populations receiving cannabinoid administrations to determine overall therapeutic potential.

Towards this goal, several systematic reviews have endeavored to summarize cannabis's putative pain-related therapeutic effects (Abrams, 2018; Campbell et al., 2001; Colombo, Annovazzi, & Comi, 2006; Deshpande, Mailis-Gagnon, Zoheiry, & Lakha, 2015; Lynch & Campbell, 2011; Lynch & Ware, 2015; Sznitman & Zolotov, 2015; Wright, 2007). These reviews have provided competing conclusions. In one review, Campbell and colleagues (2001) considered outcomes from nine randomized active- and placebo-controlled trials involving cannabinoids (five trials involved cancer-related pain, two involved chronic pain, and two acute post-operative pain), with a focus on pain intensity scores, pain relief scores, and adverse effects. Those authors concluded that the cannabinoids considered were no more effective than active control conditions, including the opioid analgesic codeine, stressing that cannabinoid administration to treat post-operative pain would be "undesirable," given unwanted central nervous system depressant effects. However, opioids have also been linked with depressant/sedative effects (Chou et al., 2009). Moreover, other – perhaps more severe – opioid-related adverse effects include respiratory depression, especially when paired with other substances, such as benzodiazepines and alcohol (Chou et al., 2009). Given the abuse potential associated with opioids, these (and other) side-effects underscore the need to consider replacement and/or adjunctive pain management approaches. Additionally, Campbell et al. noted that, among RCTs considered in the systematic review, none had examined active cannabis. That is, the trials examined pain reduction associated with THC, nitrogen-containing benzopyran derivative, benzopyranoperidine, or levonantradol. Importantly, cannabinoid-induced analgesia may stem from compound or synergistic effects associated with several cannabinoids. For example, preclinical evidence suggests that high-dose CBD modulates antinociceptive effects associated with low-dose THC, indicating that both cannabinoids may be involved in pain reduction (Varvel et al., 2006). Furthermore, work from Comelli and colleagues (Comelli, Giagnoni, Bettoni, Colleoni, & Costa, 2008) demonstrates that whole-plant cannabis extract provides improved nociceptive efficacy compared to corresponding doses of constituent cannabinoids. As such, as the corpus of cannabis-related pain investigations continues growing, it is possible that more comprehensive assessments could reach alternative conclusions regarding cannabinoid analgesia. In a more recent review, The National Academies of Sciences, Engineering and Medicine considered more than 10,000 peer-reviewed abstracts to characterize cannabis's potential therapeutic utility across several domains, including pain. That committee concluded that "there was conclusive or substantial evidence that *Cannabis* or cannabinoids are effective for the treatment of pain in adults," (Abrams, 2018). However, narrative and systematic reviews often omit representative estimates of effect magnitude and therefore cannot provide quantitative conclusions about

outcomes of interest. As such, objective techniques that determine statistical convergence across published studies involving cannabinoid-induced pain reduction are needed to more accurately characterize potential therapeutic effects.

Meta-analyses present powerful opportunities to coalesce conventional effect size estimates (e.g., *Cohen's d*) across published studies, providing clarification regarding results and permitting assessments not possible within the original, single report. Within this framework, several study-level effect size estimates derived under comparable experimental conditions are averaged, producing one pooled (representative) effect size estimate (Hedges & Olkin, 1985). Regarding pharmacologic manipulations, pooled effect sizes are used to characterize cross-study drug administration effects on specific end-points (Wilkinson et al., 2018), or to make comparisons between two (or more) drug administration conditions (Bushe et al., 2016). Towards this goal, several meta-analyses have provided some insight into cannabinoid-related pain reduction (Andreae et al., 2015; Aviram & Samuely-Leichtag, 2017; De Vita, Moskal, Maisto, & Ansell, 2018; Goldenberg, Reid, IsHak, & Danovitch, 2017; Iskedjian, Bereza, Gordon, Piwko, & Einarson, 2007; Martin-Sanchez, Furukawa, Taylor, & Martin, 2009; Phillips, Cherry, Cox, Marshall, & Rice, 2010; Whiting et al., 2015). For example, Iskedjian and colleagues (2007) synthesized results from six studies examining cannabinoid administration within the limited context of multiple sclerosis (MS). When considering baseline versus end-point pain ratings among 298 patients, Iskedjian et al. observed that cannabinoids were associated with greater pain reduction relative to placebo. However, whether these effects extend beyond MS-related pain (e.g., neuropathic pain) remained unclear. In a more comprehensive meta-analysis, Aviram and Samuely-Leichtag (2017) examined pain reduction associated with cannabinoid-based medicines across 24 RCTs. Those researchers considered several pain populations, including neuropathic pain, cancer-related pain, non-cancer pain, and post-operative pain, as well as active-control and placebo-control designs. Overall, Aviram and Samuely-Leichtag reported “limited” support for cannabinoid-based medicines across considered RCTs. However, a more focused assessment that excluded active-control designs – which were believed to have increased analgesic efficacy compared to placebo – demonstrated improved analgesic outcomes associated with cannabinoid-based medicines. Surprisingly, the extent to which specific study-level characteristics, such as sample size, age, and sex composition (sex ratio), may modulate observed pain outcomes remains to be meta-analytically explored. Indeed, these active research areas have received considerable attention in recent years (Lauer, 2016). Here, we address this open-ended question using meta-regression to examine cannabinoid- and placebo-related pain reduction with respect to several study-level characteristics (Baker et al., 2009).

To determine cross-study cannabinoid-related standardized effect sizes regarding self-reported pain reduction, and to examine potential associations with important study-level characteristics, we leveraged a combined meta-analysis and meta-regression approach. In a primary assessment, we used meta-analysis techniques to coalesce drug-induced pain reduction standardized effect sizes associated with cannabinoid and placebo administrations to produce pooled effects and enable statistical comparison. In a second assessment (Glass, Smith, & McGaw, 1981), we used meta-regression to examine relationships between various continuous and categorical explanatory variables and drug-induced pain reduction effect

sizes. Specifically, we used multiple linear regression to examine relationships between several study-level characteristics (sample size, age, sex composition, experimental design, and pain population) and drug administration conditions. Overall, we posited that cannabinoid administration would be associated with pain reduction across included studies, and that placebo administration would be less effective. Furthermore, we expected that study-level characteristics would be associated with pain reduction standardized effect sizes. Providing clarification about potential pain-mitigating effects associated with cannabinoids should enable enhanced scientific understanding about possible therapeutic applications.

