

**Letters to the Editor**



## The Perils of Overestimating the Efficacy of Cannabis-Based Medicines for Chronic Pain Management

### **TO THE EDITOR:**

We read with interest the systematic review of Aviram and Samuelli-Leichtag on “Efficacy of Cannabis-Based Medicines for Pain Management: A Systematic Review and Meta-Analysis of Randomized Controlled Trials” (1). We would like to voice some serious concerns regarding the methodology and results of this review:

1. The authors did not include “grey literature” into their search. A systematic review of cannabis-based medicines (CBM) for chronic neuropathic pain, which searched the literature up to November 2015, identified 3 randomized controlled trials (RCT) in clinicaltrials.gov comparing tetrahydrocannabinol/cannabidiol (THC/CBD) oromucosal spray in different neuropathic pain syndromes, which failed to demonstrate a statistical superiority over placebo (2). These RCTs were not included in the systematic review of Aviram and Samuelli-Leichtag. Therefore, in light of this omission, the authors have overestimated the efficacy of CBM in chronic pain, in general, and in chronic neuropathic pain in particular.

2. The number of participants in the CBM and control groups were not reported in the forest plots of the paper. Therefore, it is not possible to determine whether the authors have dealt with unit of analyses issues correctly.

3. The authors did not specify a minimum of study duration for study inclusion. A study duration of at least 4 weeks to 12 weeks is required by drug agencies for the approval of a drug for chronic pain management (3). Included in the analysis for this review of effect in chronic non-cancer pain were 8 studies, with a study duration of one day and 4 studies, with a study duration of less than one week. These very short duration studies fail to give any valid information on the short-term (4–12 weeks), intermediate term (12–26 weeks), and long-term (> 26 weeks) efficacy of CBM for chronic pain. In addition, the inclusion of these very short dura-

tions (experimental studies) has erroneously distorted the results of the review towards a positive judgement of the efficacy of CBM. For example, the authors found a moderate effects size of -0.76 Hedge’s *g* (-1.06 to -0.45,  $P < 0.0001$ ) (effect random-effect model) for the reduction of cancer pain by analyzing 4 RCTs with 10 study arms. One RCT, with 4 study arms, had a study duration of 6 hours and the other RCT, with 2 study arms, had a study duration of 3 days. These 2 studies were not included into 2 other systematic reviews with meta-analyses of CBM in cancer pain (4,5). These 2 systematic reviews found that CBM were not statistically superior ( $P = 0.06$ ) to placebo for cancer pain (4,5). The lack of efficacy of CBM in cancer pain was recently reported for 2 RCTs. In a study of 605 patients with chronic uncontrolled pain and advanced cancer, with oromucosal THC/CBS spray as adjunctive therapy, did not achieve the primary efficacy endpoint of percent improvement from the baseline to the end of treatment in average pain numerical rating scale (NRS) scores. Similarly, the primary endpoint of mean change in average daily NRS scores was not met for the second study (6).

4. The authors used the Jadad score (7) to assess the risks of bias in the studies included in this analysis. They conclude that the majority of the included trials were rated as moderate to high regarding risks of bias. However, the Jadad score does not capture all relevant risks of bias in chronic pain trials, such as small sample size bias, which leads to an overestimation of the treatment effect (8). This bias applies to the majority of studies with CBM in chronic pain. Our concerns regarding short study duration and small sample size bias are particularly valid for the studies with inhaled medical cannabis for chronic neuropathic pain, for which the authors found a strong effect size of -0.93 Hedge’s *g* (-1.51 to -0.35,  $P = 0.001$ ).

In summary, the authors have overestimated the

efficacy of CBM for chronic pain, as well as the quality of evidence used to reach their conclusions. Even though the authors were cautious in their conclusions ("CBMs might be effective for chronic pain treatment, based on limited evidence, primarily for neuropathic pain patients") we contend that there is no current high quality evidence for any available CBM to treat any defined chronic pain syndrome (9,10).

