**Point-by-Point Edits & Responses:**

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REVIEWER 1

Comments to the Author
The authors present the results of a nonrandomized prospective, single-arm cohort study
Who primary outcome was the effectiveness of the CBD-rich extract to reduce the dependence on opioids for pain control measured via the opioids’ dose and the willingness of the patients to taper their opioid medications by administering the readiness to Taper Visual Analog scale.

The described manuscript format is appropriate, and there are no ethical issues noted. The manuscript is referenced and structured properly, the sample size is small, but the results support the conclusions.

1. Please provide the NCT number, or the authors need to identify what registry the trial was listed in if any.

AUTHOR RESPONSE AND ACTION TAKEN:

The IRB, Advarra, gave the study approval at the reference number: Pro00025315. Due to the observational nature of the study, it was not required to have an IND or be registered on any site, such as clinicaltrials.gov.

2. Limitations of the study are identified, but they need to be expanded on.

AUTHOR RESPONSE AND ACTION TAKEN:

See additions in discussion section. **Action taken:** Limitations expanded on include: study length, lack of control group, small sample size, third variables, subjective nature of quality of life variables, lack of distinct MEQ data, and risk of cannabis use generally.

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REVIEWER 2

Comments to the Author
Dear editor,
I read with the interest this manuscript on use of cannabidiol in chronic pain patients on opioids. Opioids are not that effective in chronic pain management. Recent systematic review and meta-analysis indicates that less than 12% on opioids may benefit a meaningful pain reduction (>1 cm on 10-cm scale). Thus, any attempts to help these patients are more than welcome.

Some countries have allowed cannabis to substitute opioids. However, this is not based to any hard evidence.

This study investigated  the impact of cannabidiol on opioid use in chronic pain, disability, physical and psychosocial symptoms, sleep, and motivation to taper opioids.

Unfortunately the samples size is relatively small, the follow up period is relatively short and there was no control group. These shortcomings limits any conclusions these data allows.

1. Page 5 line 49: CBD is not intoxicating - I am not sure if this is true

AUTHOR RESPONSE AND ACTION TAKEN:

The World Health Organizations 2018 review of CBD stated that it is not associated with abuse potential due to its non-intoxicating nature: <https://www.who.int/medicines/access/controlled-substances/5.2_CBD.pdf>

The mechanism of action for other cannabinoid intoxication, especially THC, is largely considered to be due to agonism of CB1 receptors in the brain and central nervous system. CBD is a potent antagonist of CB1 receptors, which likely explains its lack of “psychoactive” or intoxicating effects. The author does not like to state the industry norm that CBD is not “psychoactive,” because CBD demonstrates some anxiolytic and antipsychotic properties. These effects, to the author, are “psychoactive.” But without supratherapeutic doses or a potential for a side effect of drowsiness, CBD has not demonstrated a change in cognitive functioning or motor impairment.

**Action taken:** These findings by the WHO are supported by references 15-17 and the WHO report is referenced in the discussion section as well.

2. Page 7 line 26: well-informed - what do the authors mean by this

AUTHOR RESPONSE AND ACTION TAKEN:
**Action taken:** Changed to: “ In addition, all enrolled participants had to sign an IRB approved informed consent form at a standard of care visit.”

3. Page 9 lines 1-4: No significant adverse events were reported - please report all AEs.

AUTHOR RESPONSE AND ACTION TAKEN:

**Action taken:** Additions in red: “Three participants chose not to use CBD. Two initiated the CBD but reported adverse effect of drowsiness and stopped using the soft gels. One participant declined CBD and expressed his concern in that he could not afford to pay out of pocket for the product after the end of study if it was successful. One participant reported that CBD “made her heart race” and combined twice daily dosing into one dose to manage the side effect. One participant reported nausea from CBD but continued using the product. One participant reported “heart burn and dry mouth” after initiating CBD. One participant reported CBD increased her night time anxiety and disturbed sleep. No significant adverse events were reported.”

4. Page 10 line 15: the three levels of CBD-rich extract use - should be clarified

AUTHOR RESPONSE AND ACTION TAKEN:

The sentence meant that CBD use (yes/no) and level of CBD use was collected at each data collection point.

**Action taken:** Changed to: “Three data collection points were assigned for each participant: baseline, week 4, and week 8 with corresponding levels of CBD-rich extract use at each interval. with corresponding levels of CBD-rich extract use at each interval.”

5. Page 10 lines 50-53: Fifty of the 94 (53.2%) participants using the CBD hemp extract were able to reduce opioid medications at week 8, while 55 of the 94 (58.5%) participants were able to reduce opioid medications at week 12. - wasn't this 8 weeks study? Please give more precise data how much they were able to decrease opioid consumption.

AUTHOR RESPONSE AND ACTION TAKEN:

Yes, this was an 8 week study. We asked whether or not participants would volunteer for additional follow-up at 12 weeks. Many said yes, but we had to conclude the study without reaching a significant number. **Action taken:** The data on 12 week follow up has been eliminated from the manuscript.