Methods

Search

We conducted a literature search to identify pharmacological manipulation studies that assessed cannabinoid-induced alterations in subjective pain ratings. Primary searches were carried out using PubMed (www.ncbi.nlm.nih.gov/pmed/) and Web of Science (<http://webofknowledge.com>) with the search terms: cannabis OR cannabinoids OR delta-9-tetrahydrocannabinol OR THC OR cannabidiol OR CBD OR marijuana OR nabilone OR dronabinol OR nabiximols AND pain OR noxious OR analgesia OR visual analog scale OR VAS OR numeric rating scale OR NRS. We further reviewed the reference sections of each record identified during the exhaustive search, in particular, systematic and narrative review papers (Campbell et al., 2001; Colombo et al., 2006; Deshpande et al., 2015; Lynch & Campbell, 2011; Lynch & Ware, 2015; Sznitman & Zolotov, 2015; Wright, 2007) and existing meta-analyses (Andreae et al., 2015; Aviram & Samuelly-Leichtag, 2017; De Vita et al., 2018; Goldenberg et al., 2017; Iskedjian et al., 2007; Martin-Sanchez et al., 2009; Phillips et al., 2010)

Screen

During screening, record abstracts were inspected to determine appropriateness. Specifically, records that did not represent peer-reviewed original research studies were removed from the meta-analysis review pipeline (e.g., letters to editors, reviews, conference proceedings). Records involving non-human models were also not considered. This meta-analysis was restricted to RCTs that: (A) assessed drug-induced pain reductions following cannabinoid administration across studies, including whole-plant cannabis, whole-plant cannabis extracts, and synthetic cannabinoids (i.e., Dronabinol, Nabilone, CT3), and corresponding active or placebo administrations, (B) described pain reductions as differences between baseline (pre-administration) and end-point (post-administration) measurements, and (C) used a parallel-groups (i.e., independent samples) or crossover (i.e., repeated measures) design to examine pain reductions. Importantly, although active control studies were considered in the current meta-analysis (Frank, Serpell, Hughes, Matthews, & Kapur, 2008; Pini et al., 2012), drug-induced pain reductions associated with active control administration (e.g., ibuprofen) were not included in placebo sub-group analyses. The current meta-analysis reflects papers published through August 2018.

Data Extraction and Primary Meta-Analysis

Remaining records were obtained as complete published articles and assessed by two reviewers (J.A.Y and Z.E.M). Reviewers cross-checked extracted data points and resolved disagreement before commencing meta-analyses. Extracted data points included: author, publication year, sample size(s), pharmacological manipulation(s) (whole-plant cannabis, whole-plant cannabis extract, synthetic cannabinoid, and placebo), pain population (pain linked with various medical conditions), baseline mean pain score, end-point mean pain score, and associated variance estimates. Studies that involved more than two (k_j) administration conditions (e.g., THC:CBD extract, THC extract, and placebo) contributed k_j ($k = 3$) mean gain standardized effect sizes to quantitative assessment, where k describes total standardized effect sizes considered in the current meta-analysis. Because we sought to pool cannabinoid-related standardized effect sizes across included studies, and because we sought to pool placebo-related standardized effect sizes across included studies, baseline and end-point pain severity scores were extracted from cannabinoid and placebo conditions separately. Studies that omitted baseline and/or end-point pain severity scores were excluded. When required, pain severity scores were computed using available summary data (e.g., mean pain percent reduction (Abrams et al., 2007; Johnson et al., 2010; Langford et al., 2013; Narang et al., 2008; Skrabek, Galimova, Ethans, & Perry, 2008). Data points collected from one record required reverse scoring (Wade, Robson, House, Makela, & Aram, 2003). Although baseline and end-point pain severity scores were necessary for inclusion, several records omitted associated variance estimates (Abrams et al., 2007; Blake, Robson, Ho, Jubb, & McCabe, 2006; Buggy et al., 2003; Chou et al., 2009; Corey-Bloom et al., 2012; Johnson et al., 2010; Karst et al., 2003; Langford et al., 2013; Narang et al., 2008; Nurmikko et al., 2007; Portenoy et al., 2012; Rog, Nurmikko, Friede, & Young, 2005; Skrabek et al., 2008; Svendsen, Jensen, & Bach, 2004; Wilsey et al., 2008). In such cases, we employed several strategies to secure missing variance data. First, we contacted the lead and/or corresponding authors with data requests. Second, to supplement remaining records, we leveraged the freely available service WebPlotDigitizer (<https://automeris.io/WebPlotDigitizer>) to compute variance estimates using manuscript figures – an accepted technique to extract numeral data from data visualizations (Rohatgi, 2018). Third, when data requests and data extraction from visualizations were not possible, missing variance estimates were reconciled via mean imputation using assembled variance estimates (Cooper, Hedges, & Valentine, 2009). Notably, imputed variance estimates represented approximately 35% (46/130) of total variance data. Outcome measures included quantitative pain-rating scales, such as numeric rating scales (NRS) (Hartrick, Kovan, & Shapiro, 2003) and visual analog scales (VAS) (Ferraz et al., 1990). Quantitative pain-rating scales involve asking participants to describe pain severity, routinely anchored by zero, indicating “no pain,” and 10, indicating “worst pain.” Results from studies using 100-point ranges were scaled to enable pooling and comparison.

Following data extraction, baseline pain severity scores, end-point pain severity scores, and associated variance estimates, were used to compute study-level standardized mean gain effect size (i.e., *Cohen's d*) (Becker, 1988). Standardized effect sizes were used to calculate associated standard errors (Lipsey & Wilson, 2001) and confidence intervals (Nakagawa & Cuthill, 2007). To facilitate meta-analytic comparison, study-level standardized effect sizes

were then inverse-variance weighted and pooled to produce an average cannabinoid-induced effect and an average placebo-induced effect (Hedges & Olkin, 1985). Monte Carlo simulations suggest that inverse-variance weighting produces optimal pooled effect sizes in meta-analysis assessments (Sánchez-Meca & Marin-Martinez, 1998). Forest plots were created to visualize standardized effect sizes. We assessed the degree to which variation among cannabinoid and placebo administrations was attributed to chance via the I^2 statistic and associated confidence intervals (Higgins & Thompson, 2002; Higgins, Thompson, Deeks, & Altman, 2003). Pooled effects were compared with an independent-samples mean difference test (Hedges & Olkin, 1985; Hedges & Pigott, 2001).

