Journal of Pain Research

Dovepress
Taylor & Francis Group

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LETTER

Refining Cannabinoid Ratios for Geriatric Pain: Methodological and Clinical Reflections on the CARE Study [Letter]

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Dear editor,

We read with great interest the recent article by Überall et al, "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".[1] This study provides timely and high-level real-world evidence for a demographic—patients aged ≥65 years—that is historically underrepresented in clinical trials. The findings, particularly the 85.7% full response rate in the CBD-dominant cohort compared to 21.9% in the THC/DRO group, offer a compelling argument for the multidimensional benefits of CBD-rich formulations. We commend the authors for their rigorous methodology and valuable contribution to the field. To further enhance the clinical translation of these results, we wish to offer several methodological and clinical observations.

Unmeasured Confounding: The Role of Frailty and Cognitive Baseline

While the authors utilized propensity score matching (PSM) to harmonize baseline variables, retrospective registry studies are inherently susceptible to unmeasured confounding. In geriatric pain management, frailty and pre-existing cognitive impairment are critical prognostic factors. As Pickering et al emphasize, pharmacological pain management in older persons requires careful consideration of age-related physiological changes and vulnerability to adverse effects.[2] Given that THC is associated with increased risks of falls and cognitive side effects, a potential prescriber bias may exist where physicians favored CBD-dominant extracts for more vulnerable patients. If Cohort A (CBD > THC) had a different baseline frailty profile not captured by ICD-10 codes, this could influence the observed tolerability advantage.

Methodological Implications of Missing Data Handling in High-Discontinuation Cohorts

The study reports a substantial difference in treatment retention, with 43.6% of patients in the THC/DRO group discontinuing treatment by week 24, primarily due to adverse drug reactions (19.2%). The authors applied Baseline Observation Carried Forward (BOCF) for primary endpoints. While BOCF is a conservative approach, the marked disparity in dropout rates (14.0% vs. 43.6%) may introduce attrition bias. We suggest that future sensitivity analyses employing multiple imputation (MI) or mixed-effects models could further validate whether the magnitude of the CBD group's superiority remains robust under different statistical assumptions.

Polypharmacy and Pharmacokinetic Considerations of High-Dose CBD

A salient feature of the CARE population is the high degree of polypharmacy, with nearly half of the patients taking medications from six or more ATC clusters. Patients in Cohort A received a mean daily CBD dose of 33.5 mg. Since

https://doi.org/10.2147/JPR.S608085
Received: 9 March 2026
Accepted: 23 March 2026
Published: 25 March 2026

CBD is a known modulator of the cytochrome P450 enzyme system, as detailed in Friedman et al's comprehensive review on cannabinoids in neurological disorders,[3] it would be clinically valuable to discuss whether the researchers observed any specific trends in dose adjustments of non-pain medications during the 24-week period. This is particularly relevant given that 63.6% of the population had circulatory system comorbidities, where drug-drug interactions may carry significant implications.

The Clinical and Public Health Significance of Opioid-Sparing Effects

The most impactful finding from a public health perspective is the dramatic reduction in strong opioid use—from 56.2% at baseline to 8.3% at 24 weeks in the CBD-dominant cohort. This aligns with the systematic review and meta-analysis by Nielsen et al, which demonstrated consistent opioid-sparing effects of cannabinoids across preclinical and clinical studies.[4] This suggests that CBD-dominant extracts may not only serve as adjuncts but as pivotal "rescue" tools for opioid tapering in the elderly. We recommend that future prospective trials explicitly investigate standardized "cannabinoid-for-opioid" transition protocols to mitigate the risks of opioid-related toxicities in older adults.

In conclusion, the CARE study establishes a novel paradigm for cannabinoid therapy in geriatric pain. The observation that CBD may attenuate THC-induced adverse reactions—possibly through its role as a negative allosteric modulator of the CB1 receptor, as elucidated by Laprairie et al[5]—warrants further exploration in prospective trials with predefined cannabinoid ratio arms. Addressing these methodological dimensions will further refine the role of CBD-dominant preparations within multimodal pain management.

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.

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https://doi.org/10.2147/JPR.S608085