As included in the discussion, we were unable to determine a specific MEQ change for every participant who stated that they reduced or eliminated opioid use. This was due to a variety of factors, including low health literacy with the study population, psychosocial challenges and variable decreases. For example, two participants reported completely eliminating opioids over the 8 week trial. Many gave quantifiable answers, *i.e*. that they reduced from 4 opioid doses a day to 2 doses a day. Most, however, stated that they found themselves forgetting/skipping doses most days or having pills left over at the end of the month but they were unable (or perhaps unwilling) to give a definitive number. **Action taken:** This is included and expanded on in the discussion, pasted below.

“Two participants reported completely eliminating opioid use over the 8 week period, while others reported deliberately skipping or forgetting doses of opioid medication. Some reported skipping or missing doses every day, whereas others did so irregularly. Still, more detailed data on average MEQ change over time would have improved clarity of study outcomes.”

6. In discussion the authors may discuss a little bit addiction potential of cannabis and the data indicating that cannabis use may lead to other substance abuse also.

AUTHOR RESPONSE AND ACTION TAKEN:

Agreed. While many studies show the addiction potential and comparative risk assessment of cannabis to be relatively low, it is often misinterpreted as absent. THC is considered the be the compound responsible for cannabis intoxication and its concentration correlates with risk. But research gaps remain, and even low concentrations of THC, such as those in a hemp-derived product used in this study, need further evaluation. Lastly, one potential risk has not been studied and cannot be ignored: the scent of cannabis, even absent of any THC, could hypothetically trigger a cue-induced relapse.

**Action taken:** Added to the discussion: “According to the World Health Organization, public health risk of CBD is considered limited, but cannabis use is not absent of abuse risk or addiction potential [33, 34]. Cannabis derived from hemp, including the product used in this study, is high in CBD and low in THC, and is considered less harmful than the alternative [35]. Still, cannabis use disorder is real and some studies show cannabis may perpetuate the cycle of addiction or lead to other substance abuse [36, 37]. Additionally, even with cannabis products with low THC concentration, the aroma of cannabis itself could present the risk of cue-induced drug-seeking behavior in those with previous substance use disorder.”

7. Abbreviations should be spelled out when they appear the first time, and should be use consequently. e.g. either US or U.S. but not both.

AUTHOR RESPONSE AND ACTION TAKEN:
**Action taken:** All United States references have been edited to be U.S. and not US. The first use of any abbreviation is spelled when it first appears, the abbreviation is demonstrated then in parentheses, and consequently used consistently.

8. References should be provided according the journal style.

AUTHOR RESPONSE AND ACTION TAKEN:
**Action taken:** References edited in accordance with the journal style.

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REVIEWER 3

Comments to the Author
This is an interesting study on the use of CBD in chronic pain patients.

1. I propose that Authors consider a reorganizing a Discussion chapter starting with main findings of the study they have conducted, then discuss it with available literature, and outline study limitations, ending up with conclusions.

AUTHOR RESPONSE AND ACTION TAKEN:

**Edits made. The discussion is now in this format.**

2. I propose to use "oxycodone controlled release" and "oxycodone/acetaminophen" instead of "oxycontin" and "perocet", respectively

AUTHOR RESPONSE AND ACTION TAKEN:

**Action taken: Edits made, “…**as was possible with short-acting oral medications, such as oxycodone/acetaminophen and oxycodone controlled release.”

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EDITORS COMMENTS

1. TRANSPARENCY: If the acknowledgments section in your manuscript identifies people by name, please confirm that these individuals have provided permission to be acknowledged.

AUTHOR RESPONSE AND ACTION TAKEN:

**Yes, they have.**

2. COLOR FIGURES: Please confirm which figures, if any, you would like reproduced in color in the online edition (no charge) and the print edition ($400/€350/£300 per figure; figures 5 and above are $75/€65/£50 per figure). Depending on your location, these charges may be subject to Value Added Tax.

AUTHOR RESPONSE AND ACTION TAKEN:

**Color figures in online edition. No need for color images in print edition.**

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AUTHOR RESPONSE AND ACTION TAKEN:

**No third-party content was used and therefore no permissions are necessary.**

4. TRIAL REGISTRATION: If your manuscript describes a clinical trial, the trial must be registered in a public repository, with the registry name and trial registration number included in the abstract and the Methods section of the paper. Retroactive registration is acceptable as long as the date of registration is included in the above mentioned sections of the manuscript.

AUTHOR RESPONSE AND ACTION TAKEN:
**The study was an observational design, not a clinical trial and therefore not registered on clinicaltrials.gov or other registries.**

5. ETHICS APPROVAL & INFORMED CONSENT: If your manuscript describes a clinical trial, please confirm that the research was conducted with approval from a formal ethics review committee (or followed the principles of the Declaration of Helsinki) and with written consent from the patients. This information should be included in the Methods section of the manuscript.

AUTHOR RESPONSE AND ACTION TAKEN:

**N/A (see above)**