Multiple Linear Regression (Meta-Regression)

Meta-regression examines the relationships between continuous and/or categorical explanatory variables (e.g., sample size, sample age, sample sex composition) and a continuous outcome variable (e.g., study-level standardized effect sizes) (Green & Higgins, 2005). Specifically, we used an exploratory fixed-effects multiple linear regression (meta-regression) approach (Greenland, 1987; Luebke & Brunkwall, 2015), to explore relationships between pain reduction effects and: *drug administration condition* [placebo, cannabinoid (whole-plant, whole-plant extract), synthetic cannabinoid (Dronabinol, Nabilone, CT3)], *sample size* (reported sample size), *sample age* (mean sample age), *sample sex composition* (sample sex ratio), *experimental design* (parallel versus crossover), and *pain population* (abdominal pain, arthritis, cancer, chronic pain, diabetes, fibromyalgia, headache, human immunodeficiency virus (HIV), multiple sclerosis, neuropathic pain, post-operative pain, and “various,” or mixed pain populations within one effect). Data were examined using statistical assumptions associated with regression, including normality, residual normality, and equal variances. Outliers among standardized effect sizes [i.e., median effect \pm interquartile range (IQR) \times 1.5] were adjusted using upper/lower quartile replacement (Tukey, 1977). Categorical variables (e.g., placebo, cannabinoid, synthetic cannabinoid) were dummy coded to facilitate meta-regression assessment (Wolf & Cartwright, 1974).

Ethics and Open Science Practices

As is common with meta-analytic assessments, the current report did not involve human subjects and therefore did not require institutional review board approval (Sullivan, 2011). In line with current recommendations and open science best practices (Open Science, 2015), we have made meta-data and corresponding code associated with this work freely available on GitHub (<https://doi.org/10.5281/zenodo.1463262>).

Results

Primary Meta-Analysis

Literature search and review results are depicted in Table 1 and Figure 1. The search produced 954 records which underwent screening. Using exclusion criteria described above, 899 records were removed during abstract review, and another 30 were removed during full-text review. The current meta-analysis included data from 25 records that met inclusion criteria, providing data from $k = 65$ individual pharmacologic manipulations (39 cannabinoid manipulations versus 26 placebo manipulations), involving 2,248 participants.

On average, studies reported that participants' mean age ranged from 43.50 to 62.80 years (mean = 52.09). Included studies assessed drug-induced pain reductions associated with several cannabinoid administration conditions, including whole-plant cannabis ($n = 5$), whole-plant cannabis extract ($n = 11$), and synthetic cannabinoids ($n = 9$). Pain-related clinical samples (pain populations) considered were neuropathic pain ($n = 7$), cancer ($n = 4$) diabetes ($n = 3$), MS ($n = 3$), abdominal pain ($n = 1$), arthritis ($n = 1$), chronic pain ($n = 1$), fibromyalgia ($n = 1$), headache ($n = 1$), HIV ($n = 1$), post-operative pain ($n = 1$), and "various" ($n = 1$). Standardized effect sizes are organized according to pain population in Supplemental Figure 1. On average, studies reported that 51.57% of participants were women. Fifteen studies provided data from parallel-group designs and 10 provided data from crossover designs.

Inverse-variance weighting and pooling across cannabinoid standardized effect sizes revealed that cannabinoid administration was associated with a 'medium-to-large' effect, *Cohen's d* = -0.58, 95% CI (-0.74, -0.43) (Figure 2). An assessment of variation revealed considerable heterogeneity among cannabinoid effect sizes, $I^2 = 91.47\%$, 95% CI (87.93%, 92.37%). On the other hand, inverse-variance weighting and pooling across placebo standardized effect sizes revealed that placebo administration was associated with a 'small-to-medium' effect, *Cohen's d* = -0.39, 95% CI (-0.52, -0.26) (Figure 3). An assessment of variation revealed considerable heterogeneity among placebo effect sizes, $I^2 = 92.66\%$, 95% CI (89.18%, 93.70%). Overall, cannabinoid administration was associated with greater pain reduction compared to placebo administration, $t(64) = -4.06$, $p < 0.05$. Visual inspection revealed some overlap between drug administration condition confidence intervals.

Exploratory Multiple Linear Regression (Meta-Regression)

Overall, the meta-regression model explained a moderate proportion of variance among individual studies, $R^2 = 0.37$ (adjusted $R^2 = 0.30$), $F(6,48) = 4.62$, $p < 0.05$. Reported p -values are associated with corresponding coefficient hypotheses tests. Meta-regression results revealed that, when controlling for other explanatory variables, drug administration conditions were linked with pain reduction among included studies, such that cannabinoids (whole-plant cannabis and whole-cannabis extracts) $\beta = -0.43$, 95% CI (-0.62, -0.24), $p < 0.05$ (Figure 4), and synthetic cannabinoids (Dronabinol, Nabilone, and CT3) $\beta = -0.39$, 95% CI (-0.65, -0.14), $p < 0.05$ (Figure 4), performed better than placebo. Furthermore, meta-regression results showed that, when controlling for other explanatory variables, sample size was linked with pain reduction, $\beta = 0.01$, 95% CI (0.00, 0.01), $p < 0.05$, such that studies involving smaller samples tended to report greater pain reduction effects (Figure 4). There were no observed interactions between drug administration conditions and sample size. Finally, meta-regression results showed that, when controlling for other explanatory variables, sample sex composition was linked with a modest, however non-significant, effect, $\beta = -0.64$, 95% CI (-1.37, 0.09), $p = 0.09$, such that studies including more female participants tended to report greater pain reductions (Figure 5).

Discussion

In this meta-analytic study, we coalesced results from peer-reviewed primary research articles that characterized cannabinoid- and placebo-induced reductions of subjective pain ratings across medical conditions. Our findings extend current understanding about cannabinoids and pain, taking a meta-regression approach to examine relationships between various study-level characteristics and drug-induced pain reductions. When considering reductions in self-reported pain, we observed that cannabinoid administration was associated with a ‘medium-to-large’ (Cohen, 1988) pooled effect size across included studies. Importantly, cannabinoid administration was associated with statistically significant greater pain reduction than placebo administration, which yielded a ‘small-to-medium’ (Cohen, 1988) pooled effect size. Indeed, placebo administration has been shown to enhance expectations about pain reduction (Bushe et al., 2016), potentially assuaging negative emotional/motivational aspects about pain experiences. Finally, results from our meta-regression analysis suggested that, when controlling for other explanatory variables, drug administration conditions and sample size predicted observed pain reduction. Taken together, these meta-analytic outcomes provide some evidence that cannabinoids, relative to placebo, might mitigate subjective pain reporting among those experiencing chronic pain tied to various medical conditions. However, more research is needed to understand nuances in cannabinoid-induced pain reduction, including outcome differences between single-dose versus long-term cannabinoid treatments, complex interactions with concurrent analgesic pharmacotherapies, and changes in cannabis conditional dependence rates as a function of increased access.

