

Beyond Methodological Considerations: Clinical Implications of Real-World Evidence from the CARE Study [Response to Letter]

Michael A Überall ¹, Philipp Christian Gerhard Müller-Schwefe², Michael A Küster³,
Gerhard HH Müller-Schwefe²

¹IFNAP – Private Institute of Neurological Sciences; O. Meany-MDPM GmbH, Nürnberg, 90411, Germany; ²Interdisciplinary Center for Pain & Palliative Care Medicine, Göppingen, 76033, Germany; ³Interdisciplinary Center for Pain & Palliative Care Medicine, Bonn, 53177, Germany

Correspondence: Michael A Überall, Private Institute of Neurological Sciences – IFNAP, Center of Excellence in Health Care Research, Nordostpark 51, Nürnberg, 90411, Germany, Tel +49 911 21773760, Fax +49 911 21773761, Email michael.ueberall@ifnap.de

Dear editor

We sincerely thank Qiang et al for their thoughtful and well-articulated comments¹ on our recently published CARE study.² We appreciate their recognition of the clinical relevance of real-world data in older patients with chronic pain and their constructive reflections, which provide an opportunity to further contextualize and sharpen the interpretation of our findings.

Unmeasured Confounding and Geriatric Vulnerability

We fully agree that frailty and cognitive status are highly relevant determinants of treatment outcomes in geriatric populations. As correctly noted, such parameters are not comprehensively captured in non-interventional datasets and therefore cannot be directly incorporated into propensity score matching. However, our matching approach included a broad spectrum of clinically meaningful variables, including age, comorbidity burden, pain phenotype, disease duration, and concomitant analgesic use, resulting in highly comparable baseline characteristics between cohorts.

Importantly, the potential direction of the hypothesized prescribing bias warrants careful consideration. If clinicians preferentially selected CBD-dominant formulations for more vulnerable or frail patients due to their anticipated tolerability advantages, such a bias would be expected to dilute rather than inflate the observed treatment differences. The magnitude and consistency of the superiority observed in the CBD-dominant cohort therefore argue strongly against residual confounding as a sufficient explanation of our findings.

Handling of Missing Data and Treatment Discontinuation

We acknowledge the differences in treatment retention between cohorts and the inherent challenges associated with missing data in longitudinal real-world analyses. The use of baseline observation carried forward (BOCF) for primary endpoints was deliberately chosen as a conservative approach to avoid overestimation of treatment effects.

However, it is critical to emphasize that treatment discontinuation—particularly when driven by adverse drug reactions—is not merely a statistical nuisance but a clinically decisive outcome in geriatric pain management. This is explicitly reflected in our composite primary endpoint, which integrates both effectiveness and tolerability. In this context, the substantially higher discontinuation rates observed in the THC/DRO cohort should be interpreted as a direct expression of reduced treatment acceptability rather than as a source of bias. Accordingly, attrition in this setting represents an outcome signal rather than a methodological limitation.



Polypharmacy and Pharmacokinetic Considerations

We concur that polypharmacy represents a defining feature of geriatric care and that cannabidiol may modulate cytochrome P450-mediated drug metabolism. The CARE population reflects this reality, with nearly half of patients receiving medications from six or more ATC classes.

While the potential for pharmacokinetic interactions via CYP450 pathways is well established in vitro, clinical evidence indicates that such effects are dose-dependent and primarily observed at substantially higher CBD doses than those typically used in routine care.^{3–5} The mean daily CBD doses observed in our study were comparatively low, making it unlikely that such interactions translate into clinically relevant effects within this range.

Notably, despite the high degree of polypharmacy, CBD-dominant therapy was associated with markedly lower rates of adverse drug reactions and treatment discontinuations compared to THC/DRO. If pharmacokinetic interactions had been a dominant driver of clinical outcomes, an increased burden of adverse events would be expected in the CBD cohort. The opposite pattern was consistently observed, supporting the conclusion that, under real-world conditions and within the investigated dosing range, CYP450-mediated interactions did not result in clinically meaningful safety disadvantages.

Nevertheless, we agree that prospective studies specifically designed to address drug–drug interactions would be of high value.

Opioid-Sparing Potential and Clinical Implications

We appreciate the emphasis placed by Qiang et al on the opioid-sparing effects observed in our analysis. From both a clinical and public health perspective, this represents one of the most consequential findings of the CARE study. The pronounced reduction in strong opioid use in the CBD-dominant cohort suggests that such therapies may extend beyond adjunctive use and function as facilitators of meaningful opioid de-escalation strategies in older adults.

We fully support the call for prospective investigations of structured “cannabinoid-for-opioid” transition protocols. In this regard, our findings provide a robust real-world signal that may inform the design of such studies.

Conclusions

As with all non-interventional research, our study is subject to inherent methodological constraints. However, in a population that remains largely underrepresented in randomized controlled trials, the consistency, magnitude, and clinical coherence of the observed effects provide a compelling signal in favor of a more favorable benefit–risk profile of CBD-dominant full-spectrum extracts compared with THC/dronabinol.

We are grateful for the opportunity to engage in this scientific dialogue and believe that such exchanges are essential for advancing evidence-based, patient-centered pain management strategies in older adults.

Data Sharing Statement

Data sharing is not applicable as no new data was generated for this communication.

Funding

The authors report no funding for this communication.

Disclosure

The authors declare that they have no competing interests in this communication.

References

1. Qiang D, Zheng C, Xu Y. Refining cannabinoid ratios for geriatric pain: methodological and clinical reflections on the CARE study [letter]. *J Pain Res.* 2026;19:1–2. doi:10.2147/JPR.S608085
2. Überall MA, Müller-Schwefe PCG, Küster MA, Müller-Schwefe GHH. CARE - A retrospective, dual-cohort, 24-week real-world study from the German Pain e-Registry on the Effectiveness and Safety of CBD-dominant oral cannabis extracts versus THC/dronabinol in older patients with chronic pain. *J Pain Res.* 2026;19:551457. PMID: 41821925; PMCID: PMC12977999. doi:10.2147/JPR.S551457
3. Zendulka O, Dovrtělová G, Nosková K, et al. Cannabinoids and cytochrome P450 interactions. *Curr Drug Metab.* 2016;17(3):206–226. PMID: 26651971. doi:10.2174/1389200217666151210142051

4. Brown JD, Winterstein AG. Potential adverse drug events and drug-drug interactions with medical and Consumer Cannabidiol (CBD) use. *J Clin Med.* 2019;8(7):989. PMID: 31288397; PMCID: PMC6678684. doi:10.3390/jcm8070989
5. Fonseca CDF, Zendulka O, Juřica J. Cannabinoids and the endocannabinoid system in the regulation of cytochrome P450 metabolic activity-a review. *Front Pharmacol.* 2025;16:1599012. doi:10.3389/fphar.2025.1599012

Dove Medical Press encourages responsible, free and frank academic debate. The content of the Journal of Pain Research 'letters to the editor' section does not necessarily represent the views of Dove Medical Press, its officers, agents, employees, related entities or the Journal of Pain Research editors. While all reasonable steps have been taken to confirm the content of each letter, Dove Medical Press accepts no liability in respect of the content of any letter, nor is it responsible for the content and accuracy of any letter to the editor.

Journal of Pain Research

Publish your work in this journal

The Journal of Pain Research is an international, peer reviewed, open access, online journal that welcomes laboratory and clinical findings in the fields of pain research and the prevention and management of pain. Original research, reviews, symposium reports, hypothesis formation and commentaries are all considered for publication. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/journal-of-pain-research-journal>

Dovepress
Taylor & Francis Group