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Dronabinol for the Treatment of Agitation in Alzheimer's Disease: A Mini-Review

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ABSTRACT

Background: Neuropsychiatric symptoms affect up to 70% of individuals with dementia and place a heavy burden on patients, carers and health care systems. Current pharmacological therapies have historically centered on SSRIs and antipsychotics, which carry a black box warning on increased mortality from all causes in patients with dementia. Two FDA-approved treatments for agitation in AD now exist, brexpiprazole (2023) and Auvelity/dextromethorphan-bupropion (2026), yet limitations persist and the need for additional well-tolerated options remains.

Objective: The endocannabinoid system (ECS) has emerged as a promising therapeutic target. This review assesses the clinical evidence supporting the use of dronabinol (synthetic delta 9-tetrahydrocannabinol; THC) for the treatment of agitation in Alzheimer's disease and reviews the literature on the recently completed randomized controlled trial THC-AD.

Methods: A narrative review of PubMed and ClinicalTrials.gov was conducted through February 2026 using the keywords dronabinol, agitation, Alzheimer's disease, and cannabinoids.

Results: The review included results from open-label pilot studies, a crossover randomized clinical trial (RCT) with nabilone and a multicenter parallel group RCT (THC-AD). The THC-AD study demonstrated a clinically relevant reduction in agitation as measured by the Pittsburgh Agitation Scale (PAS; p=0.015; ES = 0.53 per week). Dronabinol was generally well-tolerated, with somnolence identified as the only notable side effect occurring at a higher frequency in the treatment group than in the placebo group.

Conclusions: Accumulating clinical evidence supports the need for a more definitive Phase III trial to establish dronabinol as a viable and potentially approvable treatment for agitation in Alzheimer's disease. Dronabinol's distinct endocannabinoid mechanism, favorable safety profile, and absence of antipsychotic-class mortality risk position it as a complementary option within a treatment landscape that now includes brexpiprazole and Auvelity (dextromethorphan HBr/bupropion HCl).

Introduction: The Unmet Clinical Need

Agitation is one of the most disabling and distressing symptoms of Alzheimer's disease (AD), occurring in up to 70% of patients at some point along the disease course.[1] It encompasses a range of behaviors, including verbal and physical aggression, motor restlessness and disinhibition, which can trigger early institutionalization, accelerate cognitive and functional decline and take a heavy toll on the well-being of carers.[2] With the global prevalence of AD set to triple by 2050, the social and psychological costs of neuropsychiatric symptoms will increase accordingly.[3]

The pharmacological treatment of agitation in AD has long been defined

by frustrating compromises. Off-label antipsychotics, most commonly risperidone, quetiapine, olanzapine and haloperidol, are widely used. However, these medications only modestly reduce symptoms and carry a 2005 FDA box warning on increased risk of mortality in dementia in the elderly.[4] In May 2023, brexpiprazole became the first FDA-approved pharmacological treatment for agitation in AD.[5] While this marks a significant regulatory achievement, brexpiprazole shares the class-wide antipsychotic-related mortality warning. Its clinical benefits, primarily assessed using the CMAI, have been considered modest compared to placebo.[6] There is an urgent and unmet need for more effective interventions with favorable safety profiles, especially in fragile elderly patients.

This treatment gap has prompted interest in the endocannabinoid system (ECS), which regulates mood (particularly anxiety), stress response, sleep, appetite and inflammation.[7] Dronabinol (synthetic Δ9-tetrahydrocannabinol; THC), a CB1/CB2 receptor agonist, has the most extensive clinical dataset in this population and has been investigated in AD since the late 1990s.[8] Our group recently completed THC-AD, the largest multicenter randomized controlled trial (RCT) of dronabinol. We propose to place these results in context, thereby advancing the current understanding of dronabinol's role and offering insights into its overall positioning.