Neuropsychological Impact of Cannabinoid-Based Administrations

When considering cannabis’s effect on pain, our primary meta-analysis outcomes suggest that cannabinoids may represent a viable option regarding pain management and treatment-outperforming corresponding placebo conditions across included studies. That cannabinoids were associated with pain reduction is not surprising, given that the most common medicinal cannabis applications throughout documented human history involve administration for pain (Parker, 2017). Indeed, early evidence suggests that medicinal cannabis may have been used to relieve pain around 400 CE (Zlas et al., 1993). However, it was just in the 1990s that several reports described an *endogenous* cannabinoid framework embedded within the central nervous system (Devane et al., 1992) and peripheral nervous system (Munro, Thomas, & Abu-Shaar, 1993), which interacts with *exogenous* cannabinoids to modulate pain.

Processing pain signals starts with nociceptive sensation signal transduction throughout the peripheral nervous system and terminates with subjective pain perception within the central nervous system (for an extended review, see Millan, 1999). First, peripheral sensory neurons detect noxious stimulation, which is then communicated to neuronal bodies around the spinal column. Next, sensory neurons synapse onto central dorsal horn neurons within the spinal cord, where pain signals are integrated across pathways. Finally, central dorsal horn neurons forward pain signals via ascending pathways to the brainstem, thalamus, and cortical brain regions, which process higher-order pain behavior. Notably, cannabinoid

receptors are densely concentrated in the frontal and limbic cortices- brain regions also associated with processing pain, including the anterior cingulate cortex (ACC) (Glass, Faull, & Dragunow, 1997). As such, cannabinoid receptor agonists may work to mitigate subjective pain experiences via interactions with brain regions responsible for processing more complex mental operations, such as pain-related affective and motivational dimensions. Consistent with such an interpretation, recent reports have examined the relationship between cannabis and pain-related brain function. For example, Lee and colleagues (2013) used functional magnetic resonance imaging (fMRI) to investigate cannabis's impact on blood-oxygen-level dependent (BOLD) signal fluctuations in response to experimental chemical pain (i.e., capsaicin) among normal participants. Those researchers observed that, when compared to placebo, cannabinoid administration (i.e., 15 mg THC) reduced pain unpleasantness, but not pain intenseness. That is, cannabinoid administration may modulate pain perception (unpleasantness) without affecting pain sensation (intenseness), a position supported by a recent meta-analysis of cannabinoid-induced modulations in experimental pain (De Vita et al., 2018). Moreover, cannabinoid-induced reductions in pain unpleasantness correlated with less ACC activation. Indeed, ACC functioning has been implicated in various affective-motivational components in higher-order pain processing, such as conditioned place avoidance (Johansen, Fields, & Manning, 2001; LaGraize, Labuda, Rutledge, Jackson, & Fuchs, 2004), perceived threat from noxious stimulation (Foltz & White Jr, 1962), and monitoring survival-relevant goals (Lieberman & Eisenberger, 2015). Although acute cannabinoid receptor agonism dampens ACC responding to pain, effectively reducing pain-related negative affect, whether these effects endure beyond acute administration remains unclear. In a recent neuroimaging meta-analysis, Yanes and colleagues (2018) examined neurofunctional alterations associated with chronic cannabis use. When considering cannabis's impact across various mental tasks, those researchers observed that chronic cannabis was linked with, among other changes, decreased ACC activation. Furthermore, ancillary assessments revealed that activity within the ACC has been consistently linked with pain-related taxonomic descriptors (i.e., *Pain, Pain Monitor/Discrimination*) across the functional neuroimaging literature. To summarize, the neurobiological outcomes discussed here may represent potential higher-order, brain-level mechanisms that support demonstrated cannabis-induced pain reduction.

Outcomes from Meta-Regression

Meta-regression results showed that sample size was associated with pain reduction standardized effect sizes across studies, such that studies involving smaller samples reported greater pain reduction. Moreover, there was no interaction between reported sample size and drug administration conditions (i.e., cannabinoid, synthetic cannabinoid, and placebo), suggesting that this was the case across pharmacologic manipulations considered. Sample size represents an important determinant regarding how generalizable research results are to target populations (Wiedermann & Wiedermann, 2015). Often, studies with smaller samples have reported better therapeutic outcomes (Sterne & Egger, 2001). This phenomenon has been linked to outcome reporting biases (Chan & Altman, 2005), such as data omission when results lack statistical significance, poorer methodological parameters (Kjaergard, Villumsen, & Gluud, 2001), and increased between-study heterogeneity among studies with small samples (Int'Hout, Ioannidis, Borm, & Goeman, 2015). Moving forward, it is

important that researchers, healthcare providers, and law makers consider outcomes from studies on cannabinoid-induced pain reductions within the context of the sample sizes that derived them.

When considering sex-dependent effects in cannabinoid-induced pain reduction, meta-regression results suggested that among included studies, those studies that recruited more female participants reported greater, although non-significant, standardized effect sizes across drug administration conditions. It is worth noting that meta-regression outcomes derived using summary statistics (e.g., sample sex composition) may exhibit ecological confounding (Morgenstern, 1982) compared to using patient-level data (Thompson & Higgins, 2002). As such, the relationship between biological sex and cannabinoid analgesia should become clearer as new studies emerge that provide within-sample comparisons. Accumulating preclinical evidence suggests that females may be more sensitive to cannabis's pain-reducing effects. Indeed, greater pain reduction among females following cannabinoid-receptor agonism has been shown in acute pain and non-acute pain animal models (Craft, Marusich, & Wiley, 2013; Craft, Wakley, Tsutsui, & Laggart, 2012; Tseng & Craft, 2001). However, whether these sex-dependent effects extend to humans remains unclear. One recent report from Cooper and Haney (2016) examined pain reduction among male and female cannabis users following active cannabis consumption (3.65–5.60% THC) and placebo consumption (0.00% THC). Among male cannabis users, those researchers found that cannabis consumption increased pain-onset latency compared to placebo—presumably by reducing pain sensitivity. Among female cannabis users, however, no differences were observed between active cannabis and placebo conditions. These discordant outcomes may highlight important nuances about cannabinoid-related reductions in reported pain. Specifically, findings from the current meta-analysis represent data from participants with various clinical conditions. Growing evidence suggests that women experience greater clinical pain (Rosseland & Stubhaug, 2004; Unruh, 1996), often endorsing increased pain-related distress (Paller, Campbell, Edwards, & Dobs, 2009). It is then possible that reported sex-differences in cannabinoid-induced pain reduction stem from differences in pain reporting— not pain sensation and/or perception. With this in mind, one important question facing subsequent research involves our current understanding of sex-dependent effects in cannabinoid-induced pain reduction. Moreover, subsequent research may consider sex differences across complimentary pain outcomes, such as pain tolerance, pain ratings, and pain questionnaires/scales.

