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COMMENTARY

Methodology considerations for 'Safety and effectiveness of cannabinoids to Danish patients with treatment-refractory chronic pain' by Horsted et al.

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The recently published exploratory, non-controlled, study by Horsted et al. (2023) reports on the potential safety and pain-relieving effects of cannabinoids (THC, CBD), or mixed in a non-randomized order. The authors conclude that 'oral cannabinoid therapy in general appears to be safe and effective for relief of chronic pain in some patients, including a subset of patients with cancer-related pain (9%), not responding adequately to conventional treatment regimens or experiencing intolerable adverse events'.

1 | REFERENCE TO STUDIES WITH HIGH QUALITY OF EVIDENCE

The author's conclusion is in direct contrast to the conclusion and recommendations from the International Associations for the Study of Pain (IASP) Cannabis Task Force. Based on a thorough evaluation of current evidence, Rice et al. (2021) concluded 'That the available clinical evidence neither supports nor refutes claims of analgesic

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efficacy or safety for cannabinoids, cannabis, or cannabis-based medicines' and suggested future studies and recommendations should follow rigid rules of conclusive randomized, placebo-controlled randomized controlled trials (RCTs) to provide evidence (Haroutounian et al., 2021).

The study by Horsted et al. is a retrospective study and hence is not monitored by the Danish medical agency and executed as a good clinical practice (GCP) study although investigating the effect of a new treatment modality. Furthermore, the study was not registered at ClinicalTrials.gov as this is not normally mandatory for retrospective studies submitted to the European Journal of Pain.

Many RCTs have been published demonstrating no effect of cannabinoids on clinical pain or potential underlying pain mechanisms when compared to placebo (e.g. Zubcevic et al., 2022). None of such studies and only one of the 14 IASP statement's current state-of-the-art papers are referenced in the manuscript by Horsted et al. and hence not discussed in the light of the current best evidence.

2 | INTERPRETATION OF THE PUBLISHED RESULTS

The study found an average decrease in clinical pain intensity of 1.8 (baseline pain approx. 7 on a 0–10 numerical rating scale), which corresponds to an effect of approx. 25%. This is in the low end of placebo effects reported in previous high-quality pain studies and what is reported in other well-controlled placebo-controlled pain studies (McQuay et al., 1996). The expectancy and placebo effects are largely (and often exclusively) found responsible for the therapeutic effects of non-pharmacological treatments such as, e.g. cannabis. The Horsted et al. study was conducted in Denmark and here cannabis has attracted much attention in the media. The positive media promotion of cannabis products will increase the placebo effects and as the study was conducted without any control or placebo groups the effect size and the placebo responses can obviously not be separated. Most recent meta-analysis likewise concluded that 'placebo responses contribute significantly to pain reduction in cannabinoid clinical trials' and 'the unusually high media attention surrounding cannabinoid trials, with positive reports irrespective of scientific results, may uphold high expectations and shape placebo responses in future'.

The authors state that 'with the relatively long follow-up it is likely that the placebo effect is of less importance'. This is not empirically validated as studies have shown long-lasting (up to 5 years) placebo effects in trials.

The Horsted et al. study enrolled 826 patients, yet only 214 patients were follow-up for the last visit, 243 patients were registered as 'lost to follow-up' and an additional 122 patients were discontinued. In addition, among the included patients, data of interest were missing (e.g. 39 (18%) of the 214 included patients with the last visit recorded had missing values regarding pain intensity measured as numeric rating scale). Only 25.9% (214/826) of the included eligible patients were included in the analysis. All these excluded patients are likely to not benefit from the study drug (no effect or severe side effects), which is not addressed in details. Thus, the excluded patients (constituting +40% of the original sample) are a likely source of a major selection bias, compromising the study's validity and conclusions. The authors do refer to the supplementary material for a description of the excluded patients, but this material is not presented in a way that allows for further analyses.

3 | CONCLUSION

The exploratory nature of this non-placebo controlled cannabis study does not provide new evidence for the use of cannabinoids for the treatment of pain. The pain alleviation reported is at its best similar to placebo responses reported in multiple randomized pain cannabis trials. The concerningly high number of patients excluded from the analysis further compromises the integrity and validity of the study.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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REFERENCES

Haroutounian, S., Arendt-Nielsen, L., Belton, J., Blyth, F. M., Degenhardt, L., Di Forti, M., Eccleston, C., Finn, D. P., Finnerup, N. B., Fisher, E., Fogarty, A. E., Gilron, I., Hohmann, A. G., Kalso, E., Krane, E., Mohiuddin, M., Moore, R. A., Rowbotham, M., Soliman, N., … Rice, A. S. C. (2021). International Association for the Study of Pain presidential task force on cannabis and cannabinoid analgesia: Research agenda on the use of cannabinoids, cannabis, and cannabis-based medicines for pain management. *Pain*, *162*, S117–S124.

Horsted, T., Hesthaven, K. L., & Leutscher, P. D. C. (2023). Safety and effectiveness of cannabinoids to Danish patients with treatment refractory chronic pain-a retrospective observational real-world study. *European Journal of Pain*, *27*, 234–247.

McQuay, H., Carroll, D., & Moore, A. (1996). Variation in the placebo effect in randomised controlled trials of analgesics: All is as blind as it seems. *Pain*, *64*, 331–335.

Rice, A. S. C., Belton, J., & Arendt Nielsen, L. (2021). Presenting the outputs of the IASP presidential task force on cannabis and cannabinoid analgesia. *Pain*, *162*, S3–S4.

Zubcevic, K., Petersen, M., Bach, F. W., Heinesen, A., Enggaard, T. P., Almdal, T. P., Holbech, J. V., Vase, L., Jensen, T. S., Hansen, C. S., Finnerup, N. B., & Sindrup, S. H. (2022). Oral capsules of tetra-hydro-cannabinol (THC), cannabidiol (CBD) and their combination in peripheral neuropathic pain treatment. *European Journal of Pain*, *27*, 492–506.

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