Literature Search Methods

We conducted a narrative review of PubMed and ClinicalTrials.gov for the period of January 1, 2000, through February 28, 2026. We used the following MeSH terms and their respective free-text versions: 'Agitation', 'dronabinol', 'tetrahydrocannabinol', 'nabilone', 'nabiximols', 'Alzheimer's disease', and 'dementia'. Reference lists from identified reviews and meta-analyses were cross-referenced to identify additional studies. The initial search yielded 901 articles; after removal of duplicates and exclusion of records that were not cannabinoid-related, did not assess agitation as an outcome, or fell outside an AD or dementia population, 44 articles proceeded to full-text review, of which 12 met all inclusion criteria: 8 primary interventional clinical studies and 4 systematic reviews or meta-analyses. We included open-label, crossover, and parallel-group randomized controlled trials (RCTs) that reported baseline and outcome data for cannabinoid pharmacotherapy in treating behavioral symptoms of dementia. Note: Following the literature search cutoff of February 28, 2026, the FDA approved Auvelity (dextromethorphan HBr/bupropion HCl) on April 30, 2026 for agitation associated with dementia due to Alzheimer's disease. This post-cutoff development is discussed in Section 5 to ensure the pharmacological context remains current.

Mechanistic Rationale: The Endocannabinoid System in Alzheimer's Disease

The therapeutic rationale for cannabinoids in AD is based on the wide-ranging regulatory function of the ECS and its documented dysregulation in AD.[9] The ECS consists of two major G-protein coupled receptors, CB1 and CB2, and their endogenous ligands (mainly anandamide [AA] and 2-arachidonoylglycerol [2-AG]), as well as the enzymes responsible for their synthesis and elimination.[10] CB1 receptors are expressed most strongly in the hippocampus, amygdala, prefrontal cortex, basal ganglia, especially the striatum and globus pallidus, and in the cerebellum., while the CB2 receptors are mainly expressed in the microglia and peripheral blood lymphocytes.[11] Network meta-analyses of ECS changes in AD suggest that CB1 receptor expression is significantly decreased, especially in the frontal cortex, while 2-AG and its degradation enzyme MAGL are increased, suggesting a compensatory, but ultimately dysregulated, endocannabinoid tone in the cerebral cortex of AD.[7]

Preclinically, CB1 and CB2 agonism are associated with several mechanisms of potential therapeutic importance: reduction of neuroinflammation and microglial hyperactivation, reduction of excitotoxicity mediated by glutamate, reduction of oxidative stress, modulation of circadian rhythms and increased cerebral perfusion.[12] Biomarker sub-studies from an RCT of nabilone showed that pre-treatment levels of tumor necrosis factor-alpha (TNF-α) and 4-hydroxynonenal (4-HNE), markers of neuroinflammation and oxidative stress, respectively, were significantly correlated with baseline agitation severity, and that TNF-α reduction was significantly correlated with the reduction in agitation.[13] These findings provide a biologically plausible and mechanistically consistent basis for the use of cannabinoid agonists in agitation in AD.

The Clinical Evidence Base: From Open-Label Studies to Randomized Trials

Early Open-Label Studies

Clinical research on cannabinoids for treating agitation in Alzheimer's disease (AD) began in the mid-1990s. In a 1997 crossover study of 15 patients with severe AD, Volicer et al.[14] demonstrated that dronabinol at a mean dose of 7 mg daily produced significant reductions in nighttime motor agitation and decreased severity on the CMAI while also improving body weight, establishing important early proof-of-concept for cannabinoid agonism in this population. Subsequent open-label and pilot studies, typically utilizing dronabinol at doses of 2.5 to 5 mg daily, consistently observed improvements in agitation, appetite, and sleep, with sedation and somnolence as the primary adverse effects. However, these early findings were constrained by significant methodological limitations, including small

sample sizes, lack of blinding, and inconsistent outcome measures. Meta-analyses such as Bahji et al.[15] reported significant standardized mean differences for the CMAI (SMD=-0.80) and Neuropsychiatric Inventory (SMD=-0.61), yet categorized the overall evidence as low-quality and underpowered.