Limitations

Findings presented here should be considered in the context of several methodological limitations. First, as is common with meta-analyses, our outcomes and associated interpretations are constrained by the state of the current literature. Accordingly, results obtained here should be considered preliminary given the modest sample size (*i.e.*, 25 papers). Moreover, recommendations regarding sub-group analyses and meta-analytic modeling prevented more refined assessments, such as estimating standardized effect sizes as a function of cannabinoid sub-classifications (e.g., whole-plant cannabis, whole-plant cannabis extract, synthetic cannabinoid, THC, CBD, THC/CBD), dose (e.g., 2.5mg THC, 5mg THC), administration route (e.g., smoke, oromucosal spray, capsule), and pain

population (e.g., central/peripheral neuropathic pain, cancer pain, multiple sclerosis pain) (Green & Higgins, 2005). The inclusion of studies that involved several drug conditions and clinical samples into the same meta-analysis presumably contributed to observed between-study heterogeneity. More granular meta-analytic approaches should become possible as additional relevant studies are made available. Second, even though included studies involved comparable end-point measures (i.e., numeric rating scale, visual analog scale), these studies may contain confounds and/or biases that have not been addressed, such as temporal variation in societal attitudes towards cannabis, regional policies that promote medicinal cannabis, and inter-individual differences regarding cannabis's expected effectiveness. With this in mind, we used fixed-effects multiple linear regression (meta-regression) to control confounding effects where possible (e.g., experimental design) (Stanley & Jarrell, 1989). Also, moving forward, researchers may consider systematically collecting/reporting concomitant end-point measures [e.g., McGill Pain Questionnaire (Melzack, 1975)], to provide more complete characterizations of cannabis-related analgesic effects. Third, despite rigorous review methods, several records were excluded from the current meta-analysis due to missing data. According to the Open Science Collaboration (2015), problematic practices within psychological science include selective reporting, omitting analyses, and insufficient specification regarding experimental parameters. Moreover, the current meta-analysis cannot consider studies that were conducted but never reported (i.e., "the file drawer problem") (Rosenthal, 1979). Thus, improved reporting practices should enable enhanced meta-analysis assessments in general, and regarding cannabinoids in particular. Finally, despite showing that cannabinoid administration was associated with pain reduction, many studies included in this meta-analysis did not give full consideration to neurocognitive side-effects linked with cannabis (for an extended review, see Crane, Schuster, Fusar-Poli, & Gonzalez, 2013). Future investigations should systematically examine cannabis's therapeutic properties in the context of co-occurring undesired neurocognitive effects.

Conclusions

Our meta-analysis outcomes show that cannabinoid administration was associated with reductions in subjective pain across included studies, making them viable candidates for pain management and treatment. Moreover, meta-regression results suggested that drug administration condition and sample size predicted pain reduction effects. Finally, we observed that sample sex composition was associated (although, not statistically significant) with observed pain reduction, suggesting that this may be an important biological variable when considering cannabis-induced pain reduction. As social, societal, and political attitudes towards cannabis evolve, it is becoming increasingly important to provide enhanced scientific understanding regarding risks and potential therapeutic applications. Such understanding should lead to more informed decision-making regarding cannabis among patients, care providers, and law makers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Public Significance Statement

Chronic pain states are an ever-growing concern in the United States, costing an estimated \$600 billion annually in lost labor and healthcare expenses. These, and other, conditions have resulted in an over-reliance on opioid-based pharmacotherapies. Results from the current meta-analysis provide some support that cannabinoids might mitigate subjective pain among patients with pain-related clinical conditions.

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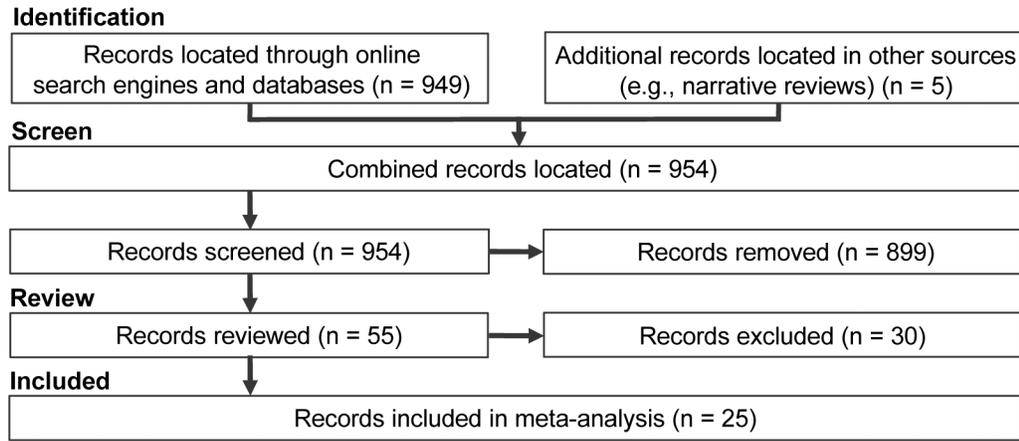


Figure 1. Literature Search and Review Pipeline.

Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) pipeline diagram showing search and review results. A preliminary search produced 949 records, with an additional 5 assembled from additional resources (e.g., narrative reviews), totaling 954 records overall. During abstract review, 899 records were removed from the meta-analysis pipeline. During complete manuscript review, an additional 30 records were discarded based on study exclusion criteria. Finally, the 25 remaining records underwent data extraction and subsequent meta-analytic assessment.

