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COMMENTARY

Response to Arendt-Nielsen et al. (Methodology considerations for the paper by Horsted et al., 2023)

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We appreciate that we have been given the opportunity to respond to the commentary by Arendt-Nielsen et al. (2023) aiming to clarify different methodological issues (1–6) raised by the authors. Of notice, most of the issues have already been addressed and amended as part of a thorough peer-review process. Even not expressed in the commentary, we hope that the authors acknowledge the premises of our study (Horsted et al., 2023) addressing the need of generating new knowledge about the potential use of cannabis medicine as a supplementary, or alternative, therapeutic option in relief of chronic pain being reported treatment refractory to conventional analgesics by the patients.

Firstly, our retrospective study has been conducted in conjunction with the national medical cannabis pilot program in Denmark in 2018 being launched and administered by the Danish Medical Agency. The purpose of the program was 'to offer patients a lawful way of testing treatment with medicinal cannabis if they have experienced no benefits from authorized medicines'. Moreover, evaluation of the pilot program by assessment of collected patient data was another expected outcome. In this context, the authors should view the published study.

Secondly, it is stated in the commentary that 'many randomized controlled trials (RCTs) have been published demonstrating no effect of cannabinoids on clinical pain'. This biased statement conflicts with the conclusion by Fisher et al. (2021), and not Rice et al (as referred to in the commentary): '... clinical evidence neither support nor refutes claims of analgesic efficacy...'. We concur with this nuanced conclusion. Although, an expert panel in National Academies of Sciences, Engineering and Medicine (2017) has concluded 'There is substantial evidence that cannabis is an effective treatment for chronic pain in adults' one should still be cautious about drawing any final conclusions until more solid data documentation is available from RCTs of higher quality as opposed to the previously performed trials biased in different manners.

Thirdly, aiming at elucidating clinical evidence within the area of cannabis medicine, attention should be paid towards collection of clinical data originating from observational studies as those data also contribute to the evidence pyramid. Obviously, the data have their limitations due to lack of controls and presence of biases, However, they are useful as they provide information about daily clinical practice (dosing, routes of administration, response, side-effects, etc.). This information is applicable in the process of developing treatment protocols to be tested in forthcoming RCTs. Of notice, RCTs do also have their limitations (restriction to interventions supposed to have a positive effect, selected study populations etc). Hence, our real-world study results serve an important purpose simply by adding another brick of clinical knowledge to the overall cannabis medicine evidence pyramid.

Fourthly, the authors of the commentary express scepticism about the clinical relevance of the reported changes in mean NRS values from baseline to follow-up.

For clarification, those data present secondary study outcomes. The primary outcome in relation to effectiveness in this study is clearly stated as NRS ≥30% (even ≥50%) in accordance with international guidelines for assessment of pain reduction.

Fifthly, regarding the potential placebo contributing significantly to pain reduction in cannabinoid clinical trials. This phenomenon does not occur only in cannabinoid trials. Placebo effect occurs in any chronic pain treatment study without any exception and has been reported likewise in the range of 20%–40% in studies of virtually all conventional analgesics being used today (Moore et al., 2013). Whether a higher placebo effect is occurring in cannabinoid clinical trials in comparison to conventional analgesics trial, and possible reasons for that, is poor speculation by the authors.

Sixthly, lost for follow-up is common among patients with chronic pain attending health care clinics and it was, therefore, not a surprising observation in this study. Different factors may contribute to decision by the patient to stop attending the clinic, including lack of adequately perceived relief of pain or occurrence of side-effects to initiated treatment. Both reasons for lost for follow-up are plausible in our study as well as for similar studies assessing conventional analgesics. However, an additional reason for lost for follow-up in our study could be that treatment with cannabinoids is costly (in the range of 250–400 euro on monthly basis), which may retain patients from redeeming the prescription for economic reasons. Instead of making different speculations about the implications and impact of the lost for follow-up scenario, we have simply presented the effectiveness primary outcomes in a fair and transparent manner by stating *intention-to-treat* as well as *per-protocol* figures at the two follow-up visits. Hence, clinically relevant pain reduction figures (NRS ≥30%) reported by the patients were observed in the range of 10%–45%.

In conclusion, the reported findings in this retrospective observational real-world study relate to a group of *difficult-to-treat* patients with a history of chronic pain being refractory to different conventional analgesic regimens. We hope that the authors of the commentary for the sake of the patients will acknowledge the imperative need of joined clinical research collaboration as opposed to academic disputes.

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CONFLICT OF INTEREST STATEMENT

TH has provided medical care to the patients in the study.

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