While Hillen et al.[16] concluded that dronabinol and THC were associated with significant neuropsychiatric improvements with no serious adverse reactions, recent comprehensive reviews reflect a more cautious consensus. The 2021 Cochrane review highlighted "low to very low certainty" in the existing data,[8] and another systematic review from the same year emphasized that while results are promising, the field remains divided due to lack of longitudinal designs and standardized dosing.[15] This critical evidentiary gap positioned large-scale, multicenter efforts like the THC-AD study as essential for providing definitive high-rigor data required for clinical decision-making.

The Nabilone RCT

Herrmann et al. performed a crossover RCT on nabilone.[17] Thirty-nine nursing home residents with moderate to severe AD meeting the DSM-5 criteria for major neurocognitive impairment were randomized in a double-blind, 14-week crossover study to nabilone (an analogue of synthetic THC) or placebo, titrated to a maximum of 2 mg daily for one week with a washout period. Patients on stable doses of cognitive enhancers for at least 3 months were eligible for the study. Nabilone significantly reduced the level of agitation as measured by CMAI compared with placebo, with a treatment difference of -4.0 points on the CMAI (95% CI: -6.5 to -1.5; p=0.003). Notably, 47% of patients experienced cognitive improvement during the nabilone phase compared with 23% during the placebo phase - an unexpected finding that requires further investigation. The main adverse event more frequent during treatment with nabilone was sedation, manageable by dose reduction. A companion analysis of biomarkers[13] found that baseline markers of inflammation and oxidative stress moderated the response to treatment, indicating the potential usefulness of enriching patients with biomarkers in future studies. Critically, the crossover design, although rigorous, prevents the assessment of carryover effects and limits the generalizability as compared with parallel group randomized clinical trials.

Prior THC and Dronabinol RCTs

Several small parallel-group studies utilizing low-dose herbal THC (1.5 to 4.5 mg daily), conducted primarily in European nursing homes, did not show statistically significant improvements in agitation compared to placebo. A meta-analysis by Ruthirakuhan et al.[18] confirmed this lack of a significant pooled effect on agitation (SMD=0.69; p=0.10), while identifying significant heterogeneity (I^2=86%) and noting that sedation was significantly more common with cannabinoids than with placebo (RR=1.73; p=0.04). Their analysis further demonstrated that cannabinoid efficacy was significantly associated with greater cognitive impairment at baseline, a finding with direct implications for patient selection.

Conversely, another systematic review and meta-analysis reached more optimistic conclusions.[15] Pooling data from nine studies (N=205), Bahji et al. found significant improvements in the CMAI (SMD=-0.80; 95% CI -1.45 to -0.16), total neuropsychiatric scores (SMD=-0.61), and nighttime behaviors (SMD=-1.05). These seemingly contradictory findings are likely attributable to differences in study populations, inclusion criteria, and statistical methodologies, specifically regarding dementia severity and the chemical profile of the THC preparation used.

The THC-AD Trial

The THC-AD study is the largest multicenter, parallel-group RCT of dronabinol for agitation in AD to date. While previous studies often relied on broad behavioral inventories, this trial used two co-primary outcomes: the Pittsburgh Agitation Scale (PAS) and the Neuropsychiatric Inventory – Clinician Version sum of Agitation and Aggression (NPI-C A/A). Results were asymmetric: PAS showed a statistically significant reduction on drug versus placebo (difference of -0.74 per week; p=0.015; ES=0.53), while the NPI-C A/A did not reach pre-specified significance. This co-primary asymmetry is an important caveat that should temper interpretation of the overall efficacy signal. The Neuropsychiatric Inventory – Clinician Version sum of Agitation and Aggression (NPI-C A/A) decreased (-1.26 per week; SE=0.67; p=0.094; ES=0.36), reflecting a consistent directional signal that did not reach pre-specified statistical significance.[18]

The study's design reflected "real-world" complexity by including participants with severe cognitive impairment (confirmed via MMSE or SIB-8) and allowed concomitant psychotropic medications. Despite this high-acuity population, the trial maintained an 84% retention rate, and dronabinol demonstrated a favorable safety profile, with somnolence as the only notable adverse effect.