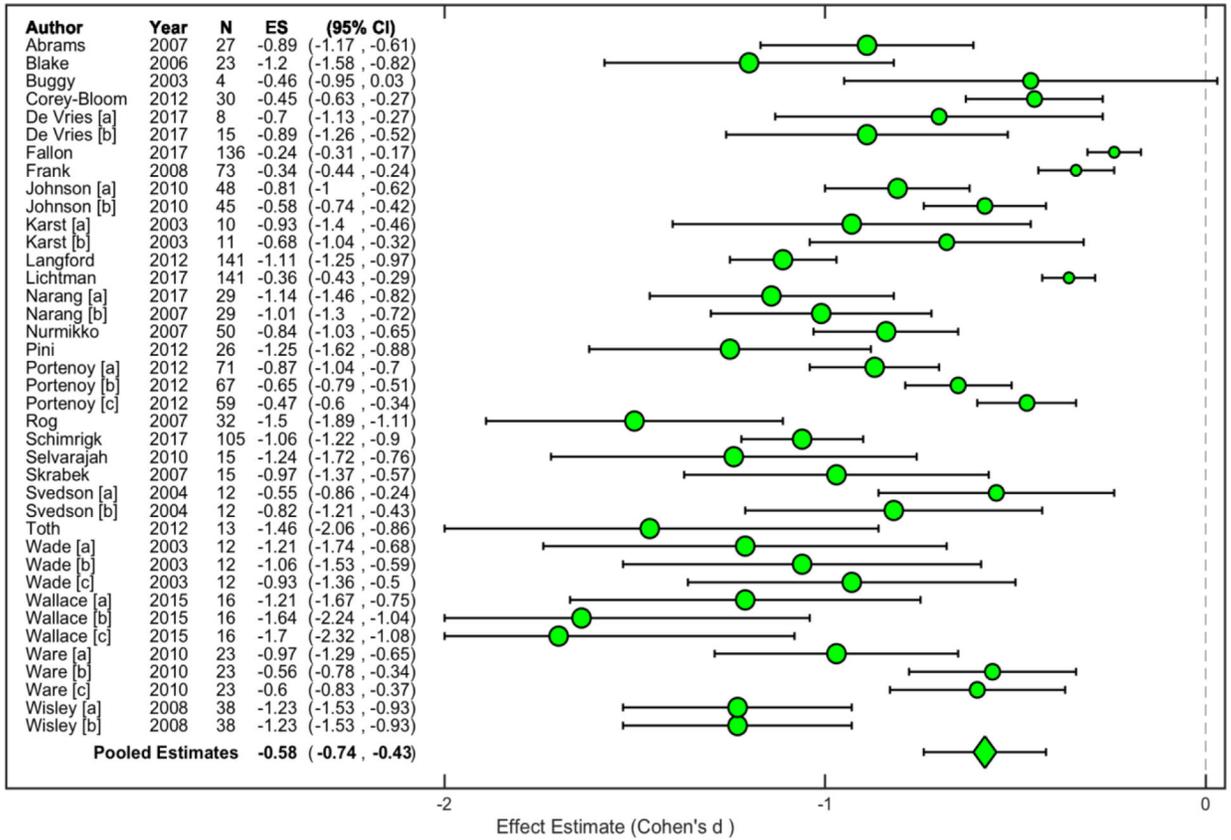


Figure 2. Pooled Cannabinoid Administration Effect.

Study-level standardized effect size estimates (*Cohen's d*) were computed for each cannabinoid administration across included studies. Circle sizes are proportional to small, medium, and large effect size estimate interpretations (Cohen, 1988). Study-level estimates were inverse-variance weighted and pooled to determine a representative estimate. When considering overall pain reduction effects, cannabinoid administration was associated with a medium-to-large effect across studies, *Cohen's d* = -0.58, 95% CI (-0.74, -0.43). N, sample size; ES, standardized effect size estimate; CI, confidence interval.

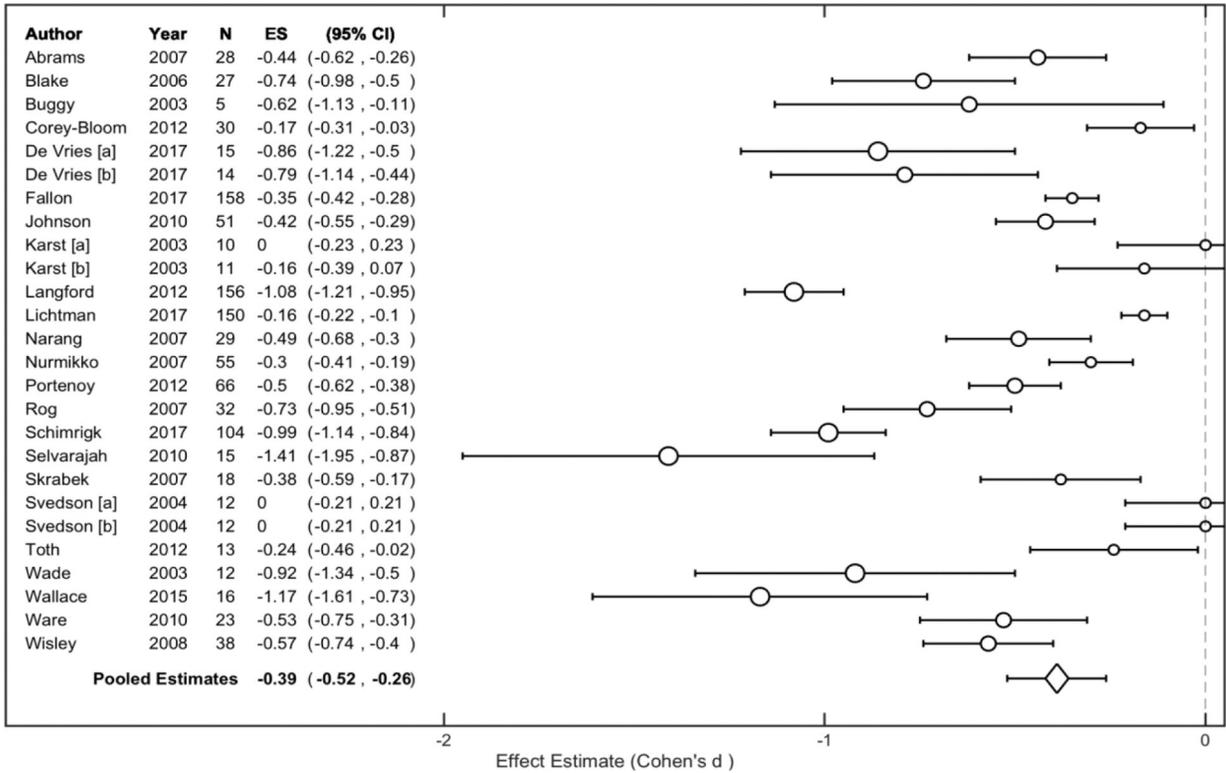


Figure 3. Pooled Placebo Administration Effect.

Study-level standardized effect size estimates (*Cohen's d*) were computed for each placebo administration across included studies. Circle sizes are proportional to small, medium, and large effect size estimate interpretations (Cohen, 1988). Study-level estimates were inverse-variance weighted and pooled to determine a representative estimate. When considering overall pain reduction effects, placebo administration was associated with a small-to-medium effect across studies, *Cohen's d* = -0.39, 95% CI (-0.52, -0.26).

N, sample size; ES, standardized effect size estimate; CI, confidence interval.

