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Cannabinoids for Alzheimer's disease: A promising trial, although not yet ready for the prescription pad

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Abstract

Cury et al. present the first randomized placebo-controlled trial of a low-dose balanced tetrahydrocannabinol–cannabidiol extract targeting cognition in Alzheimer's disease (AD). The study marks a milestone in a field long dominated by anecdotes and low-certainty evidence. While it demonstrated modest cognitive improvement on the Mini-Mental State Examination, the lack of functional and behavioral outcomes raises questions about real-world benefits. Methodological limitations, including a small sample size and limited power, temper interpretation but highlight the need for larger studies. For clinicians, this trial transforms speculation into evidence-based counseling, promoting informed dialogue while cautioning against premature clinical use of unregulated cannabis products in AD care.

Keywords

Alzheimer's disease, cannabidiol, cannabinoids, CBD, clinical trial, cognition, tetrahydrocannabinol, THC

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As clinicians caring for patients with Alzheimer's disease (AD), we are engaged in a constant dialogue with families as they navigate the challenges of the disease. Amidst limited effective treatments, a growing number of families are turning to alternative therapies, with cannabis products being among the most frequently discussed. Caregivers, often driven by desperation and narratives from media or social networks, are increasingly inquiring about or independently using unregulated cannabis oils, edibles, and tinctures to manage AD symptoms.

Until now, clinicians have been poorly equipped to guide these conversations. The existing evidence base has been sparse, consisting primarily of a few small, heterogeneous studies of synthetic tetrahydrocannabinol (THC) analogues for agitation, with systematic reviews and meta-analyses concluding that while there may be a benefit, the evidence remains of low certainty, and no firm recommendations can be made.[1–9] We have lacked robust placebo-controlled data on the effects of a balanced THC–cannabidiol (CBD) extract, especially on cognition. The trial by Cury and colleagues[10] is therefore a welcome contribution as the first piece of randomized controlled evidence on a low-dose formulation targeting cognitive outcomes in AD.

While this study does not primarily justify the prescription of cannabinoids to AD patients, it lays the groundwork for informed, evidence-based discussions on the subject. It allows us to move beyond speculation and acknowledge to families that this is an area of ongoing scientific inquiry. We can validate their interest by referencing this well-designed, albeit modestly sized, clinical trial (29 patients randomized; 28 receiving treatment, 14 per arm analyzed). Simultaneously, we can leverage the study's limitations and findings to explain why recommending currently available commercial products would be premature and potentially unsafe. This trial redefines the clinician's role from one of uninformed dismissal to one of evidence-based counseling, fostering a therapeutic alliance built on shared uncertainty and mutual quests for applicable data.

While the statistically significant improvement on the Mini-Mental State Examination (MMSE) is the headline finding of the trial, the pragmatic clinician must ask a fundamental question: Does this result translate into a meaningful, tangible benefit for the patient and their family? For those dealing with the reality of dementia, a change

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in a test score can seem abstract, as what matters most to patients and caregivers are preserving function, reducing distressing behaviors, and maintaining quality of life.[11] For these patient-centric outcomes, however, the low-dose cannabis extract fell short of showing benefits in the battery of secondary outcome measures. If an intervention stabilizes a patient's MMSE score without enhancing or preserving their capacity for daily activities, alleviating agitation or apathy, or improving the reported quality of life for the patient or caregiver, its practical value appears constrained. The trial results indicate a potential disparity between what is statistically quantifiable on a cognitive assessment and what is humanistically meaningful in a patient's life. It reinforces the wisdom of regulatory guidance that increasingly favors co-primary or composite endpoints that integrate both cognition and function, ensuring that a declaration of *therapeutic success* is anchored in real-world impact.[12] For the clinician counseling families, the message is that while this specific treatment may have an effect on cognitive performance, it is uncertain how that would translate into improvement in the daily struggles that define the experience of living with AD.

We need, however, to contextualize this lack of effect on secondary outcomes within the study's methodological limitations. The trial, which enrolled 28 patients receiving treatment (14 per arm), below its *a priori* target of 37 participants required to achieve 80% power for the primary outcome, might also not have been powered to detect more subtle effects on secondary measures of function and behavior. This is a salient point given the well-established between-subject variability intrinsic to AD., a phenotypically diverse condition, with individuals exhibiting substantial differences in their rates of cognitive, functional, and behavioral decline related to demographic, genetic, and neuropathological factors.[13] In a small sample of 28 patients drawn from a phenotypically heterogeneous population, a true therapeutic between-group benefit can be obscured by this between-subject *statistical noise*. Therefore, the absence of a signal on these secondary outcomes of this trial should be interpreted not as definitive evidence of "*no effect*," but as an inconclusive finding that indicates the need for larger trials capable of detecting a signal amidst the disease's inherent variability.

Similarly, in the realm of power, but in the other direction, we also need to examine safety signals. Although the overall incidence of adverse events was not statistically different between groups, certain side effects are not quite trivial in a frail, elderly population with cognitive impairment, who are already at high risk for falls, delirium, and psychosis. Clinicians may be hesitant to implement an intervention that nearly doubles the rate of somnolence and quintuples the rate of paranoia due to its safety profile.[4] Therefore, the lack of statistical power reemerges here as a concern, as a larger sample may well have found these differences to be statistically significant, once again distinguishing the intersubject variability from the effects attributable to the intervention. Larger trials may also yield more accurate risk–benefit evaluations by stratifying patients according to their phenotypes, comorbidities, and concurrent medications to identify patients predisposed to specific side effects.[13]

The trial by Cury and colleagues[10] is a landmark study, being the longest placebo-controlled trial of a cannabinoid extract in AD and one of the first to test a cognitive primary endpoint. It provides a teasing piece of evidence that modulation of the endocannabinoid system may hold promise for AD. However, it is a first step, not a final destination.

For the practicing clinician, the message is one of watchful waiting and responsible counseling. This study provides a resource for educating patients and caregivers about the potential of cannabinoids, while also highlighting the uncertainties regarding real-world efficacy and safety profile. It is our responsibility to channel the hope generated by this study away from the premature use of unregulated products and toward advocating for the kind of research that can provide assuring answers. The responsibility is now shared with the scientific and pharmaceutical communities to build upon this preliminary signal with the large-scale trials needed to determine if this promising hypothesis can be translated into a safe, effective, and prescribable medicine for our patients.

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