However, it must be noted that no secondary outcomes (sleep, ADCS-ADL, CMAI, CGI-C) differed significantly between treatment arms. Secondary outcomes were analyzed using Generalized Estimating Equations (GEE) to handle within-person correlations. No adjustments for multiple comparisons were applied to secondary outcomes; thus, findings should be interpreted cautiously due to an increased risk of Type I error.

Nabiximols and Emerging Cannabinoid Formulations

The STAND feasibility trial evaluated nabiximols (1:1 THC:CBD oromucosal spray) in 29 participants with probable AD and clinically significant agitation across UK care homes. Participants received nabiximols, with each oromucosal spray actuation delivering 2.7 mg Δ9-THC and 2.5 mg CBD; participants were up-titrated over 4 weeks to a maximum of 12 actuations per day (delivering up to 32.4 mg THC and 30 mg CBD daily). Due to COVID-19 pandemic-related recruitment challenges, the trial fell short of the prespecified feasibility threshold of 60 participants. No statistically significant treatment effects on agitation were observed; however, positive clinical signals were noted, and the intervention demonstrated a favorable safety profile with no safety concerns reported throughout the trial. The inclusion of cannabidiol (CBD), which has independent anxiolytic and anti-inflammatory properties at CB2 receptors, raises the possibility that combined THC:CBD formulations may offer complementary mechanistic advantages over THC alone,[19] though direct comparative data are not yet available.

Non-Cannabinoid Pharmacotherapies for Agitation in AD

The contextualization of dronabinol in the wider pharmacological environment is essential for the evaluation of its clinical benefit. The approval of brexpiprazole by the FDA in May 2023 for agitation in AD was an important regulatory precedent, demonstrating that agitation in AD may be an approvable indication and setting CMAI as an acceptable primary endpoint for registration. However, brexpiprazole carries a class-wide black box warning about increased risk of mortality with antipsychotics in elderly patients with dementia, a risk that reflects a consistent and reproducible signal across multiple antipsychotics.[5] Therefore, the benefit-risk balance for brexpiprazole requires careful individualized assessment, and its use may be particularly problematic in the most fragile and vulnerable patients with severe AD.

More recently, on April 30, 2026, the FDA approved Auvelity (dextromethorphan HBr/bupropion HCl) for agitation associated with dementia due to Alzheimer's disease, making it is the second approved pharmacotherapy for this indication. Auvelity is a first-in-class oral agent that targets the NMDA receptor and sigma-1 receptor via its dextromethorphan component, with bupropion serving as a CYP2D6 inhibitor to increase dextromethorphan bioavailability. Its approval was supported by the Phase 3 ADVANCE-1 trial, a 5-week, double-blind, parallel-group study in which Auvelity was statistically superior to placebo on the CMAI total score at Week 5, and the ACCORD-2 long-term randomized withdrawal trial, which demonstrated a statistically significantly longer time to relapse of agitation symptoms compared to placebo. Importantly, Auvelity does not carry an antipsychotic class-wide black box warning for mortality in elderly patients with dementia. The most common adverse reactions in ADVANCE-1 were dizziness and dyspepsia, with a discontinuation rate due to adverse events of 1.3%, matching placebo. This approval further validates agitation in AD as a regulatorily achievable indication and expands the non-antipsychotic treatment landscape against which dronabinol must be positioned.[20] One caveat is that to date these results have not been published in a peer-reviewed publication.

In contrast, THC-AD did not show an increase in all-cause adverse events compared to placebo (except somnolence), nor did it impair cognition or daily functioning during the three weeks of treatment. The duration was too short to measure a mortality signal. The lack of cognitive deterioration is particularly remarkable in view of long-standing concerns about cannabinoid-induced impairment in this population. The safety profile of dronabinol positions it as a candidate in patients in whom antipsychotic use is contraindicated or not well tolerated, a subgroup with clinical relevance.

Limitations

The THC-AD study has several limitations that bear directly on the interpretation of its findings. First, the failure of the NPI-C A/A co-primary endpoint to reach pre-specified statistical significance (p=0.094) means that the trial did not achieve a clean dual-endpoint demonstration of efficacy; the significant PAS result, while meaningful, represents only one of two pre-specified primary tests. Second, the three-week treatment duration does not address whether efficacy is maintained over clinically relevant time periods (months to years) or whether tolerance to chronic CB1 agonism develops. Third, the sample size of 75 was powered to detect signals rather than to provide a definitive estimate of efficacy, and the study was not powered to detect subgroup differences in dementia severity, gender, ethnicity, or concomitant medication status: limitations typical of a Phase II trial. In the wider literature, methodological diversity, including differences in cannabinoid types, dosing strategies, duration, patient populations, and outcome measures, has complicated synthesis and meta-analysis; Charernboon et al. assessed the evidence base as low to very poor, stressing the need for larger and more definitive studies.[21]

Future Directions

The evidence now amassed is sufficient to justify a more definitive hypothesis-testing Phase III clinical trial of dronabinol for agitation in AD. Several priority areas merit attention in the future design of such trials:

- **Biomarker-based patient enrichment** is a

particularly promising strategy. Data from the nabilone sub-study suggest that cannabinoid therapy may be more beneficial in patients with a higher baseline neuroinflammatory burden (increased TNF-α). Integrating inflammatory, oxidative stress, and possibly neuroimaging biomarkers into patient selection algorithms could improve the signal-to-noise ratio and targeting accuracy. Additionally, future studies can use amyloid biomarkers for inclusion or for stratifying analyses.

- **Dementia severity stratification** is warranted. Cannabinoid efficacy appears enhanced in patients with greater cognitive impairment, justifying inclusion across a wide range of severity and appropriate stratification of subgroup analyses.
- **Longer trial duration** is needed to assess the durability of responses, tolerability, and safety signals that may not be evident after weeks of treatment.
- **Regulatory-grade primary endpoints**, particularly CMAI, which served as the brexpiprazole registration endpoint, should be incorporated to facilitate cross-study comparison and regulatory submission.
- **Cannabinoid combination strategies** warrant investigation: future work should assess THC:CBD formulations and examine the relative contribution of CB1 and CB2 agonism to the observed clinical effects.

Conclusions

Dronabinol is a scientifically plausible, mechanistically based, and empirically supported treatment option for agitation in Alzheimer's disease. The THC-AD study demonstrated statistically significant and clinically meaningful efficacy on the PAS (ES=0.53), with an 84% completion rate and no detectable safety signals (cognitive impairment, intoxication, increased mortality risk) that limit existing pharmacotherapeutic options. Results from comparable studies, the nabilone crossover trial, the STAND feasibility study on nabiximols, open-label data, and systematic reviews, provide convergent evidence favoring endocannabinoid system modulation for agitation in AD. Dronabinol's favorable safety profile makes it particularly attractive in fragile elderly patients at risk from antipsychotic use, a clinically important and pharmacologically underserved population. The preliminary evidence supports a definitive Phase III trials establishing dronabinol's efficacy for one of the most challenging neuropsychiatric symptoms in AD.

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Conflicts of Interest

Surafel Tsegaye, Brent P. Forester and Paul B. Rosenberg report no commercial conflicts of interest related to the content of this article.

Readers should note that P.B. Rosenberg and B.P. Forester serve as Co-principal investigators of the THC-AD trial. This involvement represents a potential non-commercial conflict of interest. To mitigate this, findings are presented alongside their limitations, negative secondary outcomes are explicitly reported, and the conclusions are framed within the context of the broader cannabinoid literature and its acknowledged evidentiary gaps.

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