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## Invited Perspective

# Tetrahydrocannabinol Has Potential for Treating Agitation in Alzheimer's Disease

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Neuropsychiatric symptoms (NPS) add greatly to the public health burden of Alzheimer's disease (AD) and adversely impact patient and caregiver quality of life. Agitation is one of the most prominent NPS in AD with high prevalence and persistence. Nonpharmacologic interventions are recommended as first-line treatment for NPS in AD, but are limited by a delayed onset of effect and lack of efficacy for more severe agitation and aggression. Although medications are widely used to treat NPS in AD, none are U.S. Food and Drug Administration (FDA) approved and one widely used class of medications (antipsychotics) is associated with increased mortality and risk of cerebrovascular adverse effects (AEs). More effective and better tolerated medications for NPS in AD are sorely needed.

There is increasing interest in the therapeutic potential of cannabinoids, including delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) for NPS in AD. THC and CBD are the predominant biochemical constituents of cannabis, and both are FDA approved (THC for anorexia and nausea, CBD for Dravet and Lennox-Gastaut syndrome). The brain has two major cannabinoid receptors: cannabinoid receptor type 1 (CB1), likely responsible for anxiolytic and euphoric effects, and cannabinoid receptor type 2 (CB2), with possible anti-inflammatory effects. Although THC is active at both receptors centrally, psychotropic effects are mediated through CB1.<sup>1</sup> Synthetic THC has been increasingly used off-label for agitation in AD; the largest case series involved 40 AD inpatients whose mean agitation score improved

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with a mean dose of approximately 7 mg THC daily for a mean of approximately 17 days. Common AEs included sedation (~25%) and delirium (~10%).<sup>2</sup> A recent RCT of THC in the Netherlands at a dose of 4.5 mg daily for 3 weeks was null, and there were no significant differences in AEs between treatment and placebo groups.<sup>3</sup>

In this issue, Herrmann et al. report on a randomized, double-blind crossover trial of nabilone (a synthetic THC analog) at a dose of 1–2 mg daily in 39 AD patients with agitation from outpatient clinics and nursing homes.<sup>4</sup> Each treatment phase was 6 weeks in duration with a 1-week washout in between phases. There were few medication exclusions and study drug was added to current psychotropic medications. Subjects were significantly, but not severely, agitated with a mean Cohen-Mansfield Agitation Inventory (CMAI) score of 68 (50 typically used as a cutoff for agitation). Study participants were severely cognitively impaired (mean standardized Mini-Mental State Examination (sMMSE) of 6.5) and elderly (mean age 87 years).

Nabilone treatment was associated with significant improvement in the primary agitation outcome (CMAI) with a moderate effect size (Cohen's *d* of 0.52). They observed similar improvements in the Neuropsychiatric Inventory Agitation/Aggression subscale, total Neuropsychiatric Inventory score, caregiver distress, and CMAI subdomains. Remarkably, they report improved cognition of about one point on sMMSE. Patients on nabilone had better nutrition but no change in weight or pain. AEs were expected and manageable: 17 patients experienced significant sedation during the nabilone phase versus 6 during placebo, but 12 of 17 instances of sedation resolved with dose decrease and those 12 still had improved agitation on nabilone. Falls and serious AEs were similar in both phases, and there were no cases of delirium.

These data suggest that nabilone is a well-tolerated and reasonably effective treatment for agitation in AD. Agitation and caregiver distress improved significantly, and there was even a small improvement in cognition, although the clinical significance is questionable in the context of severe cognitive impairment. Sedation was frequent but manageable with dose reduction, and agitation improved at those reduced doses. Despite the known effects of CB1 agonism at increasing appetite, they saw no significant

weight gain on nabilone. The study was well designed for generalizability since nabilone was added to current psychotropic medications. While the variety of these psychotropic medications might confound findings, the results are unchanged covarying for psychotropic medication use, stratified by medication class. Another issue is the crossover design, in which carry-over between the treatment phases could confound results and the 1-week washout might not be sufficient in duration to eliminate these effects. However, the investigators reported no carry-over or treatment order effects.

It is important to consider pharmacologic differences between nabilone and THC. Both are agonists at CB1 and CB2 receptors, but nabilone has a slightly greater affinity and efficacy at these receptors than THC, and better gut absorption.<sup>5</sup> However, both undergo extensive metabolism and have similar time to peak pharmacodynamic effects (about 2 hours) and rate of elimination. Nabilone fully substitutes for THC in drug discrimination trials, and a 10 mg THC dose appears to have comparable pharmacodynamic effects as the 2 mg/day nabilone dose used by Herrmann et al. The null Netherlands trial used 4.5 mg daily of botanically derived THC,<sup>3</sup> which, in the context of the present study, suggests that dose of THC may have been insufficient. Two of the authors (PR and BF) are principal investigators of an NIH-funded RCT of dronabinol at a target dose of 10 mg/day for agitation in AD (NCT02792257). Caution must be maintained in dose escalation with this population as pharmacokinetic variability may lead to AEs.<sup>6</sup>

Given the rapidly changing landscape of cannabis regulation in the United States and increasingly widespread use of medicinal cannabis, research is needed to determine the comparative efficacy and safety of alternative cannabis or cannabinoid preparations. For example, cannabidiol has exhibited anxiolytic effects in preclinical and clinical studies.<sup>7</sup> Because anxiety is common in dementia and may exacerbate agitation in this population, there may be added benefit of medication formulations that contain both THC and CBD. Empirical data are needed to better understand if "whole-plant" cannabis products confer improved clinical efficacy with fewer AEs compared with single molecule products, such as dronabinol or nabilone.

In this context, the results of this trial are important, suggesting that nabilone has significant potential for safely treating agitation in AD with appropriate

clinician supervision. In coming years we expect more data on the safety and efficacy of nabilone and other cannabinoids in AD, which will help establish clinical guidelines for the use of cannabinoids in the treatment of agitation in a vulnerable AD population.

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