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## REFERENCES

1. Aviram J, Samuely-Leichtag G. Efficacy of cannabis-based medicines for pain management: A systematic review and meta-analysis of randomized controlled trials. *Pain Physician* 2017; 20:E755-E796.
2. Petzke F, Enax-Krumova EK, Häuser W. Efficacy, tolerability and safety of cannabinoids for chronic neuropathic pain: A systematic review of randomized controlled studies. *Schmerz* 2016; 30:62-88. Erratum: *Schmerz* 2017; 31:619.
3. European Medicines Agency: *Guideline on clinical medicinal products intended for the treatment of neuropathic pain*. 2007. [www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003478.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003478.pdf) (Accessed on 1 March 2017).
4. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, Keur-entjes JC, Lang S, Misso K, Ryder S, Schmidtkofer S, Westwood M, Kleijnen J. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 2015; 313:2456-2473. Erratum: *JAMA* 2016; 315:1522.
5. Mücke M, Carter C, Cuhls H, Prüß M, Radbruch L, Häuser W. Cannabinoids in palliative care: Systematic review and meta-analysis of efficacy, tolerability and safety. *Schmerz* 2016; 30:25-36.
6. Lichtman AH, Lux EA, McQuade R, Rossetti S, Sanchez R, Sun W, Wright S, Kornyeveva E, Fallon MT. Results of a double-blind, randomized, placebo-controlled study of nabiximols oromucosal spray as adjunctive therapy in advanced cancer patients with chronic uncontrolled pain. *J Pain Symptom Manage* 2017, Sep 15. pii: S0885-3924(17)30465-7. [Epub ahead of print]
7. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials* 1996; 17:1-12.
8. Dechartres A, Trinquart L, Boutron I, Ravaud P. Influence of trial sample size on treatment effect estimates: Meta-epidemiological study. *BMJ* 2013; 346: f2304.
9. Häuser W, Petzke F, Fitzcharles MA. Efficacy, tolerability and safety of cannabis-based medicines for chronic pain management - An overview of systematic reviews. *Eur J Pain* 2017; Oct 15. [Epub ahead of print]
10. Häuser W, Fitzcharles MA, Radbruch L, Petzke F. Cannabinoids in pain management and palliative medicine. *Dtsch Arztebl Int* 2017; 114:627-634.

## In Response: Aviram J et al The Perils of Overestimating the Efficacy of Cannabis-Based Medicines for Chronic Pain Management

We would like to thank the Editor for the opportunity to respond to Häuser and Fitzcharles's Letter to the Editor titled "The Perils of Overestimating the Efficacy of Cannabis-Based Medicines for Chronic Pain Management" in response to our paper titled "Efficacy of Cannabis-Based Medicines for Pain Management: A Systematic Review and Meta-Analysis of Randomized Controlled Trials" (1). Häuser and Fitzcharles make some important comments worthy of our response:

1. Häuser and Fitzcharles note that 3 unpublished studies from [www.clinicaltrials.gov](http://www.clinicaltrials.gov) should have been included in our analysis. However, as stated in the section titled "Risk of limitations across studies," we note that, "unpublished studies could have given our study more evidence for either direction, but this would have come at the expense of our study's reliability." This highlights the point that, including unpublished studies that did not reach their designated endpoint and did not undergo the strict process of peer review needed for publication, would have made our results less reliable. Our decision not to include unpublished data and "grey literature" in our analysis is in line with a previous meta-analysis published by Iskedjian et al (2).
2. Häuser and Fitzcharles note that the number of participants in the cannabis based medicines (CBMs) and control groups were not reported in the forest plots of the paper, therefore it is not possible to determine whether we dealt with unit of analyses issues correctly. We agree that the number of patients should have been mentioned in the forest plot. However, in order to make the forest plots easier to read, we instead listed the number of patients and dropouts for each study in Tables 1-3 and Tables 5-7. Moreover, in Tables 5-7 we indicate the number of patients in each arm of each trial and the number of patients reporting adverse effects.
3. Häuser and Fitzcharles also note that our study did not specify a minimum study duration for study inclusion and that a study duration of at least 4–12

weeks is required by drug agencies for the approval of a drug for chronic pain management. We agree that this is important data, as we listed in Tables 1-3 and Tables 5-7 of our study. However, research of CBMs is highly variable and lacks standardization. In order to conduct a wide and comprehensive systematic review and meta-analysis, we chose not to deal with the issue of treatment duration and to exclude studies of very short treatment duration (> 4 weeks). Additionally, our decision not to limit studies inclusion by excluding short duration studies is in line with 3 previous meta-analyses (2-5), except for one meta-analysis that was published after publication of our study (6). We would like to note that after receiving the Letter to the Editor, we ran the analysis again without the very short duration studies. Results for chronic non-cancer pain remained significantly beneficial for CBMs over placebo: standardized mean differences (SMD) for a fixed-effect model of -0.30 Hedge's *g* (-0.45 to -0.15,  $P < 0.0001$ ) and for a random-effect model of -0.41 Hedge's *g* (-0.69 to -0.13,  $P < 0.003$ ) utilizing 7 short duration trials (4–12 weeks) (7-13) and 2 intermediate duration arms of a trial (12–26 weeks) (14). Moreover, Häuser and Fitzcharles cite a study that was not included in our paper, which reported not to meet the primary end point for effectiveness (15). However, the study cited by Häuser and Fitzcharles was published after the predefined date for trials inclusion (July 2015). Furthermore, we would like to note that long term benefits have recently been published, and although not from randomized controlled trials (RCT), for long term follow-up of 6 months to one year, showing significant improvement of chronic pain and associated symptoms by medical cannabis inhalation (16-18) and similarly in 9 months follow-up of tetrahydrocannabinol/cannabidiol (THC/CBD) spray treatment (19). We agree that future meta-analyses should include analyses for very short/short/intermediate/long trials duration.

4. Häuser and Fitzcharles note that we used the Jadad

score (20) to assess the risks of bias in the studies included in our analysis and that we concluded that the majority of these trials were rated as moderate to high risk of bias. Furthermore, they stated that the Jadad score does not capture all relevant risks of bias in chronic pain trials, such as small sample size bias, which leads to an overestimation of the treatment effect (21). This bias applies to the majority of studies with CBM in chronic pain. Häuser and Fitzcharles raised concerns regarding short study duration and small sample size bias that are particularly valid for the studies with inhaled medical cannabis for chronic neuropathic pain for which we found a strong effect size of -0.93 Hedge's *g* (-1.51 to -0.35, *P* = 0.001). In reply to these notes, we would like to point out that we did not claim any study duration restrictions to our study inclusion, as stated in page 4 "even though the studies were not required to have a quality threshold level other than the preexisting inclusion criteria, their validity was assessed by the Jadad scale." Furthermore, we found the Jadad scale to be satisfactory, as did previous meta-analyses that used it (2,4).

- Häuser and Fitzcharles concluded that we overestimated the efficacy of CBM for chronic pain, as well as the quality of evidence used, to reach these conclusions. Häuser and Fitzcharles also note that, there is no current high-quality evidence for any available CBM to treat any defined chronic pain

syndrome (18,19). We believe that our conclusions erred on the side of caution ("CBMs might be effective for chronic pain treatment, based on limited evidence, primarily for neuropathic pain patients"). We further believe there are numerous limitations in the RCTs for CBMs and herbal cannabis for chronic pain management by many levels: relatively short study duration, variance of THC/CBD content between different CBMs, variance of THC content in herbal cannabis trials and no regard to other cannabinoids and terpenoids and their analgesic effects and difficulty to mask placebo. Due to these study limitations, we were extremely cautious in our conclusions about the beneficial effects of medical cannabis for chronic pain treatment.

We would like to thank Häuser and Fitzcharles for their important comments.

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## REFERENCES

- Aviram J, Samuelly-Leichtag G. Efficacy of cannabis-based medicines for pain management: A systematic review and meta-analysis of randomized controlled trials. *Pain Physician* 2017; 20:E755-E796.
- Iskedjian M, Bereza B, Gordon A, Piwko C, Einarson TR. Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain. *Curr Med Res Opin* 2007; 23:17-24.
- Whiting PF, Wolff RF, Deshpande S, Hernandez AV, Keurentjes JC, Lang S, Misso K, Ryder S, Schmidkofer S, Westwood M, Kleijnen J. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 2015; 313:2456-2473.
- Martín Sánchez E, Furukawa TA, Taylor J, Martin JL. Systematic review and meta-analysis of cannabis treatment for chronic pain. *Pain Med* 2009; 10:1353-1368.
- Andrae MH, Carter GM, Shaparin N, Suslov K, Ellis RJ, Ware MA, Abrams DI, Prasad H, Wilsey B, Indyk D, Johnson M, Sacks HS. Inhaled cannabis for chronic neuropathic pain: An individual patient data meta-analysis. *J Pain* 2015; 16:1221-1232.
- Meng H, Johnston B, Englesakis M, Moulin DE, Bhatia A. Selective cannabinoids for chronic neuropathic pain: A systematic review and meta-analysis. *Anesth Analg* 2017; 125:1638-1652.
- Wade DT, Makela P, Robson P, House H, Bateman C. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. *Mult Scler* 2004; 10:434-441.
- Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology* 2005; 65:812-819.
- Wissel J, Haydn T, Müller J, Brenneis C, Berger T, Poewe W, Schelosky LD. Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-related pain. *J Neurol* 2006; 253:1337-1341.
- Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology (Oxford)* 2006; 45:50-52.
- Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterised by allodynia: A randomised, double-blind, placebo-controlled clinical trial. *Pain* 2007; 133:210-220.
- Selvarajah D, Gandhi R, Emery CJ, Tesfaye S. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in

- painful diabetic neuropathy: Depression is a major confounding factor. *Diabetes Care* 2010; 33:128-130.
13. Toth C, Mawani S, Brady S, Chan C, Liu C, Mehina E, Garven A, Bestard J, Kornqut L. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. *Pain* 2012; 153:2073-2082.
  14. Langford RM, Mares J, Novotna A, Vachova M, Novakova I, Notcutt W, Ratcliffe S. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. *J Neurol* 2013; 260:984-997.
  15. Lichtman AH, Lux EA, McQuade R, Rossetti S, Sanchez R, Sun W, Wright S, Kornyeveva E, Fallon MT. Results of a double-blind, randomized, placebo-controlled study of nabiximols oromucosal spray as adjunctive therapy in advanced cancer patients with chronic uncontrolled pain. *J Pain Symptom Manage* 2017; Sept 15. [Epub ahead of print]
  16. Yassin M, Garti A, Robinson D. Effect of medicinal cannabis therapy (mct) on severity of chronic low back pain, sciatica and lumbar range of motion. *International Journal of Anesthesiology & Pain Medicine* 2016; Nov. 29. [Epub ahead of print]
  17. Haroutounian S, Ratz Y, Ginosar Y, Furmanov K, Saifi F, Meidan R, Davidson E. The effect of medicinal cannabis on pain and quality of life outcomes in chronic pain: A prospective open-label study. *Clin J Pain* 2016; 32:1036-1043.
  18. Aviram J, Pud D, Schiff-Keren B, et al. The Israeli multi-center registry of medical cannabis (MC) for chronic pain: Current findings 2017 doi:10.13140/RG.2.2.14742.45126.
  19. Hoggart B, Ratcliffe S, Ehler E, Simpson KH, Hovorka J, Lejcko J, Taylor L, Lauder H, Serpell M. A multicentre, open-label, follow-on study to assess the long-term maintenance of effect, tolerance and safety of THC/CBD oromucosal spray in the management of neuropathic pain. *J Neurol* 2015; 262:27-40.
  20. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials* 1996; 17:1-12.
  21. Dechartres A, Trinquart L, Boutron I, Ravaud P. Influence of trial sample size on treatment effect estimates: Meta-epidemiological study. *BMJ* 2013; 346:f2304.