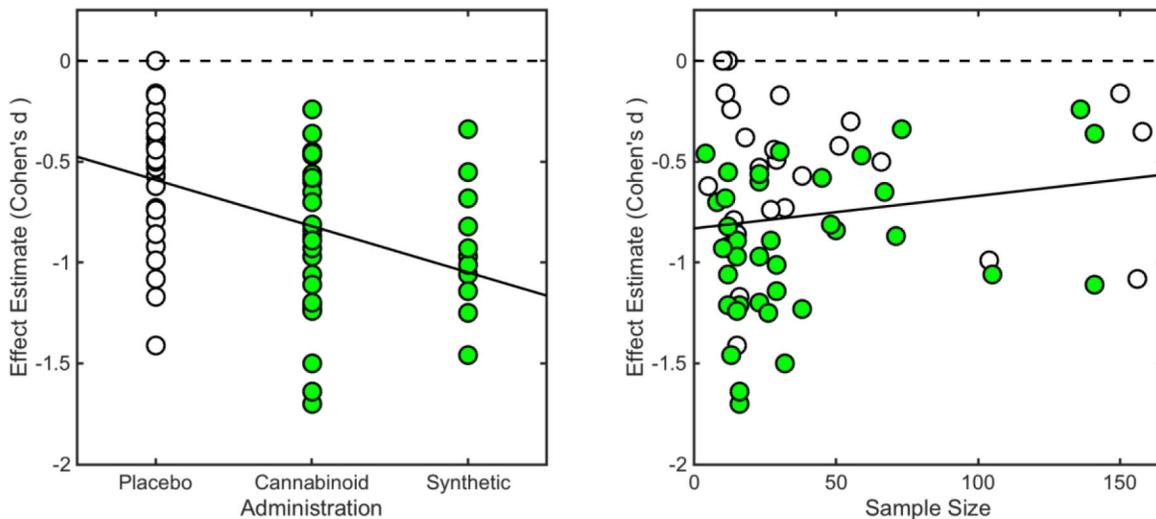


Figure 4. Bivariate Relationship Between Effect Size Estimates and Significant Predictors. Meta-regression results revealed that, when controlling for other explanatory variables, drug administration conditions were linked with pain reduction among included studies, such that cannabinoids (whole-plant cannabis and whole-cannabis extracts) $\beta = -0.43$, 95% CI $(-0.62, -0.24)$, $p < 0.05$, and synthetic cannabinoids (Dronabinol, Nabilone, and CT3) $\beta = -0.39$, 95% CI $(-0.62, -0.24)$, $p < 0.05$, performed better than placebo. Furthermore, meta-regression results showed that, when controlling for other explanatory variables, sample size was linked with pain reduction, $\beta = 0.01$, 95% CI $(0.00, 0.01)$, $p < 0.05$, such that studies involving smaller samples tended to report greater pain reduction. Cannabinoids = shaded (green) circles; placebo = unshaded circles.

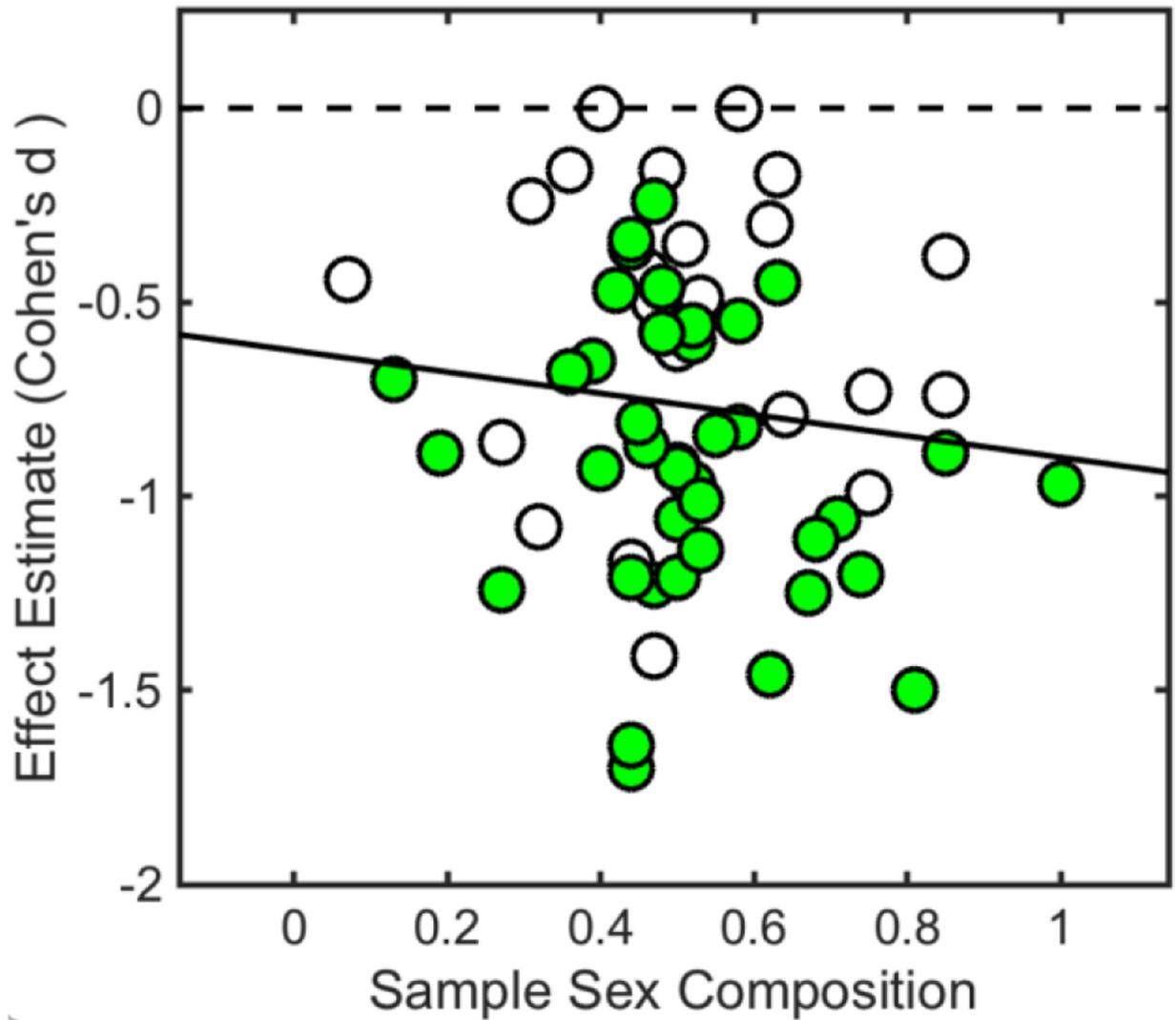


Figure 5. Bivariate Relationship Between Effect Size Estimates and Sample Sex Composition (Sex Ratio).

Meta-regression results showed that, when controlling for other explanatory variables, sample sex composition was linked with a modest, albeit non-significant, effect, $\beta = -0.64$, 95% CI $(-1.37, 0.09)$, $p = 0.09$, such that studies including more female participants tended to report greater pain reductions.

