

# A Systematic Review and Meta-Analysis of Cannabidiol for Pain

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**Disclosure:** None.

**Introduction:** Management of any pain condition especially chronic pain is challenging coupled with the epidemic of opioid crisis that has claimed a lot of lives. There is a growing interest in exploration of opioid sparing and non-intoxicating analgesics in particular medical cannabis. Evidence exists on the effect of tetrahydro cannabinoids (THC) in combination with cannabidiol (CBD) the non-intoxicating component of medical cannabis for management of chronic pain. Preclinical studies suggest that cannabidiol alone exerts analgesic and anti-inflammatory effects amongst other non-pain related benefits. There is insufficient evidence on the use of cannabidiol alone for pain in human. This study aims to conduct systematic review and meta-analysis on available randomized controlled trials to update clinicians and end users on the benefits of cannabidiols for pain management.

**Study design:** Systematic review and meta-analysis

**Method:** We performed electronic searches in PubMed, EMBASE, Cochrane, CINAHL, SportDiscus, Scopus, and reviewed relevant conference abstracts published through March of 2023. We included only randomized studies that investigated the effect of CBD on pain in humans. Study eligibility, methodological quality of included studies and data extraction were independently accessed by two reviewers with a third reviewer resolving any disagreements. We performed fixed and random effects meta-analyses, explored publication bias, and performed a GRADE assessment of the evidence across studies.

**Results:** We screened 859 non-duplicate abstracts for inclusion, resulting in a total of 16 included studies. The results of 16 RCTs (a total of 1,018 participants) were included in this review of which 9 RCTs (a total of 488 participants) were eligible for meta-analysis. Both the fixed and random effects model resulted in a non-statistically significant result in support of pain relieving effects of cannabidiol compared to placebo (SMD = -0.08, 95% CI: -0.25, 0.1) and -0.11 and (95% CI: -0.37, 0.15,  $p = 0.41$ ) respectively Fig 1. A single study looked at the opioid sparing effects of CBD with 53% of included participants having reduced or eliminated opioids and decreased pain. The included studies overall have a low to moderate risk of bias and the GRADE of evidence was reduced to moderate because of the small effect size and wide confidence interval. A funnel plot was used to explore publication bias and it suggested that there is no publication bias.

**Discussion:** Overall, we found a small non-significant effect of CBD on pain compare to placebo. The observed effect could be because of variation in the characteristics of the included studies (e.g., participant, pain conditions, cointerventions, CBD dose). The main drawback of this study is that the included studies are extremely heterogeneous which could be because of variation in dose of CBD used in these studies or varying follow-up time. In conclusion, the evidence is insufficient to determine if CBD alone is a better alternative in pain conditions. More research is required to delineate the specific effects of CBD for pain and opioid use mitigation.

**Significance:** This review has highlighted that cannabidiol has analgesic effect which may not significantly different from placebo (Non cannabidiol analgesics), but that there was significant heterogeneity across the studies.

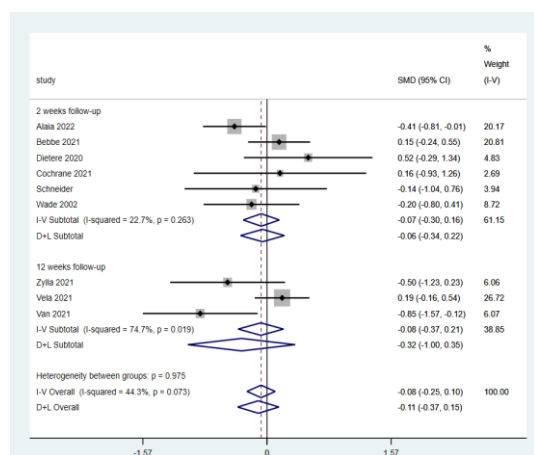


Fig 1: Forest plot comparing pain score between Cannabidiol and placebo

Table 1: Summary of findings from GRADE

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with Placebo	Risk with Cannabidiol			
Reduced pain score on visual analogue scale	-	SMD 0.11 SD lower (0.37 lower to 0.15 higher)	-	488 (9 RCTs)	⊕⊕⊕⊙ <sup>b</sup> Moderate

CI, Confidence interval; SMD, Standardized Mean Difference; <sup>b</sup> downgraded one level for imprecision and further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate