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 Samuelly-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 Samuelly-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 durations (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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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 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: standarized 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).

5. 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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Magnesium Efficacy to Improve Analgesic Effects of Transversus Abdominis Plane Blocks

To the Editor:

I read with great interest the article of Abd-Elsalam et al (1) in a recent issue of the journal where the authors demonstrated an analgesic benefit of magnesium added to bupivacaine in transversus abdominis plane (TAP) blocks. The authors should be congratulated for performing a well-designed, randomized clinical trial to evaluate an important issue in perioperative medicine (e.g., acute pain) (2).

I believe the readers of the journal would benefit from some methodological clarifications from the authors. First, it is unclear if the patients received any multimodal analgesics in addition to the TAP block. Multimodal analgesics are commonly used perioperatively and the benefits observed by Abd-Elsalam et al (1) can be altered by the use of multimodal analgesics. In addition, it is unclear why the authors decided to use a lower dose of bupivacaine than previously used in other similar studies evaluating the TAP block (3,4). Lastly, the authors did not specify if patients received prophylactic antiemetics and, in the case of dexamethasone, the use of a prophylactic antiemetic can have an important implication on postoperative analgesic effects (5).

The study of Abd-Elsalam et al (1) is innovative as it uses a new adjunct (e.g., magnesium) to increase analgesic benefits of TAP blocks. I would welcome some comments from the authors in order to further establish the validity of this important study.

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In Response: Magnesium Efficacy to Improve Analgesic Effects of Transversus Abdominis Plane Blocks

It is always a pleasure to hear from you and reply to inquiries from valuable readers of our research work.

Here is a point-by-point response to the 3 questions:

Regarding multimodal analgesia, we didn't use it in our work. This study aimed mainly at highlighting the analgesic effects of the study agent used (magnesium sulfate). We didn't use analgesics preoperatively, and we only used intravenous morphine injections for rescue analgesia. Adding other analgesics would have affected the results and we think that other studies on the adjuvant effect of magnesium sulfate added to local anesthetic can be further carried out, but has to be designed for that purpose from the beginning.

There are 2 studies referred to in the letter, the first used a volume of 20 mL for transverse abdominis plane (TAP) block with a higher concentration of bupivacaine of 0.5%. The second study used 20 mL of 0.375% levobupivacaine injected into each side. We think that the least effective dose of any drug is the best it will be, potentially devoid of possible side effects. Our aim was postoperative analgesia, and not anesthesia, thus using a volume of 20 mL on each side of a diluted local anesthetic (0.025% bupivacaine that affects mainly sensory nerves) seems logical. In fact, I think we should ask the users of higher doses to explain why they didn't try smaller ones. The volume of 20 mL on each side is repeatedly used in TAP blocks and it guarantees a good spread of the used agents in the desired fascial planes. An overall dose of 20 mL, divided on both sides, seems little and the authors of reference (3) may have resorted to that volume in a trial not to increase the total dose of local anesthetic, as they used a higher concentration of 0.5%.

We didn't give any premedications (including antiemetics). Antiemetics were only given when vomiting occurred (rescue antiemetics) in the form of metoclopramide 10 mg intravenous injections.

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