Cannabinoids = shaded (green) circles; placebo = unshaded circles.

Table 1.
Studies Meeting Inclusion Criteria.

Numbering corresponds to studies meeting inclusion criteria. Extracted variables were administration condition (administration), including cannabis whole plant, cannabis extract, synthetic cannabinoid, and placebo, administration dose (dose), administration route (route), population with pain-related clinical condition (pain population), subjective pain outcome measure (pain measure), and associated scale (scale). THC, delta-9-tetrahydrocannabinol; CBD, cannabidiol. CT3, dimethylheptyl-delta-8-tetrahydrocannabinol-11-oic acid; HIV, human immunodeficiency virus;

No.	Author	Year	Details Regarding Sampled Studies					
			Administration	Dose	Route	Pain Population	Pain Measure	Scale
1	Abrams et al.	2007	Whole Plant	3.56 % THC	Smoke	HIV	Visual Analog Scale	0 – 100
2	Blake et al.	2006	Extract (Sativex)	2.7 mg THC / 2.5 mg CBD	Oromucosal Spray	Arthritis	Numeric Rating Scale	0 – 10
3	Buggy et al.	2003	Extract	5.0 mg THC	Capsule	Post-Operation	Visual Analog Scale	0 – 10
4	Corey-Bloom et al.	2012	Whole Plant	4.0% THC	Cigarette	Multiple Sclerosis	Visual Analog Scale	0 – 100
5	De Vries et al.	2017	Synthetic (Dronabinol)	8 mg	Tablet	Abdominal Pain	Visual Analog Scale	0 – 10
	De Vries et al.	2017	Synthetic (Dronabinol)	8 mg	Tablet	Abdominal Pain	Visual Analog Scale	0 – 10
6	Fallon et al.	2017	Extract (Sativex)	2.7 mg THC / 2.5 mg CBD	Capsule	Cancer	Numeric Rating Scale	0 – 10
7	Frank et al.	2008	Synthetic (Nabilone)	0.25 mg	Capsule	Neuropathic Pain	Visual Analog Scale	0 – 100
8	Johnson et al.	2010	Extract (Sativex)	2.7 mg THC / 2.5 mg CBD	Capsule	Cancer	Numeric Rating Scale	0 – 10
			Extract	2.7 mg THC	Capsule	Cancer	Numeric Rating Scale	0 – 10
9	Karst et al.	2003	Synthetic (CT-3)	10.0 mg	Capsule	Neuropathic Pain	Visual Analog Scale	0 – 100
10	Langford et al.	2012	Extract (Sativex)	2.7 mg THC / 2.5 mg CBD	Oromucosal Spray	Neuropathic Pain	Numeric Rating Scale	0 – 10
11	Lichtman et al.	2017	Extract (Sativex)	2.7 mg THC / 2.5 mg CBD		Cancer	Numeric Rating Scale	0 – 10
12	Narang et al.	2008	Synthetic (Dronabinol)	20.0 mg	Capsule	Chronic Pain	Numeric Rating Scale	0 – 10
		2008	Synthetic (Dronabinol)	10.0 mg	Capsule	Chronic Pain	Numeric Rating Scale	0 – 10
13	Nurmikko et al.	2007	Extract (Sativex)	2.7 mg THC / 2.5 mg CBD	Oromucosal Spray	Neuropathic Pain	Numeric Rating Scale	0 – 10
14	Pini et al.	2012	Synthetic (Nabilone)	0.5 mg	Capsule	Headache	Visual Analog Scale	0 – 10
15	Portenoy et al.	2012	Extract (Sativex)	2.7 mg THC / 2.5 mg CBD	Oromucosal Spray	Cancer	Visual Analog Scale	0 – 10
			Extract (Sativex)	2.7 mg THC / 2.5 mg CBD	Oromucosal Spray	Cancer	Visual Analog Scale	0 – 10
			Extract (Sativex)	2.7 mg THC / 2.5 mg CBD	Oromucosal Spray	Cancer	Visual Analog Scale	0 – 10
16	Rog et al.	2007	Extract (Sativex)	2.7 mg THC / 2.5 mg CBD	Oromucosal Spray	Neuropathic Pain	Numeric Rating Scale	0 – 10

No.	Author	Year	Details Regarding Sampled Studies					
			Administration	Dose	Route	Pain Population	Pain Measure	Scale
17	Schimrigk et al.	2017	Synthetic (Nabilone)	7.5 mg – 15.0 mg	Capsule	Multiple Sclerosis	Numeric Rating Scale	0 – 10
18	Selvarajah et al.	2010	Extract (Sativex)	2.7 mg THC / 2.5 mg CBD	Oromucosal Spray	Diabetes	Visual Analog Scale	0 – 100
29	Skrabek et al.	2007	Synthetic (Nabilone)	0.5 mg	Capsule	Fibromyalgia	Visual Analog Scale	0 – 10
20	Svedson et al.	2004	Synthetic (Dronabinol)	2.5 mg – 10.0 mg	Capsule	Multiple Sclerosis	Numeric Rating Scale	0 – 10
		2004	Synthetic (Dronabinol)	2.5 mg – 10.0 mg	Capsule	Multiple Sclerosis	Numeric Rating Scale	
21	Toth et al.	2012	Synthetic (Nabilone)	2.0 mg – 4.0 mg	Capsule	Diabetes	Numeric Rating Scale	0 – 10
22	Wade et al.	2003	Extract	2.5 mg THC / 2.5 mg CBD	Oromucosal Spray	Various	Visual Analog Scale	0 – 100
			Extract	2.5 mg THC	Oromucosal Spray	Various	Visual Analog Scale	0 – 100
			Extract	2.5 mg CBD	Oromucosal Spray	Various	Visual Analog Scale	0 – 100
23	Wallace et al.	2015	Whole Plant	7% THC	Humidified	Diabetes	Visual Analog Scale	0 – 10
			Whole Plant	4% THC	Humidified	Diabetes	Visual Analog Scale	0 – 10
			Whole Plant	1 % THC	Humidified	Diabetes	Visual Analog Scale	0 – 10
24	Ware et al.	2010	Whole Plant	9.4 % THC	Smoke	Neuropathic Pain	Numeric Rating Scale	0 – 10
			Whole Plant	6.0 % THC	Smoke	Neuropathic Pain	Numeric Rating Scale	0 – 10
			Whole Plant	2.5 % THC	Smoke	Neuropathic Pain	Numeric Rating Scale	0 – 10
25	Wisley et al.	2008	Whole Plant	7.0 % THC	Smoke	Neuropathic Pain	Visual Analog Scale	0 – 100
			Whole Plant	3.5 % THC	Smoke	Neuropathic Pain	Visual Analog Scale	0 – 100